Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial

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Summary

Background The use of hyperbaric oxygen for children with cerebral palsy has spread worldwide, despite little scientific evidence of efficacy. We did a randomised trial to assess the efficacy and side-effects of this form of therapy in children with cerebral palsy.

Methods 111 children with cerebral palsy aged 3–12 years were randomly assigned hyperbaric oxygen (n=57) or slightly pressurised room air (n=54). All children received 40 treatments over 2 months. Hyperbaric oxygen treatment was 1 h in 100% oxygen at 1·75 atmospheres absolute (ATA); children on slightly pressurised air received air at 1·3 ATA (the lowest pressure at which pressure can be felt, thereby ensuring the maintenance of masking). The main outcome measure was gross motor function. Secondary outcomes included performance in activities of daily living, attention, working memory, and speech.

Findings For all outcomes, both groups improved over the course of the study, but without any difference between the two treatments. The score on the global gross motor function measure increased by 3·0% in the children on slightly pressurised air and 2·9% in those on hyperbaric oxygen. The mean difference between treatments was −0·40 (95% CI −1·69 to 0·90, p=0·544). Other changes were seen in speech, attention, memory, and functional skills. Ear problems occurred in 27 children treated by hyperbaric oxygen and in 15 treated with hyperbaric air (p=0·004).

Interpretation In this study, hyperbaric oxygen did not improve the condition of children with cerebral palsy compared with slightly pressurised air. The improvement seen in both groups for all dimensions tested deserves further consideration.

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Introduction

Cerebral palsy is a collection of diverse syndromes characterised by disorders of movement and posture caused by a non-progressive injury to the immature brain.[1–3] There is no known cure. Hyperbaric oxygen[4] has been used by several centres in the USA, UK, and Canada to treat children with cerebral palsy. The rationale for this intervention is increased oxygenation of the cerebral ischaemic penumbra.[5–7] Reports of successful treatment[8,9] have circulated among the families of children with cerebral palsy who have asked for this treatment despite the lack of scientific evidence of efficacy and possible side-effects.[10]

After a pilot study,[11] we did a double-blind randomised clinical trial to assess the efficacy and safety of hyperbaric oxygen for children with cerebral palsy. The primary objective was to determine whether 40 treatments could improve gross motor function and to verify whether any improvement persisted for 3 months after the end of the intervention. Secondary objectives included assessment of the effects on performance in activities of daily living, attention, working memory, and speech and language.

Methods

Participants

Children from 17 rehabilitation centres in Quebec, Canada were referred to the study if they had a documented diagnosis of cerebral palsy with a history of hypoxia in the perinatal period, if they were aged 3–12 years, and if they had a motor developmental age between 6 months and 4 years and a psychological development of age 24 months or more. Children with cerebral palsy of postneonatal onset were excluded, as were those with other causes of encephalopathy. Children who had had one recent episode (within 1 month) of acute otitis or those with chronic otitis (three episodes or more within the previous year) were excluded, as were those with any condition that put them at risk of complications of hyperbaric oxygen (asthma, convulsions). Children with behavioural problems or those recently treated with botulinum toxin or orthopaedic surgery (within the past 6 months) or dorsal rhizotomy within the past 2 years were also excluded. Previous exposure to hyperbaric oxygen was also an exclusion criterion. Antispasticity medication or drugs affecting concentration, and physiotherapy were stopped 6 weeks before the trial. The study was accepted by the ethics committees of all five participating centres, and the Provincial Ethics Committee. All parents gave informed consent.

Methods

Children were randomly assigned hyperbaric oxygen or slightly pressurised air. Randomisation was centralised, stratified by centre with blocks of size four or six randomly distributed. Centres received a set of sealed and numbered envelopes corresponding to the computer-generated allocation list.

Hyperbaric oxygen treatment consisted of 100% oxygen at a pressure of 1·75 atmospheres absolute (ATA) for 60 min. Treatments with slightly pressurised air were of the same duration with air at a pressure of 1·3 ATA (the lowest pressure at which pressure can be felt, to keep masking). A complete intervention was 40 sessions: once per day, 5 days per week, for 8 weeks. Procedures were developed to keep parents unaware of the nature of the intervention (covering control panels, masking switches, &c).

