

# Therapeutic Use of Hyperbaric Oxygen Therapy for Children with Autism Spectrum Disorder

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## ABSTRACT

Autism spectrum disorder (ASD) is neurodevelopment disorder, characterized by impairment in social interaction, verbal and non-verbal communication and the presence of restricted and repetitive stereotyped behaviors. The condition manifests within the first 3 years of life and persists till adulthood. At present, the etiology of ASD is largely unknown, but genetic, environmental, immunological, and neurological factors are thought to play a role in the development of ASD. The prevalence of ASD has increased dramatically in the past few decades. According to current estimates from the United States Centers for Disease Control and Prevention (CDC) as many as 1 in 91 children have ASD in USA. Studies from the Middle East on this topic are limited. Autism in Saudi Arabia is slightly higher than reported in the developed countries. Hyperbaric oxygen therapy (HBOT) has been growing in popularity for the treatment of ASD over recent years. However, few studies of its effectiveness have been reported. This article reviews important publications regarding the physiologic and clinical influence of HBO on ASD. Several case series and randomized trials have all proposed that low pressure/ low oxygen concentration hyperbaric treatment can improve the clinical manifestations of autism.

**Key Words:** *Autism spectrum disorder. Hyperbaric oxygen therapy.*

## INTRODUCTION

Autism spectrum disorder (ASD) is a developmental disorder which is characterized by impairment in communication, social interaction and stereotypic or repetitive behaviors.<sup>1</sup> In general, the symptoms are manifest within the first 3 years of life and persist into adulthood.<sup>2</sup> Early and intensive intervention can have a profound impact on the quality of life for children at risk for autism. Previous studies have shown that different perinatal factors including birth asphyxia, in early infancy and exposure to toxins of various origins makes an infant susceptible to development of autism and other neurodevelopmental disorders in later life.<sup>3</sup>

The prevalence of ASD has increased by over 600% in the past few decades.<sup>4</sup> The current prevalence in the United States is estimated at 1 in 91 children.<sup>5</sup> Autism in Saudi Arabia is slightly higher than reported in developed countries.<sup>6</sup> Although there is no known unique cause of autism, there is growing evidence that autism may be influenced by genetic, neurological, environmental and immunological factors, however, its exact pathophysiology is unknown.<sup>7</sup>

The urgency to find an effective intervention after a child has been diagnosed with autism received great

attention. Thus, over 100 treatments for autism are in wide use,<sup>8</sup> despite the fact that the effectiveness of very few has been directly researched.

Hyperbaric oxygen therapy (HBOT) has been used as a treatment modality since 1930s when Behnke and Shaw used pressurized chambers to treat patients with decompression sickness.<sup>9</sup> Currently, HBOT is approved by the Undersea and Hyperbaric Medical Society (UHMS) and has been popularized and commonly used as treatment for many neurological conditions including autism in recent years.<sup>10-12</sup>

HBOT involves delivery of a mixture of gases ranging from room air (21% oxygen to 100% oxygen) at pressures greater than one atmosphere (atm) in pressurized chamber.<sup>13</sup> 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 for approximately 60 minutes. The dose of HBOT is a function of the pressure, the concentration of oxygen, the duration of exposure, frequency and the total number of treatment sessions.<sup>14</sup> HBOT is generally considered safe<sup>15</sup> at oxygen pressures below 3.0 atm and with treatment duration of less than 120 minutes.<sup>14,16-18</sup>

Most typical indications for hyperbaric treatment involve the use of hyperbaric pressures above 2.0 atm. Higher atmospheric pressures are generally required to treat conditions such as carbon monoxide poisoning and to improve wound healing.<sup>13,14</sup> However, improvements have been observed via treatments with 95 - 100% oxygen and hyperbaric pressures of 1.5 - 2.0 atm for some chronic neurological conditions, including autism.<sup>10,11</sup>

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Furthermore, improvements in autism have also been observed with the use of hyperbaric pressures of 1.3 atm and oxygen levels of 21 - 24%.<sup>10,19</sup>

