Original articles

Hyperbaric oxygen in the treatment of childhood autism: a randomised controlled trial

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Abstract

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Background: Promising results with hyperbaric therapy for children with autism have been reported, but most involved the use of only mild pressure with oxygen supplementation. To date, there has been no randomised, blinded trial of 100% oxygen administered at hyperbaric pressure. This study evaluated the efficacy of hyperbaric oxygen therapy (HBOT).

Methods: Sixty Thai children with autism, aged three to nine years, were randomly assigned to receive 20 one-hour sessions of either HBOT at 153 kPa (1.5 ATA) or sham air at 116 kPa (1.15 ATA). Effects on behaviour were measured using the Autism Treatment Evaluation Checklist score (ATEC) and clinical improvement was measured with the Clinical Global Impression (CGI) system; in particular the clinical change (CGIC) and severity (CGIS) sub-scores. These were evaluated by parents and clinicians, both of whom were blinded to the actual exposure.

Results: The mean total ATEC scores by both parents and clinicians were significantly improved after intervention in both arms of the study compared to the score before intervention ($P < 0.001$ in both groups by parents, $P = 0.015$ in HBOT group and $P = 0.004$ in sham group by clinician). There were no statistically significant differences in average percentage changes of total ATEC score and all subscales scores when comparing the HBOT and sham air groups, either by parents or clinicians. Changes in the CGI scores following intervention were inconsistent between parents and clinicians. For severity scores (CGIS), parents rated their children as more improved following HBOT ($P = 0.005$), while the clinicians found no significant differences ($P = 0.10$). On the other hand, for change scores (CGIC) the clinicians indicated greater improvement following HBOT ($P = 0.03$), but the parents found no such difference ($P = 0.28$)

Conclusions: Children with autism who received 20 sessions of either HBOT or a sham air exposure had significant improvements in overall behaviour but there were no significant differences in improvement between groups. The inconsistent changes on CGI sub-scores between parents and clinicians are difficult to interpret, but no overall clinically significant benefit from HBOT could be shown. Both interventions were safe and well tolerated with minimal side effect from middle ear barotraumas.

Key words

Autism, hyperbaric oxygen therapy, hyperbaric research

Introduction

Autism is a condition classified within the group of pervasive developmental disorders, characterised by a triad of clinical findings including qualitative impairments in speech and communication, impairments in social interaction and in stereotyped patterns of behaviour, interest and activities.[1] Global prevalence of autism is estimated at approximately 22 cases per 10,000, and there is a trend of increasing rates of prevalence by years.[2] In Thailand, the prevalence of autism in children aged one to five years is estimated at 4.4 per 10,000.[3] The gender ratio (male: female) of children with autism in Thailand was 3.3:1 and in the UK was 6.5:1 children.[4,5] Behavioural interventions are the mainstay of therapy for individuals with autism, while several drug therapies have been used to treat some target behaviours, including antipsychotics, antidepressants and psychostimulants.[6] At present, risperidone is the only medication approved by the US Food and Drug Administration to treat irritability in autism. Hyperbaric oxygen treatment (HBOT) has been suggested recently as a useful adjunctive treatment in children with autism.

Accepted indications for HBOT include air or gas embolism, carbon monoxide poisoning, clostridial myositis and myonecrosis, crush injury, decompression sickness, severe anaemia, intracranial abscess, necrotizing soft tissue infections, osteomyelitis, delayed radiation injury, compromised grafts and flaps, and acute thermal burn injury.[7] In some places, and without good clinical evidence, HBOT is also used as an adjunctive treatment in other conditions including ischaemic cerebral strokes, traumatic brain injury and cerebral palsy.[8–11] HBOT is generally considered relatively safe at pressures below 304 kPa for less than 2 hours.[12,13]

