Basic and Clinical
NEUROSCIENCE
July & August 2023, Volume 14, Number 4

Research Paper

Therapeutic Impacts of Hyperbaric Oxygen Therapy and Risperidone on Children with Autism: A Clinical Trial

Asmaa S Mohamed[1], Hosam M Ahmad[2*], Ahmed A Abdelrahman[3], Usama F Aly[4], Khaled A Khaled[4]

1. Department of Clinical Pharmacy, Faculty of Pharmacy, Deraya University, Minia, Egypt.
2. Department of Internal Medicine and Biomedical Chemistry, Egypt Ministry of Health and Population, Minia, Egypt.
3. Department of Neuropsychiatry, Faculty of Medicine, Assiut University, Assiut, Egypt.
4. Department of Pharmaceutics, Faculty of Pharmacy, Minia University, Minia, Egypt.

Use your device to scan and read the article online

Citation Mohamed, A.S., Ahmad, H.M., Abdelrahman, A.A., Aly, U.F., & Khaled, K.A. (2023). Therapeutic Impacts of Hyperbaric Oxygen Therapy and Risperidone on Children with Autism: A Clinical Trial. *Basic and Clinical Neuroscience, 14*(4), 501-510. http://dx.doi.org/10.32598/bcn.2021.3122.1

http://dx.doi.org/10.32598/bcn.2021.3122.1

Article info:
Received: 14 Dec 2020
First Revision: 01 Jul 2021
Accepted: 03 Jul 2021
Available Online: 01 Jul 2023

Keywords:
Autism, Autism treatment evaluation checklist, Childhood autism rating scale, Hyperbaric oxygen therapy, Risperidone

ABSTRACT

Introduction: In this research, we investigated any possible effect of receiving hyperbaric oxygen therapy (HBOT) or risperidone on the core symptoms of autism in children diagnosed with autism spectrum disorder (ASD).

Methods: This study was a randomized, controlled clinical trial in Minia and Assiut University hospitals in Egypt with three parallel groups. One hundred and eighty children with autism, aged 5–8 years were divided into three equal groups (n=60). Group 1 (G1) received 40 sessions of HBOT within two months, group 2 (G2) received risperidone (dose: 0.25 mg per day in children weighing less than 20 kg and 0.5 mg per day in cases weighing more) for six months, and group 3 (G3) as the control group, received a placebo for six months. The assessment was done using childhood autism rating scale (CARS) and autism treatment evaluation checklist (ATEC) at the beginning of the study (baseline) and after one year.

Results: The mean total CARS and ATEC scores significantly decreased (improved) by varying degrees in the three groups after a year of follow-up compared to the baseline scores, but the best results were found in G1, G2, and G3, respectively.

Conclusion: Using HBOT or risperidone is effective in treating the core symptoms of autism in children diagnosed with autism spectrum disorder, but using HBOT gives better results than risperidone therapy.

*** Corresponding Author:**
Hosam M Ahmad, MD.
Address: *Department of Internal Medicine and Biomedical Chemistry, Egypt Ministry of Health and Population, Minia, Egypt.*
Tel: *+20 (10) 00638308*
E-mail: *hosam.refaei@yahoo.com*

Highlights

- Non-pharmacologic therapy can be used for the treatment of the core symptoms of autism.
- Both hyperbaric oxygen therapy and risperidone reduce the core symptoms of autism.
- Hyperbaric oxygen therapy gives better effects than risperidone in reducing the core symptoms of autism.

Plain Language Summary

Since the long-term use of drug therapy in children with autism leads to the occurrence of side effects in addition to the difficulty in complying with the drugs for long-term use, efforts have begun to use non-traditional alternative treatments, such as hyperbaric oxygen therapy. The current study assessed the therapeutic effect of hyperbaric oxygen therapy and risperidone on the core symptoms of autism. The results revealed that both hyperbaric oxygen therapy and risperidone reduced the core symptoms of autism, but hyperbaric oxygen therapy gave better therapeutic results than risperidone.

1. Introduction

Autism spectrum disorder (ASD) is a developmental disorder. It affects both communication and behavior. As the signs usually occur in the first two years of life, it is said to be a "developmental disorder "(NIMH Information Resource Center, 2018).

The diagnostic and statistical manual of mental disorders (DSM-5), a guide created by the American Psychiatric Association (APA) is used to diagnose mental disorders, and based on which people with ASD have communication problems, limited interests, and repetitive habits that impair their ability to function properly at school and work, and in other fields of life (American Psychiatric Association, 2013).

With the continuously increasing number of children with ASD by an unknown cause, researchers have begun to use pharmacological and non-pharmacological therapy to improve treatment outcomes. The biggest challenge in this disease is solving the mystery of the causes leading to it and knowing the appropriate treatment methods for it.