The exact HBOT mechanism is not fully understood, however, there are several different explanations.<sup>20</sup> SPECT (single photon emission computed tomography) scan studies show that the brains of children with autism can have areas of hypoperfusion.<sup>21-23</sup> It has been hypothesized that this might leave certain brain cells at risk of dysfunction due to a chronic state of hypoxia.<sup>19,24</sup> The oxygen delivered by HBOT can reverse hypoxia in brain tissues caused by hypoperfusion.<sup>25,26</sup>

Research has also documented that children with autism show chronic inflammation both in the gut and in the brain.<sup>27-32</sup> It is also known that HBOT has an anti-inflammatory effect and has been useful in treating inflammatory bowel disease,<sup>33</sup> and many autistic children with gastrointestinal (GI) inflammation.<sup>34-36</sup>

Some children with autism have dysfunctional mitochondria. Animal studies have demonstrated increased mitochondrial efficiency<sup>37</sup> and also increased mitochondria density with hyperbaric oxygen therapy.<sup>38</sup>

Recently, a group of highly committed physicians have advocated strongly for the therapeutic benefits of HBOT in ASD. Many of these physicians work all around the world and references to this practice can be found on a number of internet sites.<sup>20</sup>

**Previous Studies on Hyperbaric Oxygen Therapy:** Several small, uncontrolled case reports and case series reported some improvements in symptom scores in children who were treated with HBOT. To-date, few studies (Table I) have been published regarding the effectiveness of HBOT as a treatment for autism.

Jepson *et al.* represented the first relatively large-scale controlled study evaluating the effects of HBOT for children with autism at the level of the individual participant on a large number of behaviors, across a relatively large number of participants.<sup>12</sup> Multiple topographies of behavior were measured under carefully controlled conditions and no consistent effects (positive or negative) were observed. Based on these results, there is no compelling evidence to suggest that HBOT, delivered at 24% oxygen and 1.3 atm, is an effective treatment modality for the core behavior symptoms of autism.

Since children with autism spectrum disorder (ASD) have been shown to have increased levels of neuro-inflammation, altered cytokine levels, and oxidative stress, some researchers have theorized that HBOT might reverse these biochemical abnormalities and, therefore, improve the symptoms of autism.<sup>19</sup>

Bent *et al.* determined whether HBOT leads to parental reported behavioral changes and alterations in cytokines in children with ASD.<sup>39</sup> Children between the ages of 3

and 8 years with a diagnosis of ASD were recruited for this study. Children received 40 days of HBOT (1.5 atm; 100% oxygen) for 1 hour, 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.

All outcome measures in the core features of autism (communication problems, social difficulties, and repetitive/restricted behavior) were assessed at baseline, after 40 days, and after 80 days of HBO treatment. Changes in plasma cytokines over the course of the study were also measured. There were no statistically significant changes in any of the 29 measured cytokines levels observed.

A randomized, double-blind, placebo controlled trial of HBOT, published in 2010, included 34 children with ASD who were randomly assigned to the same level of hyperbaric therapy consisting of 80 one-hour sessions at 24% oxygen and 1.3 atm.<sup>40</sup> Sessions were administered 6 - 10 times per week. The control group received 1 hour sessions in the HBOT chambers which were filled with ambient air at a pressure sufficient to keep the chamber inflated (not significantly above 1 atm). Results indicated that both groups improved to a small degree over time but that there was no significant difference in improvement between the HBOT and placebo groups.

Rossignol *et al.* also performed a randomized, double-blind, controlled trial to assess the efficacy of hyperbaric treatment in children with autism.<sup>11</sup> Outcome was measured including Clinical Global Impression (CGI) scale, Aberrant Behavior Checklist (ABC), and Autism Treatment Evaluation Checklist (ATEC).

Children with autism received hyperbaric treatment at 1.3 atm and 24% oxygen for 40 hourly sessions comprising of two 1 hour HBOT sessions per day, 5 days per week over 4 consecutive weeks. Statistically significant improvements were observed in overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness compared to children who received slightly pressurized room air. Data analysis indicated that children over 5 years age and children with lower initial autism severity had the healthiest improvements.

