Meta-analysis of effectiveness of Hyperbaric Oxygen Therapy in management of autism spectrum disorder children

A Ph D in childhood Studies (Care of children with special needs)
Medical Studies Department for Children

By

Amany Hassan Moussa Koheil
Msc. Pediatrics, Alexandria University

Supervised by

Dr. Mohamed Salah El Dean Mostofa

Professor of Preventive Medicine and Epidemiology, Medical Studies Department for Children, Faculty of Postgraduate Childhood Studies, Ain Shams University

Dr. Mona Medhat Reda
Professor of Psychiatry, Medical Studies Department for Children, Faculty of Postgraduate Childhood Studies, Ain Shams University

2019

Acknowledgment

First and always I would like to dedicate all my success in this thesis and throughout my practical and social life to **ALLAH**, I am in plenty of blesses and deeply grateful & thankful.

Secondly It is my pleasure to acknowledge the role of my professors who were instrumental for completition my Ph.D. thesis.

I would like to express my sincere thanks, deep gratitude and extreme appreciation to **Dr. Mohamed Salah El Dean Mostofa** professor of preventive medicine and epidemiology in medical studies department for children, Faculty of Postgraduate Childhood Studies, Ain Shams University for his supervision and valuable guidance throughout the work and who thought me the art of meta-analysis.

This thesis would not be materialized without guidance & remarkable help of **Dr. Mona Reda** professor of psychiatry in medical studies department for children, Faculty of Postgraduate Childhood Studies, Ain Shams University. Her constant support and follow up of the progress of research is really appreciated.

Great thank to all members of the central digital library of Ain Shams for their unlimited cooperation during searching for thesis and papers needed for this work.

This work is dedicated to my son **Abdullah,** hoping he is proud of his mom as

well as my sisters **Neven** & **Amel** for their patience and financial support .

Also my deep appreciation to all my colleges especially friends indeed whom

were ready to engage for full assistance.

Meta-analysis of effectiveness of Hyperbaric Oxygen Therapy in management of autism spectrum disorder children

Amany H Koheil (Msc)[1] **Salah Mostofa**(MD,FACE)[2] **and Mona M Reda** (MD)[2]

1. Pediatric clinic in RightWay Medical Center, Alexandria, Egypt.
2. Medical Studies Department for Children, Faculty of Postgraduate Childhood Studies, Ain Shams University,Cairo,Egypt.

Background: Autism is a complex neurodevelopmental condition that typically manifests in the first two years of life. The Centers for Disease Control and Prevention (2015) reported prevalence 1 in 45 US children**. .** In Egypt 23.8% of studied toddlers in enrolled Primary Health Care Units were suspected to have ASD with a male: female ratio of 3:1. Numerous studies of autistic individuals have revealed evidence of cerebral hypoperfusion and neuroinflammation abnormalities .Some investigators speculated that HBOT may be useful in improving behavioral and physiological abnormalities found in some children with ASD.

Aim: To provide the meta-analysis study of Egyptian studies regarding efficacy of HyperBaric Oxygen Therapy as adjuvant treatment for children with autism spectrum disorder and to establish Egyptian evidence based guidelines.

Methodology: The researcher reviewed the **Egyptian** theses, papers, journals, in English and Arabic language, searching for the eligible studies published to the end of December 2018. Meta-analysis was done using MedCalc software ver. 12.7.7.0. Out of 611 study (on Autism) & 84 study (on HBOT) ,The pool of eligible 4 studies were involved a total sample of 140 children with ASD and 40 of them acted as control children.

Results: The proportion was 25.7%, for all ASD children cited significantly in all four Egyptian studies with total number of 140 participants, (Q=19.9, P= 0.0002) with CI was 8.4–48.4 for all participants. The proportion of male in all four studies was, 80.8%, significant with total number 110 male participants (Q=8.8, P= 0.0315). CARS test score as diagnostic scale was mean = 33.9 before HBOT for 60 participants in two studies was significant (F=6.0, P=0.004). The usage of HBOT chamber of low pressure in two studies was near significant with total number of 90 participants (Q=2.7, P= 0.0994)., I^2 =66.05%, (95%CI for I^2 = 0.44 to 88.42), P= 0.0315 . Among 60 participants in two of our study, there was no significant improvements related to number of HBOT sessions (P= 0.601). CARS test Pre- HBOT done for 60 participants in two studies was significant P=0.004 while CARS Post-HBOT for same two studies was insignificant P=0.86 .Two of our Egyptian studies were analyzed

with total number of 46 participants having ASD & receiving risperidone (P= 0.216), and there was no significant improvement with HBOT on meta-analysis basis.