In a hyperbaric chamber, concentrated oxygen is pressurized above sea level (1 atmosphere absolute), called hyperbaric oxygen therapy (HBOT), in which patients enter and breathe oxygen (Lam et al., 2017).

Increasing cerebral perfusion during the treatment of children with autism may be one of the HBOT benefits. More pressurized oxygen inhalation may increase the partial oxygen pressure in the arterial blood and increase the oxygen that reaches the brain (Calvert et al., 2007).

Risperidone is a second-generation antipsychotic, used for the treatment of autism-related irritability. It was approved by the Food and Drug Administration (FDA) in 2006 only for children not less than five years old (LeClerc & Easley, 2015).

The results of conventional treatment for ASD are not satisfactory so far. Therefore, the aim of this study was to evaluate whether using HBOT or risperidone can decrease the core symptoms of autism by the comparison between three groups of children with ASD about their probable effects. In the present study, we tested the hypothesis that a policy of using either HBOT or risperidone in children with ASD would reduce the core symptoms of autism. We also tested which of them can give better results. The null hypothesis is that there would be no effect of HBOT or risperidone on the core symptoms of autism. We used the childhood autism rating scale (CARS) and autism treatment evaluation checklist (ATEC) scores to measure their effect on the features of autism.

2. Materials & Methods

This study is a placebo-controlled, randomized clinical trial with a blind, parallel-group design. Patients were randomly assigned to one of three parallel groups, initially in a 1:1:1 ratio, to receive either one of three HBOT, risperidone, or placebo regimens. Eligible participants were all children male or female aged 5 to 8 years, previously or newly diagnosed with ASD (Schulz

et al., 2010). Exclusion criteria were the presence of significant medical problems and any other neuropsychiatric disorder requiring drug therapy (e.g. bipolar disorder and psychosis), weight less than 15 kg because of dosing considerations for risperidone, and other systemic diseases affecting the psychological and nervous state of the child.

The study was conducted in pediatric and neuropsychiatry outpatient clinics of the Minia University and Assiut University hospitals where all evaluated medical assessments were done, and then the follow-up was done by both physicians and clinical pharmacists in these clinics.

DSM-5 (American Psychiatric Association, 2013) was used for the diagnosis and confirmation of ASD. Then, the assessment was done using the patient's baseline score on CARS (Rellini et al., 2004) and ATEC (Al Backer, 2016).

Patients (n=180) were divided into three groups: and randomly assigned to receive HBOT; G1 (n=60), risperidone (n=60; G2), or placebo (n=60; G3) in sequence.

Data were collected by structured questionnaires filled out by the investigator. Detailed history taking was done with special emphasis on the onset, course, duration of the disease, age, sex, antenatal, natal, and postnatal history, developmental history (both mental and motor), cognitive abilities, and gross and fine motor function, consanguinity between parents, mother's age, smoking in the family, and past history and family history of the similar condition or any psychological or mental disorders. In addition, the history of major childhood diseases, surgery, injuries, diet, and medications were taken.

Neuropsychiatric and systemic clinical examination

G1 received 40 one-hour sessions of HBOT. In these sessions, the oxygen concentration was 100% and the pressure was 1.5 atm absolute. It was taken either in a multiplace or monoplace chamber. The number of sessions was five sessions per week. Forty sessions were required for all children in this group within two months. G2 received risperidone (dose: 0.25 mg per day in children weighing less than 20 kg (0.5 mg per day in persons weighing more) for six months. The dose in the initial two months was based on the child's weight and clinical response. By adjusting the total daily dose according to response and/or adverse effects, at the end of these six months, the discontinuation phase was done by reducing the maintenance dose by 25% per week. Thus, the dose was 75% of the last week in the six months for the first week, followed by 50% of the last week for the second week, and 25% of the last week for the third week. G3 (the control group) received a matching placebo in the same manner as G2.

Outcomes

The primary endpoint of treatment efficacy in autism was measured by comparing baseline CARS and ATEC scores after one year to detect any effect of hyperbaric oxygen therapy or risperidone and compare this effect with the control group.

Randomization and blinding

In equal proportions, the eligible participants were simply randomized. We used a computer-generated randomization list for this purpose. This list was prepared by those who were not involved with the study. All study personnel (including clinicians and those performing baseline and outcome assessments, participants, and their families) were blinded to group assignment for the entire study. In this study, the first group was double-blinded to treatment allocation as researchers and other staff involved in the running of the study (e.g. data collectors, statisticians, etc.) did not know the type of treatment but patients knew the type of treatment (HBOT). The second and third groups were triple-blinded to treatment allocation as patients, researchers, and other staff involved in the running of the study (e.g. data collectors, statisticians, etc.) did not know the type of treatment (risperidone or placebo).