There are many theories as to the cause of ASD such as abnormal cerebral blood flow to areas of the brain. Kinaci *et al.* performed a retrospective review in search of 108 children with ASD who had done basal and control brain perfusion Single-Photon Emission Computed Tomography (SPECT) Scan.<sup>41</sup> They were all applied 50 sessions HBOT for each patient at 1.5 atm for 60 minutes/daily. They determined that after HBOT, perfusion was improved in the temporal, frontal and in other areas of brain. Autism Treatment Evaluation Checklist (ATEC) outcome score of 54 patients shows 79%, 85.5%, 87% and 75.2% improvements at speech/

language/communication, sociability, sensory/ cognitive awareness and health/physical/behavior respectively. This study showed not only behavioral, physical and brain perfusion improvements but also warned positive or negative effects of HBOT in children with ASD, who have brain inflammation secondary to high levels of toxic heavy metals.

In the first controlled study of HBOT, Lerman *et al.* evaluated the effects of HBOT on direct measures of task engagement, spontaneous communication, and problem behavior.<sup>42</sup> The study employed a multiple baseline across 3 children, aged 6 - 7 years. HBOT was delivered at 88% oxygen and 1.3 atm. Two participants received 40 sessions of HBOT and the third received 27 sessions. One participant demonstrated a potential increase in communication during HBOT treatment but the effect was not replicated across the other two participants. In addition, one participant demonstrated a potential decrease in challenging behavior during HBOT treatment and subsequent worsening of the behavior when HBOT was removed. However, this too was not replicated across participants. The decrease in behavior during HBOT could have been accounted for by the overall decrease in demands during days in which HBOT treatment was delivered.

In 7 Thai autistic children, HBOT was carried out<sup>43</sup> and assessment was done before and after treatment in five domains: social development, fine motor and eye-hand coordination, language development, gross motor development and self-help skills. Data showed that 75% of children had significant improvement in all domains while 25% did not respond to the treatment. Most beneficial results were 33.34% of children showed well sleeping, better improvement in cognitive abilities and social skills. No serious adverse effect in any case was reported.

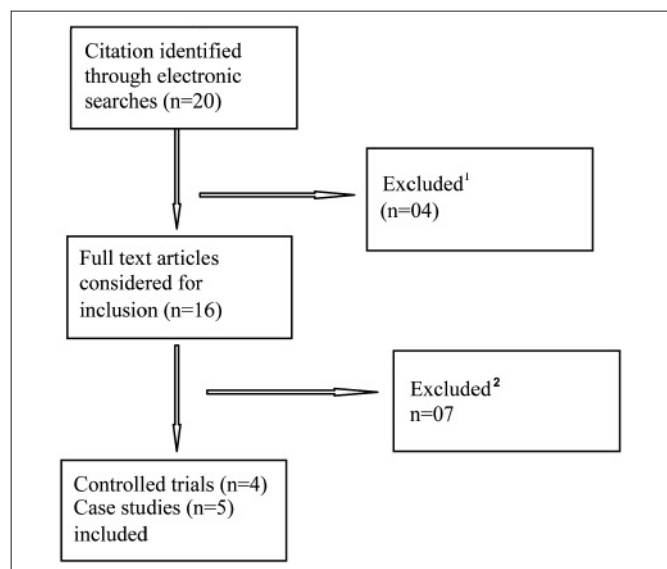
The research group<sup>10</sup> with a small open label pilot study looked at safety and efficacy measured biomarkers of inflammation (Creative protein) and oxidative stress (e.g. oxidized glutathione), as well as parent reports of behavior in 18 children with autism over a treatment course of 40 sessions. Six of the children were treated with 1.5 atm pressure and 100% oxygen, while 12 children were treated with 1.3 atm pressure and 24% oxygen. They reported no significant worsening of oxidative stress, a non-significant trend of improvement in C-reactive protein values (in a small subgroup that started out high) and improvement in parent reports of some measures associated with autism (speech, motivation and cognitive awareness). This suggested that inflammation in these children improved with treatment and HBOT at a maximum pressure of 1.5 atm with up to 100% oxygen was safe and well tolerated.