Children were assessed at baseline, after 20 and after 40 treatments, and 3 months later. Tests were administered by experienced therapists who were unaware of the treatment given. The same therapist did all the assessments for a given child. Assessments of speech and memory were restricted to children who met pre-determined criteria related to their ability to do the tests (ie, those who could use a computer mouse and who were aged 4 years or more).

The primary outcome was gross motor function as assessed by global changes in the gross motor function measure (GMFM).[12,13] GMFM assesses motor function in five dimensions. Each item is scored on a 4-point scale; the score for each dimension is expressed as a percentage of the maximum score. The global score is the average of the five percentages. Tests to assess speech and language were the Dudley/Delage tests[14] for language, and Bleile[15] and University of Montreal[16] protocols for orofacial structure and function. The Kent protocol[17] was used to assess voice. For all children who could not speak, the Bleile and Miller protocol[18] was used. Visuospatial and verbal working memory were assessed with computerised versions of the Corsi blocks and the pictures and word span tests adapted from the Institut National de la Santé et de la Recherche Médicale.[19] To eliminate learning effects, alternate versions of these tests were used at each assessment.[20] Visual and auditory attention were assessed with the test of variables of attention (TOVA).[21] Four aspects of the attentional and impulse control processes were measured: attention,

impulsiveness, speed of information processing, and attention fluctuation. The paediatric evaluation of disability inventory (PEDI)[22,23] evaluates the functional skill development in children aged 6 months to 7 years, or in older children whose functional abilities are less than those of 7-year-olds.

Statistical analysis

Sample size was calculated to yield 80% power to declare the two groups different (two-sided $\alpha=0\cdot05$) if a true difference of 3% in the GMFM global score (SD=6) existed between the two groups. Assuming a drop-out rate of 10%, the number needed for the study was 70 in each group. Data analysis was based on an intention-to-treat approach. Groups were compared by analysis of covariance. Initial models included baseline score, age, and developmental age as well as interaction terms between treatment and each cofactor. When distribution did not satisfy the parametric assumptions, non-parametric tests (Wilcoxon's) were used. Subgroup analyses were planned to study the effect by age and severity. The analyses were done with SAS version 6.12.

Results

The figure shows that 58 children were excluded because they did not conform to inclusion criteria and 27 did not participate because of the intense schedule of the intervention or family difficulties. 111 children were randomised into two groups (54 air and 57 oxygen). Four children withdrew during the course of the study (one because of side-effects), and one child received 32 treatments instead of 40. Characteristics of the children are shown in table 1.
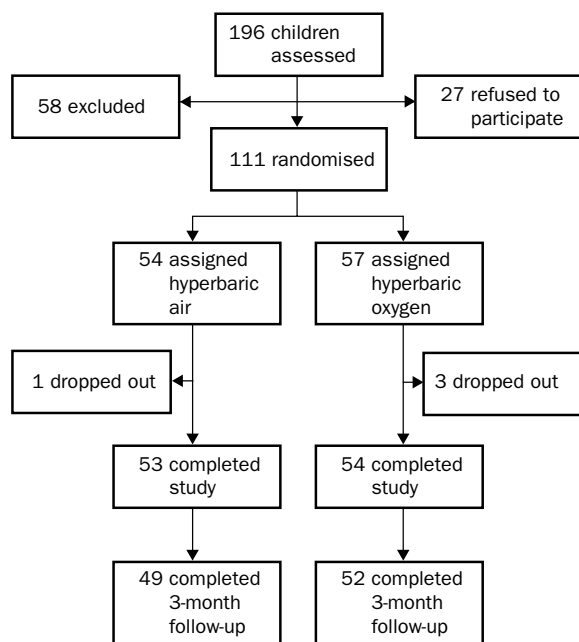
Trial profile