Statistical analysis

We started the analysis by exploring the distributions, frequencies, and percentages for each of the numeric and categorical variables. Data were analyzed using SPSS software, version 26). Descriptive analyses were used to summarize data. Results were presented as counts and percentages for categorical variables and Mean±SD or median and range for continuous variables. The comparison between two independent groups with quantitative data and parametric distribution was done by an independent t-test while the comparison between two paired groups with quantitative data and parametric distribution was done by the paired t-test. A chi-square test was used for the comparison between the two groups with qualitative data. A confidence interval of 95% and a margin of error of 5% were determined. The one-way ANOVA for quantitative data between the three groups was followed by a post hoc Tukey test between the two groups. A $P<0.05$ was set as the threshold of statistical significance.

3. Results

The withdrawal was observed in this study, as we began with 180 children with ASD, but after the first year, we followed up with 154 children because of many reasons, like partial or non-compliance to treatment, cost, adverse effects, loss of efficacy of treatment, loss of contact with the child, and withdraw consent (Figure 1).

Age-eligible participants were recruited from January 2019 to July 2020 participants attended clinic visits at the time of randomization (baseline) and after one year.

Table 1 shows baseline descriptive data of the patients. This study included 180 Egyptian children with (ASD), there were 141 males (78.33%), and 39 females (21.67%) with male to female ratio of 4:1, and their ages ranged from 5 to 8 years. Normal labor in 69 children (38.33%). Positive family history of psychiatric illness in 32 children (17.77%) of cases. 146 children live in urban areas. Positive consanguinity between parents in 18 children (10%) of cases.

Table 2 shows that G1 had a significant improvement in CARS score (P<0.001). Also, ATEC scores showed improvement in total score, and speech, cognition, and behavior subscales (P<0.001) but not the social subscale (P=0.07). The total CARS score significantly decreased from 36.2±1.47 to 31.63±1.73. The total ATEC score significantly decreased from 67.82±4.21 to 58.24±3.83. These results indicated a decrease in the severity of ASD symptoms.

G2 had a significant improvement in the CARS score (P<0.001). Also, ATEC scores showed improvement in total score, and speech and cognition subscales (P<0.001). The total CARS score significantly decreased from 34.85±1.9 to 31.75±2.02. The total ATEC score significantly decreased from 73.31±3.72 to 69.52±5.27. These results indicated a decrease in the severity of ASD symptoms. An insignificant increase was observed in the social subscale (P=0.76). An insignificant decrease was also observed in the behavior subscale (P=0.838).

G3 had an insignificant decrease in CARS score from 33.45±2.325 to 32.94±2.713 (P=0.33). Also, ATEC scores showed improvement in total score and speech subscales only with P=0.004 and P=0.02, sequentially. The total ATEC score significantly decreased from 71.6±3.02 to 69.77±3.11 (P=0.004). The speech subscale significantly decreased from 17.49±2 to 16.51±1.97 (P=0.02). Social and behavior subscales' scores insignificantly decreased with P=0.057 and P=0.07, sequentially. An insignificant increase was observed in cognition subscale (P=0.71).

According to the percent change in scale scores, regarding the CARS score, the best change was in G1 then G2, and finally G3 (Figure 2). Regarding the ATEC score, the best change was in G1 then G2, and finally G3. Regarding speech subscale score, the best change was in G1 then G2, and finally G3. Regarding the social subscale score, the best change was in G1 then G3, and finally G2. Concerning the cognition subscale score, the best change was in G1 then G2, and finally G3. Regarding behavior subscale score, the best change was in G1 then G3, and finally G2 (Figure 3).

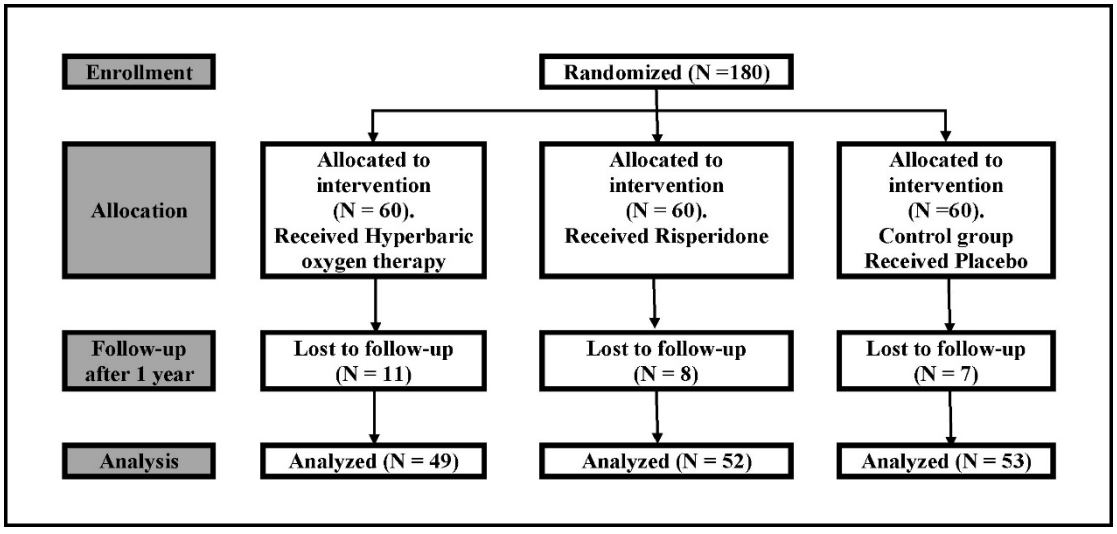

Figure 1. Flow diagram of the study.