Retrospective analysis of 6 autistic children who underwent low-pressure HBOT was carried out.<sup>19</sup> All 6 children started HBOT and 5 completed 40 one hour sessions of low pressure HBOT at 1.3 atm and 28 - 30% oxygen over a 3 months period. One child only finished 25 sessions due to scheduling conflicts and was included in the analysis. Parent rated pre-treatment and posttreatment scores were calculated for each subject using the Autism Treatment Evaluation Checklist (ATEC), Childhood Autism Rating Scale (CARS), and Social Responsiveness Scale (SRS). Low pressure HBOT was well tolerated by all 6 children with no adverse effects noted. More dramatic improvements were found in children age 4 and under when compared to those in the older group.

Heuser *et al.* treated a 4 years old child with autism using hyperbaric therapy at 1.3 atm and 24% oxygen and reported "striking improvement in behavior including memory and cognitive functions" after only ten sessions.<sup>44</sup>

**Table I:** Trial summary for treatment of ASD with HBOT.

Nature of evidence	Subjects, age	HBOT protocol	Outcome	Reference
Controlled study	16 children, aged 3-11 years	1.3 atm (24% O <sub>2</sub> ) x40 sessions x56 days.	No consistent effects were observed.	12
Clinical trial	10 children, aged 3-8 years	1.5 atm x (100% O <sub>2</sub> ) x1 hour x80 sessions over 20 weeks.	No change in measures of plasma cytokines.	39
Randomized double-blind placebo-controlled trial	34 children, HBO (n = 18), placebo (n = 16), aged 3-16 years.	1.3 atm (24% O <sub>2</sub> ) x1 hour x80 sessions. 6 to 10 sessions per week within 15 weeks or less.	No differences were detected between HBOT and placebo groups.	40
Randomized, controlled trial	62 children, aged 2-7 years meeting DSMV-IV criteria	1.3 atm (24% O <sub>2</sub> ) x40 treatments x40 treatment 1 hour subjects (n=33) control (n=29) room air at 103 (21% O <sub>2</sub> )	Significantly improved in the treatment group compared to controls in overall functioning.	10
NA	108 children, aged 3-12 years	1.5 atm x1 hour daily x50 sessions	improvements in behavioral, physical and brain perfusion	41
Controlled study	3 participant, aged 6-7 years	1.3 atm x (88% O <sub>2</sub> ) x40 sessions (n=2), 27 sessions (n=1)	No changes were observed consistently.	42
Case series	7 children,	1.3 atm (100% O <sub>2</sub> ) x10 treatments	75% of subjects improved.	43
Case series	18 children, aged 3-16 years	1.5 atm (100% O <sub>2</sub> ) or 1.3 atm (24% O <sub>2</sub> ) x40 treatments x45 minutes	Improvements in both groups.	10
Case series and hypothesis	6 children, ASD diagnosis by DSMV-IV	1.3 atm (28-30% O <sub>2</sub> ) x1 hour x40 treatments	Improvement in several scores of symptoms and abilities.	19



**Figure 1:** Study eligibility flow chart. Exclusion criteria: (1) no patient with autism spectrum disorder; (2) opinion, letter, interview or conference proceeding.

This child also had marked improvement of cerebral hypoperfusion as measured by pre-hyperbaric and post-hyperbaric Single Photon Emission Computed Tomography (SPECT) scans.

Recently, two reviews have appeared, apart from two undetailed Chinese studies, in which HBOT for autism have also been discussed (Figure 1).<sup>45-48</sup>

After review for inclusion criteria, we included four randomized controlled trials, five controlled clinical trials (Figure 1). We did not include articles published in languages other than English due to resource limitations. Study design characteristics and results of all studies are summarized in Table I.