	Hyperbaric oxygen group (n=57)	Slightly pressurised air group (n=54)
Demographics		
Mean (SD) age (years)	7·2 (2·6)	7·2 (2·6)
Mean (SD) developmental age (months)	21·0 (18)	21·9 (16)
Mean (SD) birthweight (g)	1865 (943)	1901 (898)
Sex		
Male	30 (52·6%)	22 (40·7%)
Female	27 (47·4%)	32 (59·3%)
Problems at birth		
Child		
Low birthweight	31 (54·4%)	30 (55·6%)
Prematurity	43 (75·4%)	39 (72·2%)
Convulsions	6 (10·5%)	6 (11·1%)
Respiratory distress	33 (57·9%)	31 (57·4%)
Cerebral haemorrhage	6 (10·5%)	11 (20·4%)
Infection	4 (7·0%)	6 (11·1%)
Other	12 (21·1%)	14 (25·9%)
Mother		
Gestational diabetes	7 (12·3%)	2 (3·7%)
Placenta praevia	2 (3·5%)	0
Placenta abruptio	8 (14·0%)	4 (7·4%)
Bleeding	4 (7·0%)	4 (7·4%)
Pre-eclampsia/eclampsia	4 (7·0%)	2 (3·7%)
Multiple birth	4 (7·0%)	8 (14·8%)
Other	19 (33·3%)	11 (20·4%)
Medical history		
Abdominal problems	2 (3·5%)	2 (3·7%)
Disorders of eyes, respiratory system, or nose	20 (35·1%)	18 (33·3%)
Convulsions	4 (7·0%)	7 (13·0%)
Asthma	6 (10·5%)	10 (18·5%)
Surgery	28 (49·1%)	18 (33·3%)
Type of cerebral palsy		
Spastic diplegia	24 (43·9%)	24 (44·4%)
Spastic quadriplegia	23 (40·4%)	15 (27·8%)
Spastic double hemiplegia	7 (12·3%)	12 (22·3%)
Spastic hemiplegia	1 (1·8%)	1 (1·9%)
Hypotonia	1 (1·8%)	2 (3·7%)

Table 1: **Baseline characteristics**

Dimensions	Group	Mean (SD) baseline score	Post-intervention Mean difference* (95% CI)		p†	3-month follow-up Mean difference* (95% CI)		p†
			Within groups	Between groups‡		Within groups	Between groups‡	
A	Hyperbaric oxygen	88·4 (13·1)	1·9 (0·4–3·3)	−1·5 (−3·3 to 0·4)	0·113	2·4 (0·7–4·2)	−0·6 (2·6 to 1·5)	0·564
	Hyperbaric air	91·1 (11·2)	2·6 (1·0–4·2)			2·3 (0·4–4·3)		
B	Hyperbaric oxygen	72·8 (31·0)	3·9 (1·3–6·4)	−0·4 (−3·6 to 2·8)	0·811	3·3 (1·2–5·5)	−0·6 (−3·3 to 2·1)	0·658
	Hyperbaric air	81·1 (28·9)	3·2 (1·0–5·5)			3·2 (1·3–5·1)		
C	Hyperbaric oxygen	58·3 (39·8)	3·9 (2·0–5·7)	0·7 (−1·7 to 3·0)	0·565	5·0 (2·2–7·8)	2·9 (−0·4 to 6·2)	0·082
	Hyperbaric air	72·0 (36·2)	2·6 (1·1–4·1)			1·6 (−0·1 to 3·3)		
D	Hyperbaric oxygen	38·1 (36·5)	3·3 (1·6–5·1)	0·7 (−1·8 to 3·2)	0·564	4·2 (2·0–6·4)	0·6 (−2·3 to 3·5)	0·685
	Hyperbaric air	51·6 (34·9)	2·8 (1·1–4·5)			3·8 (2·0–5·6)		
E	Hyperbaric oxygen	28·8 (33·6)	1·5 (0·3–2·7)	−2·0 (−3·7 to −0·4)	0·018	1·8 (0·5–3·2)	−2·6 (−4·9 to −0·4)	0·023
	Hyperbaric air	35·6 (30·4)	3·7 (2·5–5·0)			4·7 (2·9–6·6)		
Global	Hyperbaric oxygen	57·3 (28·5)	2·9 (1·9–3·9)	−0·4 (−1·7 to 0·9)	0·544	3·4 (2·2–4·5)	0·0 (−1·5 to 1·5)	0·966
	Hyperbaric air	66·3 (26·1)	3·0 (2·1–3·9)			3·1 (2·2–4·1)		

A=lying and rolling; B=sitting; C=crawling and kneeling; D=standing; E=walking, running, jumping. *Positive score means improvement in motor function over time (scores are the mean difference from baseline). †For difference between groups. ‡ANCOVA model controlling for baseline values.