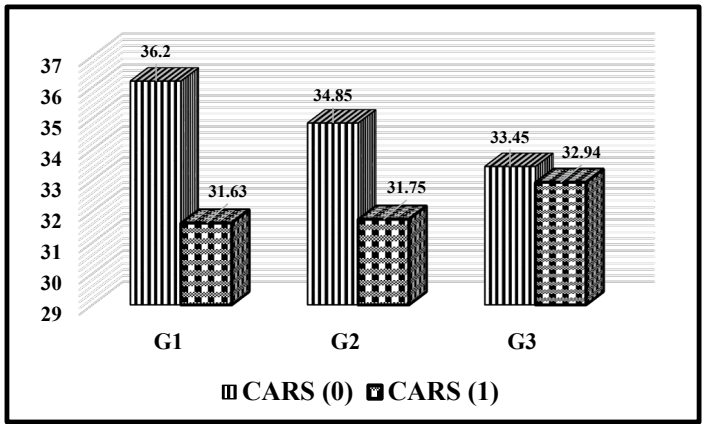

Figure 2. The comparison between the groups according to CARS score

NEUROSCIENCE

Note: CARS (0): Baseline mean of CARS score: CARS (1): Follow-up mean of CARS score.

Abbreviations: G1: Group 1; G2: Group 2; G3: Group 3; CARS: Childhood autism rating scale.

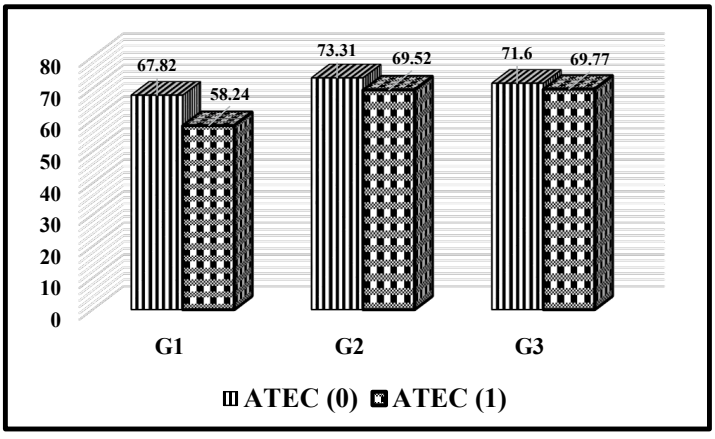

Figure 3. The comparison between the groups according to ATEC score

NEUROSCIENCE

Note: ATEC (0): Baseline mean of ATEC score; ATEC (1): Follow-up mean of ATEC score. Abbreviations: G1: Group 1; G2: Group 2; G3: Group 3; ATEC: Autism treatment evaluation checklist.

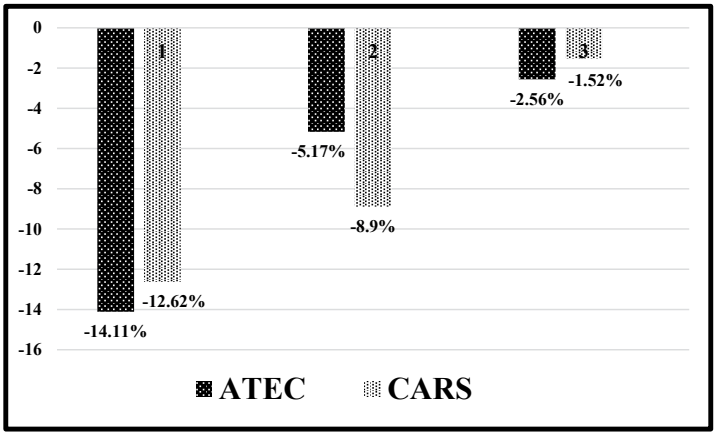

Figure 4. Percentage changes in CARS and total ATEC scores in the three groups

NEUROSCIENCE

Abbreviations: 1: Group 1; 2: Group 2; 3: Group 3; CARS: Childhood autism rating scale; ATEC: Autism treatment evaluation checklist; CARS: Childhood autism rating scale.