## DISCUSSION

Hyperbaric oxygen therapy is currently in use for the management of many diseases, and its clinical application is expanding.<sup>49</sup> Several case reports<sup>44,50</sup> and non-controlled studies<sup>19,24,43</sup> have reported clinical improvements with hyperbaric treatment at 1.3 atm. The efficacy of hyperbaric treatment for children with ASD is generally regarded as safe and well-tolerated, even at pressures of 1.5/2.0 atm and 100% oxygen for 2 hours per day.<sup>18,24</sup> The most common side effects observed during hyperbaric treatment are barotrauma (2% incidence), sinus squeeze, serous otitis, claustrophobia, reversible myopia, and new onset seizure (which occurs in 1 - 3 per 10,000 treatments).<sup>13</sup>

Jepson *et al.*<sup>12</sup> findings deviate considerably from those of Rossignol *et al.*<sup>11</sup> and extends Lerman's findings<sup>42</sup> by examining a larger number of behaviors which constitute a broader sampling of symptoms of autism and by extending the evaluation to a larger number of participants. The result of Jepson *et al.* study<sup>12</sup> did not

replicate the positive findings demonstrated in one of the participants in the Lerman *et al.* study.<sup>42</sup> Jepson *et al.*<sup>12</sup> study also extends findings from the Granpeesheh *et al.* study,<sup>40</sup> suggested that HBOT delivered at 24% oxygen and 1.3 atm may not be an effective therapy for the treatment of the behavioral symptoms of autism. As was done in the Granpeesheh *et al.* study,<sup>40</sup> parents in Jepson *et al.*<sup>12</sup> study were instructed to refrain from altering their child's therapy during the course of the study. This technique helped to more accurately account for any behavioral changes observed in study participants.

There were some potential limitations to the Jepson *et al.* study<sup>12</sup> including the observation technique used might have been insufficient to detect other benefits of HBOT (e.g., improvements in attention or memory), measures of possible changes in biochemical variables (e.g., markers of inflammation or oxidative stress) were not collected which may be affected by the HBOT procedure and finally characteristics of participants were also not included or excluded based on their physical well-being. As such, it was possible that participants with more physical dysfunction may have responded, as a group, differently than the sample that was included in this study.

The open-label design of the relatively long treatment period (20 weeks) by Bent *et al.* did not provide strong evidence either supporting or refuting the efficacy of HBOT for children with ASD.<sup>39</sup> There was also no evidence found that HBOT changed measures of plasma cytokines over 80 treatment sessions. This may indicate that HBOT did not alter cytokine levels in children with ASD. The primary limitation of Bent *et al.* study was the small sample size, which may have provided limited power to detect changes in plasma cytokines.<sup>39</sup> 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 this study was lack of cytokines measurements in the brain, CSF or mucosal components, each of which showed elevated cytokine levels in prior studies of children with autism.<sup>28,31</sup>

A randomized, placebo-controlled trial by Granpeesheh *et al.*<sup>40</sup> published in 2010 included 34 children with ASD who were randomly assigned to the same level of hyperbaric therapy as the Rossignol *et al.* study (1.3 atm and 24 - 28% oxygen) and a similar sham control.<sup>11</sup> The results of Granpeesheh *et al.* corroborate the findings of the study by Rossignol *et al.* which included a control group.<sup>11,40</sup> In both studies, treatment and control groups improved over time, but the difference in improvement between groups appeared insignificant. The reasons for the discrepant findings of the two studies were unclear. However, based upon the findings of Granpeesheh *et al.* study HBOT had no significant beneficial effect on ASD

symptoms;<sup>40</sup> it was possible that the group design used did not allow for careful examination of the results of treatment at the level of the individual participant.

