

Management of Autism by Hyperbaric Oxygen Therapy and Risperidone: A Comparative Study

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Abstract: Autism Affects Normal Development Of The Brain In Areas Of Social Communication And Interaction. Pharmaceutical Treatments As, Risperidone Can Help Alleviate Some Behavioral Symptoms Of Autism, Such As Irritability And Aggression. Hyperbaric Oxygen Therapy Is A New Effective Approach To Treating Autism.

Purpose: To Compare Between The Effects Of Using Hyperbaric Oxygen Versus Risperidone On These Children With Autistic Features.

Patient And Method: Prospective, Controlled And Comparative Randomized Clinical Trial Conducted On Eighty Children (5-7 Years Old) Diagnosed As Autism Based On The Second Edition Of Childhood Rating Scale Standard Version (Cars 2) And Follow Up For 2 Years.

Results: Was A Non-Statistically Decrease In The Childhood Rating Scale Score (Cars) Score In The Four Groups After One Year. However, There Was Statistically Significant Decrease In The Cars Score At Two Years In The Hyperbaric Oxygen Therapy Group And Hyperbaric Oxygen Therapy With Risperidone Group More Than The Risperidone Therapy Group And Control Group. So,

Conclusion: Hyperbaric Oxygen Therapy And Risperidone Maybe Using In The Treatment Of Autism Symptoms And To See Benefits On Long Term.

Keywords: Behavior; Development; Communication; Irritability; Aggression; Childhood Rating Scale Score.

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I. Introduction

Autism Is A Neurodevelopmental Disorder Distinguished By Impairments In Social Interaction And Communication, Restricted Or Repetitive Stereotyped Of Behaviors such As Hand Flapping And Head Rolling. The Diagnostic And Statistical Manual Of Mental Disorders, 5th Edition Stated That Symptoms Of Autism May Be Present In The Early Developmental Period And Impaired In Social And Other Important Aspects Of Daily Functioning. These Symptoms Must Not Be Solely Clarified By Intellectual Disability Or Overall Developmental Delay¹.

Causes Of Autism Spectrum Disorder (Asd): May Be Genetic And Environmental Factors (E.G., Prenatal Factors, Socioeconomic Status, Or Drug Exposure) Contributing To Each Individual's Unique Presentation And Severity Of Symptoms². Cerebral Hypoperfusion, Inflammation, Oxidative Stress, And Mitochondrial Dysfunction Are Accompanied With Asd³. Structured Educational And Behavioral Interventions May Be Good Treatment For Asd⁴. But Autistic Children Need Also Pharmacotherapy for Comorbid Mood, Behavior Regulation, Impulse Control, And Sleep And Thought Disorder Symptoms^{4, 5}. Hyperbaric Oxygen Therapy (Hbot) Has Been Suggested As Alternative Treatments, But Evidence For Their Benefit Is Lacking⁶.

Hbot Provides A Higher Concentration Of Oxygen Delivered In A Chamber Containing Higher Than (1 Atmosphere Absolute [Ata]). Hbot Has Been Effective In Treating Carbon Monoxide Poisoning, Air Or Gas Embolism, Gas Gangrene, Decompression Sickness. It Is Well Tolerated By Most Patients, And The Most Common Adverse Event Reported Middle Ear Barotrauma⁷.

Autistic Children Might Benefit From Hbot By Increasing In Cerebral Perfusion Occurring During Treatment. The Higher Atmospheric Oxygen Might Lead To An Increasing Arterial Partial Pressure Of Oxygen And Elevation Of Oxygen Delivery To The Brain⁸. Hbot Might Also Have Anti-Inflammatory Properties Due To The Reduction Of Pro-Inflammatory Cytokines, Improve Mitochondrial Dysfunction, And Up Regulate The Production Of Antioxidant Enzymes⁹.