Table 1. Baseline descriptive data of the patients

Variables		Mean±SD/No. (%)				P
		Group				
		G1 (HBOT)	G2 (Risp)	G3 (Plac)	Total	
Age (y)		6.53±1.05	6.47±1.14	6.68±0.98	6.56±1.06	0.52
Mother's age (y)		32.05±4.62	29.43±5.39	28.02±5.57	29.83±5.45	<0.001
Father's age (y)		33.47±4.65	33.75±6.81	31.68±6.12	32.97±5.97	0.12
Sex	Male	47(78.3)	43(71.7)	51(85)	141(78.3)	0.21
	Female	13(21.7)	17(28.3)	99(15)	39(21.7)	
Labor	Normal	22(36.7)	25(41.7)	22(36.7)	69(38.3)	0.81
	Cesarean	38(63.3)	35(58.3)	38(63.3)	111(61.7)	
Family history	Positive	10(16.7)	12(20)	10(16.7)	32(17.8)	0.86
	Negative	50(83.3)	48(80)	50(83.3)	148(82.2)	
Residence	Rural	8(13.3)	14(23.3)	12(20)	34(18.9)	0.36
	Urban	52(86.7)	46(76.7)	48(80)	146(81.1)	
Consanguinity	Positive	9(15)	5(8.3)	4(6.7)	18(10)	0.27
	Negative	51(85)	55(91.7)	56(93.3)	162(90)	
Vaccination	Vaccinated	60(100)	60(100)	60(100)	180(100)	a
Exposure to smoking	Positive	21(35)	17(28.3)	19(31.7)	57(31.7)	0.74
	Negative	39(65)	43(71.7)	41(68.3)	123(68.3)	

HBOT: Hyperbaric oxygen therapy; Risp: Risperidone; Plac: Placebo.

Note: a: No statistics are computed because vaccination is a constant.

Figure 4 shows the percentage changes in the CARS and total ATEC scores between the three groups. In G1, percentage changes in CARS and total ATEC scores were 12.63% and -14.11%, sequentially. In G2, percentage changes in CARS and total ATEC scores were -8.89% and -5.17%, sequentially. In G3, percentage changes in CARS and total ATEC scores were -1.52% and -2.56%, sequentially.

Table 3 shows that G1 showed a significant difference with G2 (follow-up scores minus baseline scores) in CARS, total ATEC, and behavior subscale with P=0.014, P<0.001, and P<0.001, sequentially.

G1 showed a significant difference with G3 (follow-up scores minus baseline scores) in CARS, total ATEC, speech subscale, cognition subscale, and behavior subscale with P≤0.001, P<0.001, P=0.02, P<0.001, and P<0.001, sequentially.

G2 showed a significant difference with G3 (follow-up scores minus baseline scores) in CARS and cognition subscale with P≤0.001 and P<0.001, sequentially.

4. Discussion

As the intervention was implemented for both genders, variable subtypes of ASD, and at different levels of severity, the results indicated that the all children with autism benefit from either treatment given the difference in outcomes between HBOT or risperidone.

Adequate and well-controlled clinical examinations and research by experts (medical specialists and clinical pharmacists) qualified by scientific training and ex-

Table 2. CARS and ATEC scores of the patients in the three groups before and after intervention in addition to the percent change

Scale		G1 (HBOT)			G2 (Risperidone)			G3 (Placebo)		
		Mean±SD	% of scores changes	P	Mean±SD	%	P	Mean±SD	%	P
CARS	Before	36.2±1.47	-12.62	<0.001	34.85±1.9	-8.9	<0.001	33.45±2.33	-1.52	0.33
	After	31.63±1.73			31.75±2.02			32.94±2.71		
ATEC	Before	67.82±4.21	-14.11	<0.001	73.31±3.72	-5.17	<0.001	71.6±3.02	-2.56	0.004
	After	58.24±3.83			69.52±5.27			69.77±3.11		
Speech	Before	14.33±1.69	-15.28	<0.001	15.63±1.22	-11.64	<0.001	17.49±2	-5.61	0.02
	After	12.14±1.71			13.81±2.22			16.51±1.97		
Social	Before	15.78±1.59	-3.42	0.07	16.92±1.73	0.83	0.76	14.47±1.42	-3.52	0.057
	After	15.24±1.77			17.06±2.56			13.96±1.34		
Cognition	Before	16.82±2.36	-11.06	<0.001	18.71±1.09	-10.69	<0.001	18.89±1.45	0.58	0.71
	After	14.96±2.07			16.71±2.19			19±1.53		
Behavior	Before	20.9±2.62	-23.92	<0.001	22.04±2.51	-0.45	0.838	20.75±1.56	-2.17	0.07
	After	15.9±2.55			21.94±1.94			20.3±1.15		

CARS: Childhood autism rating scale; ATEC: Autism treatment evaluation checklist.