Rossignol *et al.* randomly assigned 62 children with ASD to 40 one hour 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).<sup>11</sup> They reported that 9/30 (30%) of children in the treatment group were rated as either much improved or very much improved on the Clinical Global Impression-Improvement (CGI-I) score compared to placebo group. However, this study did not show improvements in other outcome measures, including the overall score and the five subscales of the Aberrant Behavior Checklist. This study was also criticized for several methodological problems.<sup>11,12</sup> Rossignol *et al.* used almost twice the average number of treatment sessions per week compared to the Jepson *et al.* study and this may contribute to the differences in outcome between two studies.<sup>11,12</sup>

Lerman *et al.* made a significant contribution by including direct measures of behavior.<sup>42</sup> Overall, participants might have experienced positive changes but the changes were not observed consistently across the 3 participants. Replication of the treatment effect across participants was required to demonstrate experimental control in a multiple baseline design. The lack of such replication in the Lerman *et al.* study<sup>42</sup> makes it difficult to determine whether the potential effects observed were due to HBOT or some other concurrent treatment.

In 2008, Chungpaibulpatana *et al.*<sup>43</sup> reported HBOT in Thai autistic children. Results showed the improvement at 75% of cases by HBOT. 1.3 atm and 100% of oxygen concentration with 10 sessions compared with previous study of Rossignol<sup>19</sup> that had shown the improvement at 31.6% of cases by HBOT 1.3 atm and 28 - 30% of oxygen concentration with 40 sessions. Differences were found in oxygen concentration and duration of HBOT that may influence the results.

Rossignol *et al.* 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.<sup>10</sup> Due to the open label design of this study, it was 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.

The weaknesses of the open-label design and the lack of a control group make it difficult to reach definitive conclusion. Specifically, it was possible that the improvement in parent report measures was due to a placebo effect, or due to improvement over time due to

other concurrent treatments taking place outside of the HBOT.

Rossignol and Rossignol also published regarding HBOT use in ASD using a retrospective, uncontrolled, within-group design.<sup>19</sup> 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);<sup>51</sup> 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.<sup>8</sup> No difference was observed between the groups.

Further case series suggested that low pressure HBOT may indeed be beneficial in the treatment of autism.<sup>19</sup> An interesting finding from this case series was that the younger children had more significant improvements in clinical outcome scores than the older children.

However, this case series did have several inherent limitations.<sup>19</sup> Children were allowed to continue all other therapies for autism and also add new ones, such as supplements. Therefore, other therapies could have contributed to some of the clinical gains. Parents were not blinded to the fact that their children received HBOT and evaluation of the children was through parent-rated scales, either of which could lead to bias. There was no placebo or control group. Thus, the improvements could have been due merely to the natural development of the children, although none of the parents reported their child as undergoing developmental spurts of similar or greater magnitude in the recent past. Finally, this series lacked power because the sample size was small. Despite these limitations, the analysis of this case series suggested substantial clinical benefits were produced. This case series suggests that low pressure HBOT improves symptoms in autistic children.

Two discussion papers by Rossignol and colleagues presented hypotheses, based on a retrospective case series of 6 children.<sup>19,24</sup> However, based on lack of an experimental design, the improvements noted within the small group should not be attributed to HBOT.

There are some limitations with our review. It is possible that we have omitted important studies by searching only English-language literature. This analysis was also limited by the heterogeneity among patient populations, interventions, and outcomes of results.

## CONCLUSION

Very few controlled and case studies have been reported on HBOT for autistic children. These studies had multiple internal and external validity problems and provided controversial and insufficient evidence to establish a clear relationship between physiologic changes after HBOT sessions, measures of clinical

improvement and the risks and benefits of HBOT for children with ASD.

It is noted that inadequate attention was paid to measuring and reporting adverse events. While the available evidence did not indicate serious, life-threatening adverse effects. Because the existing evidence is insufficient for clinicians and patients to draw conclusions, good quality observational studies, designed to minimize bias present in existing research, should be conducted.

However, in the light of the positive results of several previous studies, the use of hyperbaric treatment appears to be safe and a promising treatment for children with autism. It is also clear that previous studies have yielded promising results strong enough to warrant further study of HBO therapy in patients with autism. The recommended goal of future studies is to investigate the potential inclusion of HBO as part of standard therapy for patients with ASD.

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