Autistic Patients Can Use Medications To Improve Some Repetitive Pattern Of Behaviors And Increase Abilities To Benefit From Psychosocial Interventions¹⁰. The Pharmacological Treatment Is Aimed To Decrease Problematic Behaviors, Such As Self-Injurious Behavior, Aggression and Irritability¹¹. Low Dose Antipsychotics May Be Used To Reduce Repetitive Behaviors, Social Withdrawal And Related Symptoms As Hyperactivity And Irritability. In October 2006, Fda Approved Risperidone as Effective Treatment For Problematic Behaviors In Children And Adolescents With Asd¹². Most Clinical Researches Studied The Effectiveness Of Antipsychotic (Risperidone) On Autistic Children And Adolescents¹³.

II. Material And Methods

This Is Prospective, Controlled And Comparative Randomized Clinical Trial Conducted On Eighty Children (5-7 Years Old) Diagnosed As Autism Based On The Second Edition Of Childhood Rating Scale Standard Version (Cars 2) And Follow Up For 2 Years.

Study Design: This Prospective, Controlled And Comparative Randomized Clinical Trial.

Study Location: Clinical Pharmaceutics Department And Assiut University Hospital. Psychiatry Department.

Study Duration: September 2015 To September 2017.

Sample Size: On Eighty Autistic Children.

III. Subjects & Selection Method:

The Study Population Divided Into Four Groups:

The First Group: Twenty Subjects With Autistic Features Received 40, One-Hour Sessions In The Hbot (Hyperbaric Oxygen Therapy) Chamber. These Sessions Had Done Under 1.5 Atmospheric Pressure and Inhaled 100% Oxygen Concentration. The Number Of Sessions Per Week Allowed Is 5 Sessions Per Week, All Participants Were Required To Complete 40 Sessions Within 2 Months. After 6 Months From The Last Session, Another 40 One-Hour Sessions In The Hbot Chamber Had Taken In The Same Way. Within The First Year In The Study, Five Children Discontinued The Study And Within The Second Year In The Study, Two Children Discontinued The Study.

The Second Group: Twenty Subjects With Autistic Features 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 8 Months.

The Medication Schedule In The Initial 2 Months Based On The Child's Weight And Clinical Response. Adjusting The Total Daily Dose According To Response And/Or Adverse Events, At The End Of These 8 Months Of Treatment We Began The Discontinuation Phase. The Discontinuation Reduced The Maintenance Dose By 25% Per Week. Thus, The Dose Was 75% Of The Last Week In The 8 Months For First Week, Followed By 50% Of The Last Week For The Second Week, 25% Of The Last Week For The Third Week, And Placebo Only By The Fourth Week. Within The First Year In The Study, Three Children Discontinued The Study And Within The Second Year In The Study, Four Children Discontinued The Study.

The Third Group: Twenty Subjects With Autistic Features Received Hbot As The First Group In Addition To Risperidone (Dose: 0.25 Mg Per Day In Children Weighing Less Than (20 Kg); 0.5 Mg Per Day In Persons Weighing More For 8 Months In The Same Way As Second Group. Within The First Year In The Study, Three Children Discontinued The Study And Within The Second Year In The Study, Two Children Discontinued The Study.

The Fourth Group: Twenty Subjects With Autistic Features Received Multivitamins As A Control Group. Within The First Year In The Study, Two Children Discontinued The Study And Within The Second Year In The Study, One Child Discontinued The Study.

N.B: The Dropout In The Study Is Either From Loss Of Efficacy, Cost, Noncompliance, Adverse Effects, No Longer Interested In Medication Treatment, Or Lost To Follow-Up.

Detailed History Taking From Parents Of Children: Age, Sex Of The Patient, Antenatal, Natal, Postnatal History, Developmental History Cognitive Abilities And Gross And Fine Motor Function, Consanguinity Between Parents, Mothers Age, Smoking In The Family, Family History Related To Similar Condition Or Any Psychological Or Mental Disorders. In Addition, History Of Major Childhood Illness, Surgery, Medication, And Diet.

