Side effects of hyperbaric oxygen therapy in children with cerebral palsy.

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Muller-Bolla M, Collet J-P, Ducruet T, Robinson A. Side effects of hyperbaric oxygen therapy in children with cerebral palsy. Undersea Hyperb Med 2006; 33(4):237-244. Background - This article reports the side effects observed in a double-blind placebo-controlled multi-center randomized clinical trial carried out to assess the efficacy and safety of hyperbaric oxygen (HBO_2) therapy in children with cerebral palsy. Intention-to-treat analysis did not prove to have a beneficial effect. Material and methods - 111 children aged 3 to 12 years were included and followed for 8 weeks. They all received 40 compressions of 1 hour (5 days per week). In the treated group (n=57), HBO_2 sessions consisted of an exposure to 100% oxygen at 1.75 atmosphere absolute (atm abs) while children in the control group (n=54) received air at 1.3 atm abs. A physician carried out a general health surveillance including an ear examination prior to and immediately following each session. All clinical events occurring during the course of the study were recorded. Findings – Events were classified in 3 categories: Events related to pressure/volume changes, events related to oxygen toxicity, and other events. No events due to oxygen toxicity were noted. Only middle ear barotrauma significantly differed according to the groups (50% in HBO_2 session group versus 27.8% in control group). Other events were rare and equivalent in both groups. Conclusion – Short-term exposure to HBO_2 at medium level pressure (1.75 atm abs) was responsible for a significant increase of middle ear barotrauma compared to children that received very low external pressure (1.3 atm abs).

INTRODUCTION

Safety of hyperbaric oxygen (HBO_2) therapy has been the object of multiple reports showing that side effects are related to both high pressure (source of barotrauma i.e. compression manifestations and decompression illness) and oxygen toxicity. These side effects have often been reported in adults (1-3) though HBO_2 therapy is indicated to treat many conditions in children (4-8). Recently HBO_2 therapy has been used frequently in children with cerebral palsy (CP) in centers in the USA, UK and Canada (9). Even if Collet et al. proved no benefit in this particular case, safety of HBO_2 therapy in this population thus becomes an issue to inform both physicians and parents. This article reports the side effects observed during the systematic follow-up of 111 children who participated in a double-blind placebo-controlled multi-center randomized clinical trial (RCT) carried out to assess the efficacy and safety of HBO_2 sessions in children with CP (10).

MATERIAL AND METHODS

Study population

111 children with cerebral palsy aged 3 to 12 years (mean age ± SD: 7.2 ± 2.6 years) participated in the study. They all met criteria for inclusion (detailed description in the original manuscript), without any concomitant or recently administered co-interventions (10). Exclusion criteria included conditions associated with an increased risk of complications such as a recent episode of acute (within 1 month) or chronic (3 episodes or more within the last year) otitis, acute or chronic sinusitis, active asthma, convulsions

(within last year) or cataract. Children were randomly assigned to HBO_2 (n=57) or placebo (n=54) groups.

Treatment

Mono-place (10 children) or multi-place chambers (101 children) were used depending on the five study centers[1]. HBO_2 sessions consisted of an exposure to 100% oxygen at 1.75 atmosphere absolute (atm abs) while children in the control group received air at 1.3 atm abs (slightly pressurized air). This trivial compression was designed to maintain blinding to allocation by ensuring all children experienced the need to equalize middle ear pressure on compression. HBO_2 sessions were standardized and consisted of the 3 following phases: compression, treatment and decompression, which lasted 10, 60 and 10 minutes, respectively. Oxygen was delivered via a hood in the multi-place chambers. A complete intervention consisted of 40 sessions over a 2-month period: one session per day, 5 days per week for 8 weeks.

All children underwent a complete physical examination before the study with a special focus on the ears and respiratory system. This included lung auscultation, and ear and sinus examinations. Three children underwent prophylactic myringotomy based on standard indications just before the 40 sessions of HBO_2 or slightly pressurized air (10). During the trial, a physician carried out the same medical examinations as above prior to and immediately after each session. All health events occurring during the course of the study corresponded to the outcomes. They were recorded on a special form to describe the events, their severity and the likehood of a possible relationship with the HBO_2 sessions. These events could occur during a particular session or in between sessions. An event of ear pain was noted when this caused the session to be stopped. Middle ear barotrauma (MEBT) was diagnosed with or without ear pain when medical examination noticed the presence of a tympanic membrane with an inflammatory aspect, fluid extravasations into the middle ear space, blood vessel rupture or ultimately tympanic membrane perforation (11). We did not consider ear pain alone as a barotrauma if there was no clinical sign on examination by otoscopy. Sinus barotrauma was diagnosed when both sinus pain and fluid accumulation or inflammation of the mucosa of one or more paranasal sinuses were observed. All events were ranged using a three-category classification: events related to pressure/volume change (barotrauma), events due to oxygen toxicity and other events.