Table 2: **Between-group comparison for changes over time in gross motor function**

Table 2 shows that GMFM improved in both groups without any trend of difference in favour of either group and that changes persisted 3 months after the intervention. All the analyses were adjusted for baseline score because of the initial differences between groups. Subgroup analyses showed that in both groups, the greatest changes occurred in children who had relatively low scores at baseline: in those who had an initial GMFM score of less than 40, the mean changes were 3·2 and 3·9, respectively (oxygen vs air); when the initial score was between 40 and 70, the changes were 3·7 and 4·1 (oxygen vs air); whereas in more mobile children (GMFM score >70), mean changes were 2·0 and 2·1, respectively. Another analysis showed that changes were independent of age: in each age category (3–4, 5–7, and >7 years), mean changes in GMFM global score were all between 2·3 and 3·7, without any difference between groups.

Neuropsychological assessment was done in 75 eligible children. Working memory assessment showed that both groups improved over time but that there was no difference between the groups (table 3). Assessment of attention provided similar results. Reaction times in the attention tests did not vary over time.

Speech and language pathology assessment was limited to 73 children eligible to be tested. Table 4 shows that no changes from baseline were seen for the orofacial structure and function tests except for the group on slightly pressurised air, who did better. Language production improved over time without any difference between groups.

PEDI showed that children in both groups were more functional at the end of the study, without any difference between groups (table 5). When the same domains were assessed from the caregiver point of view, significant differences were seen for mobility (p=0·07) and social functioning (p=0·02), in favour of the group treated with air (results not shown).

With regard to safety, in the oxygen-treated group, 27 participants had 42 ear problems, whereas in the air-treated group, 12 had 15 events (p=0·004).

Discussion

This study shows that hyperbaric oxygen treatment in children with cerebral palsy does not produce any improvements greater than those seen in children treated with slightly pressurised air. Improvements were more pronounced in children who had a lower GMFM global score at baseline, and were not related to age. Given the similarity of outcomes in both groups, there is no suggestion that the study lacked power.

The improvements in GMFM scores in both groups are clinically important and in the same range as the changes seen in several studies that assessed the efficacy of intensive physiotherapy.[24,25] Children ceased physiotherapy during the course of this study. The

Tests	Group	Baseline score		Post-intervention Mean difference* (95% CI)		p†	3-month follow-up Mean difference* (95% CI)		p†
		n	Mean (SD)	Within groups	Between groups‡		Within groups	Between groups‡	
Visual span (Corsi)	Hyperbaric oxygen	31	3·03 (2·33)	0·61 (0·09–1·14)	−0·40 (−1·08 to 0·29)	0·25	1·10 (0·40–1·80)	0·05 (−0·91 to 1·0)	0·91
	Hyperbaric air	32	3·22 (2·52)	0·94 (0·35–1·52)			1·03 (0·31–1·78)		
Word span (familiar words)	Hyperbaric oxygen	32	5·19 (2·01)	−0·19 (−0·76 to 0·38)	−0·51 (−1·13 to 0·12)	0·11	0·73 (0·19–1·28)	−0·31 (−1·0 to 0·4)	0·37
	Hyperbaric air	30	5·87 (2·22)	0·10 (−0·39 to 0·59)			0·82 (0·24–1·40)		
Word span (non-familiar words)	Hyperbaric oxygen	28	4·61 (1·57)	−0·04 (−0·64 to 0·57)	−0·13 (−0·97 to 0·70)	0·75	0·15 (−0·53 to 0·84)	−0·62 (−1·3 to 0·07)	0·08
	Hyperbaric air	30	5·50 (2·37)	−0·13 (−0·81 to 0·54)			0·46 (−0·09 to 1·02)		
Visual span (images)	Hyperbaric oxygen	33	2·06 (1·99)	0·70 (0·35–1·05)	−0·19 (−0·81 to 0·44)	0·56	0·56 (0·02–1·10)	−0·39 (−1·21 to 0·41)	0·31
	Hyperbaric air	34	2·74 (2·18)	0·79 (0·27–1·32)			0·75 (0·15–1·35)		
TOVA (auditory)									
Correct responses	Hyperbaric oxygen	32	36·6 (29·0)	7·5 (1·6–13·5)	0·4 (−6·9 to 7·7)	0·91	10·1 (3·9–16·4)	0·3 (−7·9 to 8·5)	0·94
	Hyperbaric air	32	45·9 (28·1)	3·9 (−2·4 to 10·3)			5·8 (−1·8 to 13·5)		
Correct non-responses	Hyperbaric oxygen	32	160·5 (102·1)	44·8 (18·4–71·3)	10·2 (−16·7 to 36·9)	0·45	42·9 (−0·7 to 86·6)	−9·1 (−51·2 to 33·0)	0·67
	Hyperbaric air	32	183·1 (101·8)	24·3 (0·7–48·0)			31·3 (0·0–62·7)		
TOVA (visual)									
Correct responses	Hyperbaric oxygen	33	37·2 (27·4)	3·0 (−2·1 to 8·0)	−1·6 (−7·7 to 4·5)	0·59	5·2 (−1·5 to 11·9)	3·6 (−4·6 to 11·7)	0·38
	Hyperbaric air	32	37·0 (23·9)	5·1 (−0·7 to 10·9)			5·1 (−1·1 to 11·4)		
Correct non-responses	Hyperbaric oxygen	33	178·3 (88·5)	41·0 (17·4–64·5)	3·4 (−14·5 to 21·3)	0·70	53·2 (26·1–80·3)	6·9 (−25·0 to 38·9)	0·67
	Hyperbaric air	32	213·0 (64·5)	16·4 (2·1–35·0)			5·3 (−0·6 to 11·2)		