Psychiatric Evaluation Includes Childhood Rating Scale (Cars 2). It Had Measured At The Beginning Of The Study, After One Year And After Two Years To Compare The Effect Of Hyperbaric Oxygen Therapy, Risperidone And Both Of Them Together. The Cars Include 15 Items Describe The Severity Of The Disorder. The Items Are As Follows: I. Relating To People, Ii. Imitation, Iii. Emotional Response, Iv. Body Use, V. Object Use, Vi. Adaptation To Change, Vii. Visual Response, Viii. Listening Response, Ix. Taste, Smell, And Touch Response And Use, X. Fear Or Nervousness, Xi. Verbal Communication, Xii. Nonverbal Communication, Xiii. Activity Level, Xiv. Level And Consistency Of Intellectual Response, And Xv. General Impressions. Each Item Is Scored From 1 (No Pathology) To 4 (Severe Pathology) In 0.5 Intervals. A Total Score Of 15-29.5 Is

Considered Non-Autistic To Minimal; A Score Of 30-36.5 Is Considered Mild To Moderate Autism; A Score Of 37-60 Is Considered Severe Autism (These Are Based On Raw Scores)14.

- **Inclusion Criteria:** (1) Autistic Children (5–7 Years Old), (2) Either Sex, (3) And Weight Of At Least 15 Kg.
- **Exclusion Criteria:** (1) Absence Of Significant Medical Problems And Any Other Psychiatric Disorder Requiring Drug Therapy (E.G., Bipolar Disorder, Psychosis), (2) Concomitant Treatment With Psychotropic Medication Not Allowed During The Study.

Statistical Analysis Of Data:

Data Are Expressed As Mean ± Sd (Range) Or As Number (%) Of Cases. One Way Anova Test Was Used For Quantitative Data Between The Four Groups Followed By Fisher Exact Test For Qualitative Data Between The Four Groups And One Way Anova Test Was Used For Quantitative Data Between The Four Groups Followed By Post Hoc Tukey Analysis Between Each Two Groups For Comparison Of Cars Score (Raw Score) At Two Years Between The Four Groups. Analysis Was Performed By Using The Statistical Package For The Social Sciences (Spss, Version 20). The Level P < 0.05 Was Considered The Cut-Off Value For Significance.

IV. Results

This Study Included 80 Egyptian Autistic Patients. Improvements Was Noticed (Decrease) In All Groups In Cars But This Improvement Was More Significant In The Groupi That Managed With Hbotand Groupiithat Managed With Hbot And Risperidone.

Table (1): Overall Descriptive Statistics Of The Patients

	Descriptive Statistics N=80
Age	
Range	(5-7)
Mean ± Sd	5.4±0.8
Sex	
Male	64(80%)
Female	16(20%)
Mother Age	
Range	(24-39)
Mean ± Sd	29.5±3.4
Mother Age	
≤ 30 Years	53(66.3%)
>30 Years	27(33.8%)
Residence	
Urban	75(93.8%)
Rural	5(6.3%)
Labor	
Normal	23(28.8%)
Cesarean	57(71.3%)
Family History	
Absent	68(85%)
Present	12(15%)
Consanguinity	
Negative	70(87.5%)
Positive	10(12.5%)
Food Allergy	
Absent	52(65%)
Present	28(35%)
Vaccination	
Vaccinated	80(100%)
Not Vaccinated	0(0%)
Smoking	
Not Exposed	51(63.8%)
Exposed	29(36.3%)
Cars At The Begin	
Range	(32-38.5)
Mean ± Sd	35±1.7
Cars At The Begin	
Minimal	0(0%)
Mild To Moderate	73(91.3%)
Severe	7(8.8%)

The Sample Aged From 5 To 7 Years. Their Gender Was 64 Male To 16 Female With Male To Female Ratio 4:1 About 94% Living In Urban Cities And 6% In Rural Ones. Mother Age Ranged From 24-39 Years Old. The Type Of Labor 28.8% Normal Labor And 71.2% Cesarean Section. History Of Similar Cases In Their Families Was 15% And History Of Consanguinity Between Parents Was 12.5%. Some Of The Children Had Allergy To Special Type Of Food About (35%). All Of Them Were Vaccinated. Father Smoking Present By 36.2%. Cars At The Beginning Of Our Study Ranged From (32-38.5).