NEUROSCIENCE

perience were used to evaluate the effectiveness of the treatment involved. We have fully determined that this drug will have the effect claimed or shown under the prescribed or recommended conditions of use. To determine the effectiveness of the treatment in this study, we distinguished the drug effect from other effects, such as a spontaneous change in the disease course, by comparing the drug to the placebo effect. Also, avoidance of biased observation was done by randomization and blinding in patient enrollment, well-defined and reliable assessment of individuals' response (i.e. efficacy endpoint), and adequate analysis of the clinical investigation's results to assess the effects of the treatment (i.e. statistical methods). Also, there was no extensive drop-out of the trial patients and group numbers were identical at the beginning of the study and relatively close at the end of the study. The number of participants in this study was relatively sufficient for the clinical trial and withdrawal from the study was in a small percentage. The measurement of adherence to treatment was done by self-report, clinician estimates, pill counts, and clinic attendance.

With regard to gender, Table 1 demonstrated an association between the prevalence of this disorder and sex. Most of the children in this study were male (about 80%) with a male-to-female ratio of 4:1. This ratio displayed in the table is similar to the international reports (Kim et al., 2011; Zachor & Itzchak, 2010).

About 81.1% of the studied sample were living in urban areas with 18.9% living in rural areas. The role of education and a high level of culture can help in the early diagnosis of this disorder and, as a result, seek treatment that will lead to the improvement of the condition and achieving a better life. This notification was supported by several studies (El-Baz et al., 2011).

Patients with autism exposed to father smoking represent 31.7%. This observation suggested that father smoking may have no clear impact on the presence of this disorder. This observation was in agreement with that obtained by Gardener H.et al (Gardener et al., 2009).

In this study, the best change in CARS score was in G1 then G2, and finally G3, In the ATEC score the best change was in G1 then G2, and finally G3.

In line with these results, Starkestein et al. studied 30 individuals with autism compared to 14 normal control individuals. Cerebrovascular hypoperfusion or insufficient blood flow to the thalamus as measured by single photon emission computerized tomography (SPECT)

Table 3. Differences in autism scores between the groups

Group	Mean±SD					
	G1 (HBOT) Versus G2 (Risperidone)					
	CARS	ATEC	Speech	Social	Cognition	Behavior
1	-4.57±2.19	-9.57±5.5	-2.18±2.44	-0.53±2	-1.86±3.2	-5±3.3
2	-3.1±2.72	-3.79±6.33	-1.83±2.47	0.13±3.18	-2±2.3	-0.1±3.37
P	0.014	<0.001	0.5	0.17	0.78	<0.001
G1 (HBOT) Versus G3 (Placebo)						
Group	CARS	ATEC	Speech	Social	Cognition	Behavior
1	-4.57±2.19	-9.57±5.5	-2.18±2.44	-0.53±2	-1.86±3.2	-5±3.3
2	-0.51±3.74	-1.83±4.45	-0.98±3	-0.51±1.91	0.11±2.2	-0.45±1.8
P	<0.001	<0.001	0.02	0.97	<0.001	<0.001
G2 (Risperidone) Versus G3 (Placebo)						
Group	CARS	ATEC	Speech	Social	Cognition	Behavior
1	-3.1±2.72	-3.79±6.33	-1.83±2.47	0.13±3.18	-2±2.3	-0.1±3.37
2	-0.51±3.74	-1.83±4.45	-0.98±3	-0.51±1.91	0.11±2.2	-0.45±1.8
P	<0.001	0.07	0.1	0.18	<0.001	0.53

CARS: Childhood autism rating scale; ATEC: Autism treatment evaluation checklist.

NEUROSCIENCE

was observed in the autism group and significantly correlated with repetitive behaviors and unusual sensory interests (Starkstein et al., 2000).

HBOT possibly could improve cerebral perfusion in ASD and cerebral perfusion changes in children with autism. Several cases have reported an improvement in their cerebral perfusion measured before and after treatment by SPECT using HBOT at 1.3 atm/24% oxygen; one child with autism received one hour of HBOT daily for ten days (Heuser et al., 2002) and two children with autism received 40–80 treatment sessions (Rossignol & Rossignol, 2006).

A prospective clinical trial was done on 20 children with ASD who received at least 20 HBOT sessions at 1.5 ATA with 100% oxygen concentration for 1–1.5 hours per session. Magnetic resonance imaging (MRI) of the brain was done before and after HBOT for 20 sessions only for six cases. The result showed a statistically significant increase in the ratio of regional cerebral blood flow (RCBF) to substantia alba after HBOT in several brain regions. Also, there was a statistically significant decrease (improvement)in sociability, communication, cognitive awareness, and CARS post-HBOT compared to their levels before HBOT (P<0.001) (El-baz et al, 2014).