Conclusion: This Meta-analysis study had very few number of Egyptian studies with small number of participants .There was insufficient evidence that HBOT improves health outcomes for autism.Its recommended for further randomized controlled trials as well as Sham controlled studies are needed including different pressures of HBOT.

Keywords: HBOT, ASD, Autism, Children, PDD, Meta-analysis.

Contents

List of abbreviations

ABC	Abberant Behavior Checklist
ADDM	Autism & Developmental Disabilities Monitoring
ADHD	Attention Deficit Hyperkinetic Disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism diagnostic observation Schedule
ATA	Atmosphere Absolute
atm	atmospheric pressure at sea level.
ASD	Autism spectrum disorders
ATEC	Autism Treatment Evaluation Checklist
BBB.	Blood-Brain Barrier
CARS	Autism Rating Scale
CARS 2	Childhood Autism Rating Scale-2
CDC	Centers for Diseases &Control
CGI	Clinical Global Impression
CSF	Cerebral Spinal Fluid
CDC	Centers for Diseases &Control
DCS	Decompression Sickness
DNA	DexosyNucleicAcid
DSM-5	Diagnostic &Statistical Manual of Mental disorders – fifth edition
FDA	Food & Drug Adminstration
fMRI	functionalMagnetic Resonance Imaging
FMRP	Fragile X mental retardation protein
GABA	Gamma amino butyric acid
GARS 2	Gilliam autism rating scale-2

GCC	Gulf Cooperation Council
GI	GastroIntestinal
HIF–1a	Hypoxia Inducable Factor-1a
HBOT	HyperBaric Oxygen Therapy
I Q	Intelligence Quotient
IL-1	InterLeukin-1
MRI	Magnetic Resonance Imaging
OCD	Obsessive Compulsive Disorder
PDD	Pervasive Developmental Disorder
PDDNOS	Pervasive Developmental Disorder NotOtherwise Specified
PECS	Picture Exchange Communication System
PET	Positron Emission Tomography
PGI-R	Parental Global Impression –Revised
PMNs	PolyMorphNeutrophils
RRBs	Restricted Repetitive Behaviors
SCQ	Social Communication Questionnaire
SPECT	Single Photon Emission Computed Tomography
SSRI	Selective Seritonin Re-uptake Inhibitors
TD	Typical Developing
TNF-α	Tumor Necrosis Factor Alpha
UAE	United Arab Emirates
UHMS	Undersea HyperMedical Society
VEGF	Vascular Endothelial Growth Factor

List of Figures in Review & Methodology

List of Tables in Review of Literature & Methodology

List of Meta-Analysis Statistical Tables & Figures in Results

Introduction

Introduction

Hyperbaric oxygen therapy (HBOT) involves inhaling up to 100% oxygen at a pressure greater than one atmosphere (atm) in a pressurized chamber. HBOT is indicated in several clinical disorders include decompression sickness, healing of problem wounds, arterial gas embolism and carbon monoxide poisoning **(Undersea and Hyperbaric Medicine Society, 2014).**

As compared to treatment with HBOT for many classical indications, HBOT has started to be investigated to treat certain neurological disorders, some of which are as traumatic brain injury (TBI) which resulted in significant improvements in their neurological exam, IQ, memory, post-traumatic stress symptoms, depression, anxiety and quality of life **(Sahni et al.,2011)**.

Interestingly, oxygen supplementation has recently been reported in several double-blind studies of healthy young adults, the use of supplementary oxygen, When compared with room air, significantly enhanced memory, cognitive performance, word recall and reaction time for 24 hours , as well as attention and picture recognition **(Moss et al.,1996).**

Autism Spectrum Disorder (ASD) is neurodevelopmental disorder that is characterized by Deficits in social communication and social interaction and Restricted Repetitive Behaviors, interests, and activities (RRBs) .These symptoms are present from early childhood and limit or impair everyday functioning. Both components are required for diagnosis of ASD **(American Psychiatric Association, DSM5, 2013).**

The Centers for Disease Control and Prevention **(CDC, 2016)** declared, the overall prevalence of ASD among the 11 ADDM sites was one in 59 children aged 8 years.ASD prevalence estimates also varied by sex and race/ethnicity. Males were four times more likely than females to be identified with ASD**.**

(Guifeng et al. 2018) corrected the overall prevalence of Autism Spectrum Disorder among US Children &Adolescents to **2.47 %**.