TOVA=test of variables of attention. *Positive score means improvement over time (scores are the mean difference from baseline). †For difference between groups. ‡ANCOVA model controlling for baseline values, age, and developmental age.

Table 3: **Between-group comparison for changes over time in working memory and attention**

Tests	Group	Baseline score		Post-intervention			3-month follow-up		
		n	Median	Median difference from baseline*	Signed rank test†	Wilcoxon‡	Median difference from baseline*	Signed rank test†	Wilcoxon‡
Orofacial structure and function									
Peripheral oral mechanism	Hyperbaric oxygen	38	20·0	0	p=0·96	p=0·08	0	p=0·79	p=0·59
	Hyperbaric air	35	19·0	2·0	p<0·01		1	p=0·16	
Orofacial gestures									
Non-speech	Hyperbaric oxygen	37	21·0	0	p=0·75	p=0·27	1	p<0·01	p=0·67
	Hyperbaric air	35	21·0	0	p=0·28		1	p=0·10	
Syllables	Hyperbaric oxygen	37	3·0	0	p=0·28	p=0·56	0	p=0·68	p=0·93
	Hyperbaric air	34	3·0	0	p=0·80		0	p=0·61	
Words and sentences	Hyperbaric oxygen	37	4·0	0	p=0·84	p=0·69	0	p=0·5	p=0·49
	Hyperbaric air	35	4·0	0	p=0·99		0	p=0·3	
Voice and prosody	Hyperbaric oxygen	35	6·0	0	p=0·91	p=0·96	0	p=0·89	p=0·84
	Hyperbaric air	33	5·0	0	p=0·77		0	p=0·61	
Language production									
Lexical knowledge	Hyperbaric oxygen	33	32·0	1·5	p<0·01	p=0·90	4	p<0·001	p=0·60
	Hyperbaric air	32	38·0	2·0	p<0·001		6	p<0·001	
Articulation test	Hyperbaric oxygen	37	3·5	0	p=0·35	p=0·35	0	p=0·83	p=0·44
	Hyperbaric air	34	2·0	0	p=0·06		0	p=0·24	
Length and complexity of sentence	Hyperbaric oxygen	33	7·3	0·6	p=0·04	p=0·91	NA	NA	NA
	Hyperbaric air	31	7·6	0·4	p<0·01		NA	NA	
Verbal fluidity	Hyperbaric oxygen	33	2·3	0·14	p=0·88	p=0·28	NA	NA	NA
	Hyperbaric air	32	2·0	0·19	p=0·19		NA	NA	
Prelinguistic stage	Hyperbaric oxygen	33	5·0	0	p=1·00	p=0·34	0	p=1·00	p=0·33
	Hyperbaric air	35	5·0	0	p=1·00		0	p=0·25	

NA=not available. *Positive score means improvement over time except syllables, words and sentences, and articulation test. †Non-parametric test for within-group changes from baseline assessment. ‡Non-parametric test for between-group comparison.