Two studies examined the effects of HBOT on biomarkers of inflammation in children with autism (Bent et al., 2012; (Rossignol et al., 2007). The first one consisted of 12 children who received HBOT at 1.3 atm/24% oxygen, and six children received HBOT at 1.5 atm/100% oxygen. Then, biomarkers were measured before and after 40 HBOT sessions (Rossignol et al., 2007). There were decreases in C-reactive protein, which is a general marker of inflammation (P=0.021). The biggest decline was seen in children who had the highest C-reactive protein levels.

In the second study, cytokine plasma levels were measured before and after 80 sessions of HBOT delivered at 1.5 atm/ 100% oxygen within 20 weeks in ten children with ASD (Bent et al., 2012). Improvements in the behavior were observed, but the study showed no significant changes in cytokines during the study. Although at the start of the study, the authors noted,

none of the children had abnormal levels of cytokines, making it less likely that a significant change would be observed. Furthermore, since cerebrospinal fluid (CSF) cytokine abnormalities have been reported in some children with ASD, the authors noted that CSF cytokines may be altered.

A systematic review identified only one small randomized clinical trial (n=60, age 3–9 years), which showed no improvements in ASD symptoms. Adverse effects included the occurrence of ear barotrauma (Xiong et al., 2016).

A study investigated the effects and side effects of olanzapine, risperidone, and aripiprazole on ASD patients that had been treated with the three drugs for a minimum of eight weeks. The drugs significantly decreased the scores of ABC subscales (irritability, hyperactivity, social withdrawal, stereotypy, and inappropriate speech) and increased the duration of sleep in eight weeks. Weight gain was the most common adverse effect of all antipsychotics. Weight gain was more frequent with olanzapine users than with the two other drugs (Hesapcioglu et al, 2020).

Another 24-week prospective observational trial was done on 42 children and adolescents (32 males) aged 6-18 years. During follow-up, drug plasma concentrations, side effects, and efficacy were assessed. The results were higher sum risperidone concentrations predicted more sedation ($P<0.05$), higher prolactin levels ($P<0.001$), and more effectiveness measured with aberrant behavior checklist irritability score (Kloosterboer et al., 2020).

A retrospective case series was done on 18 children (mean age: 5.7 years) with ASD treated with risperidone or aripiprazole at the age of four years and older. All children showed improvement in their ASD core signs and symptoms. Significant improvement was observed in 44% of the cases, and complete resolution (minimal-to-no-symptoms) was observed in 56% of the cases based on the childhood autism rating scale 2-standard test (CARS2-ST) and the clinical global impression (CGI) scales (Alsayouf et al., 2020).

Access to targeted children, the timing of the study, financial resources for HBOT, and the preponderance of male patients (78.33%) are limitations of this study.

5. Conclusion

There was a good improvement in patients treated with HBOT and risperidone and we concluded that HBOT has a better response than risperidone in decreasing the core symptoms of autism. There are no serious side effects after using this type of treatment. The results of the treatment of autism require a certain period to appear More studies are needed to strengthen this hypothesis and investigate the benefit of a combination of the two therapies.

Ethical Considerations

Compliance with ethical guidelines

The Minia University Ethics Committee approved all methods and procedures used in this study. This study was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Written informed consent for continued participation was obtained from the parents or legal caregivers after an explanation of the study objectives and their benefits for their children.

There was no risk to study subjects during the application of the research. The right to refuse participation and withdraw from the study at any time without any reason was guaranteed to each participant.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

References

Al Backer, N. B. (2016). Correlation between Autism Treatment Evaluation Checklist (ATEC) and Childhood Autism Rating Scale (CARS) in the evaluation of autism spectrum disorder. *Sudanese Journal of Paediatrics, 16*(1), 17-22. [PMID]

Alsayouf, H. A., Talo, H., Biddappa, M. L., Qasaymeh, M., Qasem, S., & De Los Reyes, E. (2020). Pharmacological intervention in children with autism spectrum disorder with standard supportive therapies significantly improves core signs and symptoms: A single-center, retrospective case series. *Neuropsychiatric Disease and Treatment, 16,* 2779–2794. [DOI:10.2147/NDT.S277294] [PMID]

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5®). Virginia: American Psychiatric Association. [Link]

Bent, S., Bertoglio, K., Ashwood, P., Nemeth, E., & Hendren, R. L. (2012). Brief report: Hyperbaric oxygen therapy (HBOT) in children with autism spectrum disorder: A clinical trial. *Journal of Autism and Developmental Disorders, 42*(6), 1127-1132. [DOI:10.1007/s10803-011-1337-3] [PMID]

Calvert, J. W., Cahill, J., & Zhang, J. H. (2007). Hyperbaric oxygen and cerebral physiology. *Neurological Research, 29*(2), 132-141. [DOI:10.1179/016164107X174156] [PMID]