Evidence of cerebral hypoperfusion, neurological and gastrointestinal inflammation, immune dysregulation,

oxidative stress and relative mitochondrial dysfunction have all been associated with core autistic symptoms. Repetitive self-stimulatory, stereotypical behaviours and impairment of communication, sensory perception and social interaction have all been found in case subjects with cerebral hypoperfusion.[14–16] HBOT has been reported to have a beneficial effect on inflammation, improving cerebral hypoperfusion and modulating immune dysregulation.[13–15,17–20] A randomised, double-blind, controlled trial comparing the effect of 'hyperbaric treatment' consisting of 24% oxygen at 1.3 ATA, to that of slightly pressurised room air at 1.03 ATA, has been reported recently.[21] This trial showed significant improvements in the ATEC score in several domains including total score, sociability, sensory/cognitive awareness and health/physical/behaviour in the treatment group while in the control group improvements were found in total score and sociability. There were important differences between the groups at baseline in this small trial, making interpretation of the results difficult. Direct comparison between groups after the treatment found a significant improvement only in sensory/cognitive awareness.[21] There were several position statements from international societies considering such previous case series and trial controversial by using low pressure/low oxygen concentration hyperbaric treatment.[22,23]

Our open-label pilot study suggested a statistically significant effect on behaviour after completion of 20 sessions of hyperbaric oxygen treatment at 153 kPa (1.5 ATA) for one hour daily (unpublished data). Since only slightly oxygen-enriched air was used in the previously published randomised study, rather than hyperbaric oxygen, the objective of this study was to evaluate the effects of 'true' HBOT on children with autism.

Methods

ETHICAL APPROVAL

This study was approved by the Ethics Committee (Institutional Review Board) of the Royal Thai Navy Medical Department.

PROCEDURES

This study was a prospective, randomised, double-blind, controlled trial of HBOT at 153 kPa (1.5 ATA) with 100% oxygen for one hour daily, weekdays to a total of 20 sessions, versus a sham air treatment consisting of pressurised room air at 116 kPa (1.15 ATA) on the same schedule. Parents or caregivers were allowed to accompany their children along with one medical attendant. 116 kPa (1.15 ATA) was employed in the sham air group because this is the minimum pressure required to keep our multiplace chamber tightly closed and therefore to closely mimic the experience of hyperbaric treatment, in order to maintain blinding of participants and parents.

PARTICIPANTS

Children, aged three to nine years, diagnosed with autism according to DSM-IV TR™, and who had never received HBOT, were considered for inclusion in this study. Children who had seizure disorders, uncontrolled asthma, a history of previous spontaneous pneumothorax, current ear or upper respiratory tract infections, emphysema, current or recent chemotherapy, severe claustrophobia, and ongoing chelating therapy were excluded from the study. Written, informed parental consent was obtained before randomised allocation to treatment group (see below for details of randomisation and allocation concealment).

CLINICAL OUTCOME AND MEASURES

The primary outcome measures were changes of behaviour evaluated by comparing the Autism Treatment Evaluation Checklist (ATEC) scores and Clinical Global Impression (CGI) scale evaluated separately by clinician and parents before and after 20 sessions of interventions.[24–26] The ATEC consists of 4 subtests: I. Speech/Language Communication (14 items); II. Sociability (20 items); III. Sensory/ Cognitive Awareness (18 items); and IV. Health/Physical/Behaviour (25 items). The ATEC scores were analysed as absolute and percent changes of average total and subscale scores.

The Clinical Global Impression of Illness Severity (CGIS) scores were assessed before and after the interventions. The CGIS is rated on a 7-point scale using a range of responses from 1 (normal), 2 (borderline mentally ill) to 7 (among the most extremely ill patients). Average scores for the two groups were compared before and after the interventions. The Clinical Global Impression of Change (CGIC) scores were assessed after the interventions to score the improvement of each participant. CGIC scores range from 1 (very much improved), to 7 (very much worse). Average scores for the two groups as rated by both parents and clinicians were compared.

SAMPLE SIZE

Pre-study power analysis was based on the differences in means and standard deviations of ATEC score changes in our pilot study since there were no comparable data in any previously published studies. In order to achieve 80% power ($\beta = 0.2$, $\alpha = 0.05$), we calculated that we would require 24 participants. To allow for some withdrawals, we planned to recruit a total of 60 participants.