Table (2): Comparisons Of Cars Score At The Beginning Between The Four Groups.

Cars At The Beginning Of The Study	Group I (N=20)	Group Ii (N=20)	Group Iii (N=20)	Group Iv (N=20)	P Value
Range	(32-36.5)	(32-38.5)	(32-38.5)	(32.5-38.5)	0.448
Mean ± Sd	34.6±1.4	35.3±1.8	35±1.8	35.3±1.7	

- One-Way Anova Test For Quantitative Data Between The Four Groups.
- Significant Level At P Value < 0.05
- Group I:Hyperbaric Oxygen Therapy, Group Ii:Risperidone, Group Iii: Hyperbaric Oxygen Plus Risperidone, Group Iv: Control
- There Was No Significant Difference Between The Four Groups.

Table 3: Comparisons Of Cars Score At One Year Between The Four Groups.

Cars (1 Year)	Group I (N=15)	Group Ii (N=17)	Group Iii (N=17)	Group Iv (N=18)	P Value
Range	(30-35)	(30-37)	(30-36)	(30-38)	0.055
Mean ± Sd	32.9±1.8	34.1±2	32.7±1.9	34.2±2.2	
P Value (Multiple Comparisons)					
Group Ii	0.105				
Group Iii	0.752	0.047*			
Group Iv	0.062	0.809	0.025*		

- One-Way Anova Test For Quantitative Data Between The Four Groups Followed By Post Hoc Tukey Analysis Between Each Two Groups.
- Significant Level At P Value < 0.05
- Group I:Hyperbaric Oxygen Therapy, Group Ii:Risperidone, Group Iii: Hyperbaric Oxygen Plus Risperidone, Group Iv: Control

There Was No Significant Difference Between The Four Groups. However, There Was Statistically Significant Difference Between Group 3 And Group 2, 4.

Table 4: Comparison Of Cars Score At Two Years Between The Four Groups.

Cars (2 Years)	Group I (N=13)	Group Ii (N=13)	Group Iii (N=15)	Group Iv (N=17)	P Value
Range	(19-30)	(28-34.5)	(19-28.5)	(29-36)	< 0.001*
Mean ± Sd	23.1±3.7	31.6±2	22±2.7	32.2±2	
P Value (Multiple Comparisons)					
Group Ii	< 0.001*				
Group Iii	0.687	< 0.001*			
Group Iv	< 0.001*	0.927	< 0.001*		

- One Way Anova Test For Quantitative Data Between The Four Groups Followed By Post Hoc Tukey Analysis Between Each Two Groups.
- *: Significant Level At P Value < 0.05
- Group I:Hyperbaric Oxygen Therapy, Group Ii:Risperidone, Group Iii: Hyperbaric Oxygen Plus Risperidone, Group Iv: Control

There Were Decrease In Cars In All Groups With Statistically Difference But Highly Significant Difference Between Group 1 And Groups 2, 4 Also Between Group 3 And Group 2, 4

V. Discussion

The Purpose Of This Study Was To Determine The Effects Of Hbot And Risperidone In Autistic Children. Other Objectives Were To Measure These Effects In Clinical Symptoms Using Cars. The Final Intention Was To Compare Between Hbot And Risperidone Use In Autistic Children. The Present Study Provided Evidence On The Beneficial Effects Of Hbot And Risperidone In Management Of Patients With Autistic Features. In The Study, The Group Of Autistic Children Managed With Hbot Showed Decrease In Cars After One And Two Year With Mean ± Sd (34.6±1.4) At The Beginning, After One Year Decrease Was (32.9±1.8), After Two Years Decrease Was (23.1±3.7) With Significant P Value (<0.001) For The Three Results. In Addition, The Group Of Autistic Children Managed With Hbot Combined With Risperidone Showed