El-baz, F., Elhossiny, R. M., Azeem, Y. A., & Abdelsayed, M. (2014). Study the effect of hyperbaric oxygen therapy in Egyptian autistic children: A clinical trial. *Egyptian Journal of Medical Human Genetics, 15*(2), 155-162. [DOI:10.1016/j.ejmhg.2014.01.004]

El-Baz, F., Ismael, N. A., & El-Din, S. M. N. (2011). Risk factors for autism: An Egyptian study. *Egyptian Journal of Medical Human Genetics, 12*(1), 31-38. [DOI:10.1016/j.ejmhg.2011.02.011]

Gardener, H., Spiegelman, D., & Buka, S. L. (2009). Prenatal risk factors for autism: Comprehensive meta-analysis. *The British Journal of Psychiatry, 195*(1), 7-14. [DOI:10.1192/bjp.bp.108.051672] [PMID]

Hesapcioglu, S. T., Ceylan, M. F., Kasak, M., & Sen, C. P. (2020). Olanzapine, risperidone, and aripiprazole use in children and adolescents with Autism Spectrum Disorders. *Research in Autism Spectrum Disorders, 72,* 101520. [DOI:10.1016/j.rasd.2020.101520]

Heuser, G., Heuser, S., Rodelander, D., Aguilera, O., & Uszler, M. (2002). *Treatment of neurologically impaired adults and children with "mild" hyperbaric oxygen (1.3 ATA and 24% oxygen).* Paper presented at the The Proceedings of the 2nd International Symposium on Hyperbaric Oxygenation for Cerebral Palsy and the Brain-injured Child. Flagstaff, Best Publishing Co. [Link]

Kim, Y. S., Leventhal, B. L., Koh, Y. J., Fombonne, E., Laska, E., & Lim, E. C., et al. (2011). Prevalence of autism spectrum disorders in a total population sample. *The American Journal of Psychiatry, 168*(9), 904-912. [DOI:10.1176/appi.ajp.2011.10101532] [PMID]

Kloosterboer, S. M., de Winter, B. C. M., Reichart, C. G., Kouijzer, M. E. J., de Kroon, M. M. J., & van Daalen, E., et al. (2020). Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. *British Journal of Clinical Pharmacology, 87*(3), 1069–1081. [DOI:10.1111/bcp.14465] [PMID]

Lam, G., Fontaine, R., Ross, F. L., & Chiu, E. S. (2017). Hyperbaric oxygen therapy: Exploring the clinical evidence. *Advances in Skin & Wound Care, 30*(4), 181-190. [DOI:10.1097/01.ASW.0000513089.75457.22] [PMID]

LeClerc, S., & Easley, D. (2015). Pharmacological therapies for autism spectrum disorder: A review. *P & T : A Peer-Reviewed Journal for Formulary Management, 40*(6), 389-397. [PMID]

National Institute of Mental Health. (2018). Autism spectrum disorder. Retrieved from: [Link]

Rellini, E., Tortolani, D., Trillo, S., Carbone, S., & Montecchi, F. (2004). Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC) correspondence and conflicts with DSM-IV criteria in diagnosis of autism. *Journal of Autism and Developmental Disorders, 34*(6), 703-708. [DOI:10.1007/s10803-004-5290-2] [PMID]

Rossignol, D. A., & Rossignol, L. W. (2006). Hyperbaric oxygen therapy may improve symptoms in autistic children. *Medical Hypotheses, 67*(2), 216–228. [DOI:10.1016/j.mehy.2006.02.009]

Rossignol, D. A., Rossignol, L. W., James, S. J., Melnyk, S., & Mumper, E. (2007). The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: An open-label pilot study. *BMC Pediatrics, 7,* 36. [DOI:10.1186/1471-2431-7-36] [PMID]

Schulz, K. F., Altman, D. G., Moher, D., & CONSORT Group (2010). CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. *Annals of Internal Medicine, 152*(11), 726-732. [DOI:10.7326/0003-4819-152-11-201006010-00232] [PMID]

Starkstein, S. E., Vazquez, S., Vrancic, D., Nanclares, V., Manes, F., & Piven, J., et al. (2000). SPECT findings in mentally retarded autistic individuals. *The Journal of Neuropsychiatry and Clinical Neurosciences, 12*(3), 370-375. [DOI:10.1176/jnp.12.3.370] [PMID]

Xiong, T., Chen, H., Luo, R., & Mu, D. (2016). Hyperbaric oxygen therapy for people with autism spectrum disorder (ASD). *The Cochrane Database of Systematic Reviews, 10*(10), CD010922. [DOI:10.1002/14651858.CD010922.pub2] [PMID]

Zachor, D. A., & Itzchak, E. B. (2010). Treatment approach, autism severity and intervention outcomes in young children. *Research in Autism Spectrum Disorders, 4*(3), 425-432. [DOI:10.1016/j.rasd.2009.10.013]