Prevalence studies conducted to date within Arab countries yielded an estimate of the prevalence of ASD for Saudi Arabia, Oman, UAE, Jordan, Libya, Egypt, and Tunisia ***(Taha & Hussein, 2014).*** A systematic review of the epidemiology of ASD in the Gulf Cooperation Council (GCC) countries reported a prevalence rate ranging from 1.4 to 29 per 10,000 individuals ***(Salhia et al., 2014***). The difference in the prevalence rates compared to other countries does not prove that ASD is less prevalent in the Arab world, but rather reflects under-diagnosis, underreporting, and cultural attitudes ***(Taha & Hussein, 2014).*** Under-diagnosis and underreporting are attributed to the limited availability of quality specialized healthcare services for children with neurodevelopmental disorders ***(Hussein & Taha, 2013).***In Qatar: a national study showed the Prevalence was 1.14% (95% CI: 0.89-1.46) among 6- to 11-year-olds. In multivariate logistic regression, ASD severity was associated with parental consanguinity, gestational diabetes, delay in walking, and developmental regression ***(AlShaban et al., 2019).***

Prevalence of autism spectrum disorders among children with developmental disorders in Egypt and Tunisia were documented to be 33.6% and 11.5% respectively ***(Seif Eldin et al., 2008).*** A recent Egyptian community based study, 23.8% of studied toddlers in enrolled Primary Health Care Units were suspected to have ASD and needed further professional evaluation with a male: female ratio of 3:1 ***(Mohamed et al., 2016).***

As this documented increase in rate of children with ASD, many researches investigating the etiology of ASD which is unclear at this time. Although several genetic syndromes, such as Fragile X and Rett syndromes, have been associated with ASD, empirical studies have estimated that genetic syndromes only account for 6-15% of ASD cases ***(Schaefer et al.,2008).***

In recent decades, research and clinical studies in ASD have implicated physiological and metabolic systems that transcend specific organ dysfunction, such as cerebral hypoperfusion, immune dysregulation, inflammation, oxidative stress, and mitochondrial dysfunction ***(Rossignol et al., 2012).***

To date, ASD has few efficacious treatments. Applied Behavioral Analysis (ABA) is a form of behavioral therapy which has been reported to improve some children with ASD but noticed that behavioral therapies typically require long time periods to cause behavioral and cognitive changes in children with ASD ***(Lovaas, 1987 & Sallows et al., 2005).***

Treatment with HBOT has been shown to possess potent anti-inflammatory properties also has been reported to decrease the production of pro-inflammatory cytokines as well as increase counter-inflammatory levels ***(Granowitz, 2002 & Buras 2006***). Starting around 2005, some investigators speculated that HBOT may be useful in improving behavioral and physiological abnormalities found in some children with ASD ***(Rossignol, 2007)***.

In a multicenter, randomized, double-blind, controlled trial to assess the efficacy of hyperbaric treatment in children with autism showed that children who received hyperbaric treatment at 1.3 atm and 24% oxygen for 40 hourly sessions had significant improvements in overall functioning, receptive language, social interaction , eye contact, and sensory/cognitive awareness compared to children who received slightly pressurized room air. Outcome measures included Clinical Global Impression (CGI) scale, Aberrant Behavior Checklist (ABC), and Autism Treatment Evaluation Checklist (ATEC)***(Rossignol et al., 2009)***.

As HBOT is enrolled in some medical centers for treating children with ASD so this study conducts systematic review and meta-analysis of all studies published to December 2018 as regarding efficacy and safety of HBOT as adjuvant and/ or alternative therapy for children with autism spectrum disorder.

Meta-analysis is an epidemiological technique for summarizing and reviewing previous quantitative research, by using meta-analysis, a wide variety of questions can be investigated as long as a reasonable body of primary research studies exists. Selected parts of the reported results of primary studies are entered into a database and this “meta-data” is meta-analyzed in similar ways to work with other**.** Good meta-analysis aims to increase statistical power, investigate risks associated with diseases and generalize results of single studies ***(Ioannidis, 2005).***

Evidence-based Practice can be defined as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of clients*"* ***(Barwick et al., 2005).*** Thus, it is similar to several other terms that involve using research evidence to inform practice and client care, including: data-based approaches, empirically-supported treatment, best practices, empirically-validated treatment, clinical practice guidelines, and evidence-based medicine. The term "evidence-based" itself has recently burgeoned in the scientific/professional literature, demonstrating its growing influence. For example, prior to 1990, there appears to be no use of the term at all and, between 1990 and 1995, it is found only 86 times in the literature ***(Hoagwood & Johnson, 2003).***

Aim of the Study