Table 4: **Between-group comparison for speech and language (non-parametric tests)**

improvement seen in all other outcomes is also striking. We conclude that participation in the trial had a clinically important effect on development in the children.

A possible explanation is that the two treatments are equally effective—ie, that air at 1·3 ATA is sufficient to produce an effect equivalent to oxygen at 1·75 ATA. This hypothesis is difficult to sustain because the increase in alveolar partial pressure of oxygen (PaO_2) at 1·75 ATA and 100% oxygen is substantially higher than the increase at 1·3 ATA air: 1233 versus 148 mm Hg. Before the trial, the increase in PaO_2 with air at 1·3 ATA was regarded as not sufficient to produce any clinical effect. If there is an effect of an increase in PaO_2 of 148 mm Hg, hyperbaric treatment would not be necessary, because the same PaO_2 can be obtained by giving 28% oxygen with a mask, without pressure. The possibility of an effect of 1·3 ATA that would not be due to increased PaO_2 (a pure pressure effect) is not supported by any data and does not correspond to the rationale behind the hyperbaric oxygen treatment, which is based on the penumbra phenomenon.[5–7]

A learning effect to explain the improvement with time is possible, but not likely, for GMFM and PEDI because the performances being assessed corresponded to common motor activities. For the neuropsychological assessments, the learning effect was kept to a minimum by use of alternate versions of the memory tests at each assessment. In our study, the assessors were unaware of the nature of the intervention and did not have access to the previous scores when assessing the children.

Therefore, information bias is unlikely to explain these results. Another possible hypothesis to explain the results is the participation effect. The interventions had several unusual characteristics: the parents were particularly motivated and supported in their hope by anectodal reports. The context of the intervention was a source of positive communication with other children and with parents. Such an environment has been reported to accelerate intellectual, emotional, and social development.[26]

This trial shows that hyperbaric oxygen treatment has no advantages over treatment with slightly pressurised air in children with cerebral palsy. The global improvements seen in both treatments during the course of the study might be related to the context of the intervention and the selection of very motivated parents. A possible effect of increased pressure cannot be ruled out because of the slight increase in PaO_2; nevertheless, the same increase in blood oxygen can be reached by simple mask administration of 28% fractional inspiration oxygen without increased pressure—a treatment that needs to be assessed before it can be recommended.

Scales	Group	Baseline score		Post-intervention			3-month follow-up		
		n	Mean (SD)	Mean difference* (95% CI)		p†	Mean difference* (95% CI)		p†
				Within groups	Between groups‡		Within groups	Between groups‡	
Self care	Hyperbaric oxygen	56	57·6 (13·8)	2·8 (1·6–4·0)	0·1 (−1·8 to 2·0)	0·92	4·6 (2·4–6·8)	−0·9 (−3·8 to 2·0)	0·55
	Hyperbaric air	54	60·3 (13·0)	2·7 (1·3–4·0)			5·1 (3·1–7·1)		
Mobility	Hyperbaric oxygen	55	46·7 (22·2)	2·9 (1·3–4·5)	1·1 (−1·5 to 3·6)	0·41	4·0 (2·1–6·9)	0·7 (−2·0 to 3·5)	0·59
	Hyperbaric air	54	53·0 (19·2)	1·8 (−0·1 to 3·8)			2·9 (0·9–5·0)		
Social function	Hyperbaric oxygen	56	63·4 (12·0)	3·0 (0·7–5·3)	−0·5 (−3·5 to 2·4)	0·72	4·0 (1·7–6·2)	0·2 (−3·4 to 3·4)	0·93
	Hyperbaric air	54	65·5 (12·7)	3·0 (0·9–5·1)			3·0 (−0·2 to 6·2)		

*Positive score means improvement in motor function over time (scores are the mean difference from baseline). †For difference between groups. ‡ANCOVA model controlling for baseline values, age, and developmental age.

Table 5: **Paediatric evaluation of disability inventory (PEDI)**

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