Decrease In Cars After One And Two Year With Mean \pm Sd (35 \pm 1.8) At The Beginning, After One Year Decrease Was (32.7 \pm 1.9), After Two Years Decrease Was (22 \pm 2.7). Rossignol Et Al¹⁵ Randomly Assigned 62 Children With Asd Showed That Improvement Significantly On The Aberrant Behavior Checklist (Abc) Within The Treatment Group That Received 40 Sessions Of 24% Oxygen At 1.3 Atm Compared To (Control Group) That Received Regular Room Air At 1.03 Atm. However, This Study Did Not Show Significant Improvements In Other Outcome Measures, Such As: The Aberrant Behavior Checklist (Abc). Another Study On Six Participants. Statistically Significant Changes Has Been Shown In Scores Of The Childhood Autism Rating Scale (Cars) By Open-Label Prospective Study On The Same Children Who Received 24% Oxygen At 1.3 Atm Were Compared To After Receiving 100% Oxygen At 1.5 Atm.¹⁶

In Seven Thai Autistic Children, Hbot Had Carried Out And Assessment Had Done Before And After Treatment. Data Showed That 75% Of Children Had Significant Improvement By Different Evaluation Methods As Aberrant Behavior Checklist (Abc) And Clinical Global Impression Scale (Cgi). No Serious Adverse Effect In Any Case Was Reported¹⁷.

Lerman Et Al Evaluated The Effects Of Hbot On Three Children (6 - 7) Years Old. Two Participants Received 40 Sessions Of Hbot And The Third Received 27 Sessions Of 88% Oxygen And 1.3 Atm. One Participant Had Shown An Increasing In Communication During Hbot Treatment But The Effect Had Not Replicated Across The Other Two Participants. However, The Improvement Of Behavior During Hbot Had Accounted For By The Overall Decrease In Demands During Days In Treatment Group¹⁸.

In Our Study The Group Of Autistic Children Managed With Risperidone Showed Decrease In Cars After One And Two Year With Mean \pm Sd (35.3 \pm 1.8) At The Beginning, After One Year Decrease Were (34.1 \pm 2) And After Two Years Decrease Were (31.6 \pm 2).

Double Blind, Placebo-Controlled Study Examined The Efficacy Of Risperidone On Irritability Of Autistic Children For 8-Weeks. The Risperidone Group (Mean Dose 1.17 Mg/D) Had Improved Significantly Than Placebo By Decreasing Scores On The Irritability Subscale Of The Abc.¹⁹ Another Randomized Controlled Trial Examined The Efficacy Of Risperidone In Autistic Children For Six Months.²⁰ Targets Included Some Core Autism Symptoms (Social Communication) And Associated Symptoms (Irritability, Aggressiveness And Hyperactivity). Risperidone Improved Social Communication. Side Effects In The Risperidone Group Included Increased Appetite, Weight Gain (Mean 2.8 Kg), Mild Sedation And Mild, Transient Dyskinesias²⁰. Also, Changes In The Mean Global Assessment Scale Score And The Median Childhood Autism Rating Scale Rating From Baseline^{14, 21}. Statistically Significant Improvement In The Risperidone Group Than The Placebo Group On Both Outcome Measures. In 2015, Rupp Published The Results Of Eighty-Four Subjects Participated In The Follow-Up Study For 21-Month; 56 Of These Subjects Continued Risperidone Treatment Had Improvement In Targeted Symptoms Of Aggression And Irritability Scores (P=0.01)²².

VI. Conclusion

The Mechanism Of Action In How Hbot Could Alleviate Autistic Behavior May Remain Understood. However, In Our Study, There Is Better Improvement In Patients Treated With Hbotand Risperidone. While, Risperidone Is Fda-Approved, Only For Managing The Irritability Associated With This Disorder. Further Studies Are Necessary For Evaluating Not Only The Clinical Effects Of Pharmacological Treatments In Patients With Asd, But With Consideration To Potential Risks Also.

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