RANDOMISATION AND ALLOCATION

Sixty-one children were assessed for eligibility; one child was excluded after consent, but before treatment allocation, owing to parental refusal to enter the chamber because of a medical condition. Sixty children were recruited and randomly allocated to two groups. The 60 participants

were chosen from 90 children using a random number table in which the numbers 1–60 were generated by random sequence then divided into two groups according to their given numbers (even number = Group A and odd number = Group B). In each arm, participants were divided into five groups of six participants. The sequence of treatments was also randomised in order to further reduce any possibility of unblinding.

The allocation sequence remained concealed to all investigators, participants, parents, nursing staffs and all other clinical staff. All staff who participated in the pre- and post-study evaluations were banned from the hyperbaric facility during the interventions and had no access to the hyperbaric treatment record. Only the hyperbaric technicians, who had no input into the evaluation, knew the allocation of groups and individuals, and they were specifically instructed not to discuss the intervention nature or group assignments with anyone else. The effectiveness of the blinding process was estimated using parental surveys before and after the interventions.

During the first few sessions, one boy in the HBOT group dropped out because of his uncooperative behaviour during the intervention procedure, while another boy in the sham group dropped out following a febrile convulsion. The data from these two children were excluded from statistical analysis as it was considered that their inclusion on an intention-to-treat basis would not have any impact on the outcome analysis.

STATISTICAL ANALYSIS

All data were analysed using SPSS for Windows®, Version 12. Where appropriate, the data were tested for normality using the Kolmogorov-Smirnov Test. Interval scales were compared by independent Student t-test if normality was assumed and we planned to use the Wilcoxon Rank Sum Test in the absence of normality. Nominal scales were compared using chi-square test or Fisher's exact test, as appropriate. Before and after scores were analysed using the paired Student t-test and repeated measures ANOVA. Statistical significance was assumed if the *P* value for any comparison was < 0.05 (type 1 error).

Table 1
Baseline characteristics; differences between the hyperbaric oxygen (HBOT) and sham air groups not significant; means (SD) or actual numbers shown; clin. – clinicians ATEC – Autism Treatment Evaluation Checklist; CGIS – Clinical Global Impression of Illness Severity

	HBOT (n = 29)	**Sham air** (n = 29)
Age (yr)	6.10 (1.17)	5.67 (1.01)
Male/female	28/1	26/3
Risperidone	17	14
Other medications	19	16
Nutrition supplements	1	0
Current behavioural therapy	29	28
Total ATEC score (parents)	68.07 (25.43)	64.86 (22.80)
Total ATEC score (clin.)	60.21 (19.92)	60.55 (21.36)
Av. CGIS score (parents)	4.03 (1.05)	3.79 (0.98)
Av. CGIS score (clin.)	3.62 (0.78)	3.83 (0.93)

Results

Fifty-eight children, 54 boys and 4 girls (Table 1) completed 20 sessions of interventions. No serious adverse effects occurred. Only a few, minor-grade ear barotrauma events occurred in 2.6% of all HBOT sessions (15 of 580 HBOT, 11 of 29 children) and 0.5% of all sham sessions (3 of 580 HBOT, 3 of 29 children). No HBOT or sham air session was curtailed because of ear barotrauma or for any other reason.

BEHAVIOUR EVALUATION BY ATEC SCORES

The initial mean parental and clinician ATEC scores were not significantly different (parents $P = 0.615$; clinicians $P = 0.95$) (Table1). The average total parental ATEC scores decreased significantly after the interventions in both the HBOT and sham groups ($P < 0.001$ for both). Similarly, the average total clinician ATEC scores also showed significant reduction in both groups (HBOT $P = 0.015$; sham $P = 0.04$).

In the ATEC subscale scores, parents of those in the HBOT group indicated significant score reductions in three domains (sociability, sensory, and health), while parents of those in the sham group scored significant reductions in four domains (speech, sociability, sensory, health). Clinicians rated children in the HBOT group with significant score reduction in two domains (sensory and health), and in the sham group in three domains (speech, sensory, and sociability) (Table 2). There were no statistically significant differences in the average percentage changes of total ATEC score and all subscales scores when comparing the HBOT and sham groups, either by parents or clinicians.

CGI SCORES

There were no differences in initial mean parental and clinician CGIS between the groups (parents $P = 0.47$; clinicians $P = 0.42$) (Table 1). The mean parental CGIS score was significantly improved following HBOT ($P = 0.005$), but not sham air ($P = 0.1$), while there was no difference in the CGIS as indicated by the clinicians following either intervention (HBOT $P = 0.10$; sham air $P = 0.33$) (Table 3).

For the CGIC scores, the mean clinician score in the HBOT group was significantly lower than that in the sham group ($P = 0.03$), but not lower in the parental scores ($P = 0.28$). None of the children were rated by clinicians and parents as worse after the interventions (Table 3).

Table 2
Autism treatment evaluation checklist (ATEC) scores before and after trial, mean (SD); HBOT – hyperbaric oxygen therapy; ns – not significant

Outcome score and group	Pre-trial	Post-trial	*P* value
Parental ATEC scores			
Total score			
HBOT (*n* = 29)	68.07 (25.43)	58.31 (21.94)	0.001
Sham air (*n* = 29)	64.86 (22.80)	55.86 (24.93)	0.001
Speech			
HBOT	14.72 (6.34)	13.93 (6.15)	ns
Sham air	14.28 (6.35)	12.72 (6.76)	0.005
Sociability			
HBOT	15.83 (8.03)	13.45 (6.44)	0.014
Sham air	14.28 (6.84)	12.24 (6.84)	0.005
Sensory			
HBOT	16.76 (7.02)	14.83 (7.12)	0.027
Sham air	16.24 (5.93)	13.90 (7.03)	0.027
Health			
HBOT	20.24 (10.80)	16.76 (8.24)	0.025
Sham air	20.41 (10.18)	17.00 (9.43)	0.001
Clinician ATEC scores			
Total score			
HBOT	60.21 (19.92)	52.38 (19.11)	0.015
Sham air	60.55 (21.36)	52.93 (18.93)	0.004
Speech			
HBOT	14.66 (7.01)	13.66 (7.25)	ns
Sham air	15.24 (6.75)	13.93 (6.97)	0.006
Sociability			
HBOT	16.93 (6.40)	14.86 (6.52)	ns
Sham air	15.45 (7.03)	13.31 (4.58)	0.044
Sensory			
HBOT	16.31 (6.43)	13.93 (5.55)	0.027
Sham air	16.69 (6.96)	14.31 (4.86)	0.023
Health			
HBOT	13.45 (6.99)	10.79 (5.35)	0.026
Sham air	13.52 (5.98)	12.07 (6.93)	ns

Table 3
Parental and clinician Clinical Global Impression of Illness Severity (CGIS) and Clinical Global Impression of Change (CGIC) comparisons, mean (SD); HBOT – hyperbaric oxygen therapy; ns – not significant

Outcome score and group	Pre-trial	Post-trial	*P* value
Parental CGIS			
HBOT (*n* = 29)	4.03 (1.05)	3.69 (0.93)	0.005
Sham air (*n* = 29)	3.79 (0.98)	3.66 (0.86)	ns
Clinician CGIS			
HBOT	3.62 (0.78)	3.48 (0.78)	ns
Sham air	3.83 (0.93)	3.76 (0.83)	ns
Parental CGIC			
HBOT	–	2.34 (0.61)	ns
Sham air	–	2.55 (0.83)	
Clinician CGIC			
HBOT	–	2.31 (0.6)	0.03
Sham air	–	2.72 (0.8)	

PARENTAL SURVEY FOR EFFECTIVE BLINDING

Fifty-two percent of the parents whose children were in the HBOT group believed they would receive HBOT compared to 76% of those with children allocated to sham air and this difference was statistically significant ($P = 0.002$). There was an increased belief in both groups after 20 sessions (69% of HBOT group and 83% of sham air group parents, $P < 0.001$), indicating that blinding was successful.

Discussion

Hyperbaric treatment has been used for children with autism and has been reported as a successful intervention in several recent studies.[21,27] Only one of these reports was a randomised study, in which the partial pressure of oxygen was only 31.6 kPa in the 'treatment' group versus 21.9 kPa in the sham group and did not include an arm with 100% oxygen at hyperbaric pressures.[21] Good evidence to guide practitioners is, therefore, lacking.

In order to improve this situation, we have conducted a randomised, double-blinded investigation of true HBOT as a therapy in autism. While the clinicians, parents and participants were unaware of allocation, it was not possible to blind the hyperbaric technicians to therapy in the interests of safety. The high proportion of parents who believed their children had received true HBOT suggests blinding was successful.

Both the HBOT and sham air groups in this study showed significant improvements in overall behaviour after completion of 20 sessions of intervention, but HBOT failed to show any greater behavioural improvement when compared to sham air. Given the high proportion of parents who believed their children were receiving HBOT, this suggests that HBOT conferred no benefit above that owing to a participation (or placebo) effect. Although clinicians reported greater improvement in the CGIC sub-score and parents reported lower severity in CGIS sub-score after HBOT, the other sub-scores (clinician CGIS and parental CGIC) failed to show such improvements, and the importance of these findings are unclear.

These findings are interesting to compare with the previously reported trial in which a 38% improvement in the control groups who received slightly pressurised room air at 104 kPa was seen.[21] In our study, the sham group similarly received slightly pressurised room air at 116 kPa. There is no widely accepted theory for the mechanism by which either 'low pressure' air or slightly oxygen-enriched air would have a beneficial effect on the behaviour of these

children with neuro-developmental disorders. Interestingly, it has been shown that a pressure increment as small as 20 mmHg above 1 ATA decreased pro-inflammatory cytokines *in vitro* (including IL-1beta), that have been found in some children with autism.[28–30] However, this work involved 24-hour pressure exposure, and it is not known whether much shorter pressure exposures *in vivo* would have a similar effect. What is far more likely is that this is a participation or placebo effect. Considerably more evidence is needed before accepting there is a true rationale to support the routine use of low-pressure hyperbaric treatment in order to improve behaviour in children with autism.

While some unexplained biochemical mechanism may have been responsible for the improvements noted, there are a number of other possible interpretations. We observed both before and during the conduct of this study that parents of children with autism were desperately looking for help for their children. The stories of the successful use of HBOT in autism from previous reports were well circulated among these parents and were associated with high expectations for benefit. These parents eagerly searched for any slight improvement in their children. This positive attitude could have had an effect on themselves and how they treated their own child. By this reasoning, the scored responses in the sham air group might be related to their belief that the children were receiving HBOT. Furthermore, most of the participants continued their current therapies while undergoing our trial and the improvement could partly be a result of those interventions. Another possibility is that as a result of our study, these parents spent a significantly longer time than usual with their children on the days of intervention, and had increased opportunities to learn successful strategies both from each other and from the clinicians with whom they came into contact.

Conclusion

Children with autism who received 20 one-hour sessions of either HBOT at 153 kPa or sham air treatment at 116 kPa had significant improvements in overall behaviour. However, hyperbaric oxygen failed to show significant differences in behaviour improvement when compared to sham air. The improvements noted in both groups were not consistent between parents and the clinicians who were asked to evaluate the behaviours. Our study failed to show any clinically significant benefit from HBOT when compared to a sham air confinement in the hyperbaric chamber, and we cannot recommend the routine use of HBOT in this regard. Both interventions were considered safe and well tolerated.

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Conflict of interest

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The database of randomised controlled trials in hyperbaric medicine maintained by Michael Bennett and his colleagues at the Prince of Wales Hospital Diving and Hyperbaric Medicine Unit, Sydney is now at:

<http://hboevidence.unsw.wikispaces.net/>

Assistance from interested physicians in preparing critical appraisals is welcomed. Contact Assoc. Prof. Michael Bennett: <M.Bennett@unsw.edu.au>