Statistical analysis

The focus of this report was a description of adverse events experienced by the children in the trial. Data analysis was based on an intention-to-treat approach: all children included are reported in the results. Chi-square test or exact test was used to compare children with at least one event in each treatment group and the corresponding relative risks were calculated. These comparisons were conducted first according to the type of events and secondly using the three categories of events. Student's t-test was used to compare means. Finally, multivariate models (logistic regression) were used to identify predictors of middle ear complications such as gender, age, gross motor function measure (GMFM)(12) and developmental age at baseline. Level of statistical significance was set at 0.05 (type 1 error) and analyses were done with SAS version 6.12.

RESULTS

One hundred-and-eleven children were included in the study: their characteristics at baseline are presented in Table 1(see pg. 240). Four withdrew during the course of the study. Three withdrawals were due to parental decision

because of personal difficulties or family factors: one in the control group and two in the HBO_2 session group. One child in the HBO_2 session group had to leave the study because of repeated MEBT. This child completed 32 instead of 40 sessions.

Children with at least one adverse event during the 40 sessions are presented by group in Table 2(see pg. 241). The risk of MEBT was significantly higher in the HBO_2 session group (RR 1.5, 95% CI 1.1 to 2.2, p=0.02). The 43 affected children (Table 2) were treated by myringotomies with tubes in 58.2% of the cases (19 children in HBO_2 session group versus 6 in control group). The occurrence of MEBT did not significantly differ according to the children's characteristics at baseline in univariate analyses. The multivariate adjusted model did not find any factor associated to the risk of ear barotrauma (Table 3, see pg. 242); however global GMFM at baseline and gender, although not significant, are positively associated with MEBT. Children with and without MEBT had similar changes in GMFM: 3.3 ± 3.9 versus 2.7 ± 3.0 ($p = 0.22$).

Sinus barotrauma concerned 3.6% of the children in the HBO_2 session group. When children with at least one event related to pressure/volume changes were pooled in only one category of adverse events the difference approached significance (RR 1, 95% CI 0.9 to 2.1, p=0.07).

DISCUSSION

HBO_2 sessions were generally well tolerated in the RCT conditions. However, as anticipated from the literature (13-17), events related to the elevation of chamber pressure, i.e. barotrauma, were observed. Nevertheless, only occurrence of MEBT was significantly higher in the HBO_2 session group (50% of children) than in the control group (27.8%) (Table 2) and the only child who withdrew for medical reasons suffered from MEBT. The incidence of MEBT in the children in our study was higher than in adults from other studies (1-3, 11, 18) (2 to 30%); even though they had been instructed in the Valsalva technique and an adult was in the chamber to help them if necessary. The incidence may be due to a difference in anatomic structure (small Eustachian tubes in children) and the fact that children are unable to auto-inflate the middle ear (11, 19). These two characteristics may also explain the high rate (27.8%) in children exposed to minimal air pressure (1.3 atm abs). However, most of the cases occurred only once as described by Tibbles and Edelsberg (11). Because some exclusion criteria (recent episode of otitis) eliminated children who had a higher risk of events related to pressure/volume change, it is very likely that the incidence of MEBT would have been higher in both groups if selection had not been applied. On the contrary, prophylactic myringotomies were rarely performed before treatment (5.4% in HBO_2 session group and 1.9% in control group) to prevent adverse events (Table 2). Thus our results are difficult to compare with other pediatric series in which 25% of the children have had prophylactic myringotomies (6). The low level of preventive measures associated with a systematic examination of every child before and after the session may explain the high incidence of ear barotrauma in our study, which contrasts with lower incidence or even zero incidence of MEBT reported in a retrospective study (4). Our study gives an exact figure of MEBT in children exposed to 1.3 and 1.75 atm abs; and the change in rate from 27.8% to 50% is in favor of a pressure-effect relationship. It could be much higher in children exposed to 3 atm abs (100% oxygen) accepted by a large international scientific community of hyperbaric clinicians for 120 minutes (2). Indeed, the external validity of our study must be considered, as children with CP may have greater difficulties in equalizing

Table 1 Baseline characteristics of children in each group

	HBO_2 group n=57		Control group n=54	
	Mean	SD	Mean	SD
Age (years)	7.2	2.6	7.2	2.6
Developmental age (months)	21.0	18.0	21.9	16.0
Birth weight (g)	1865.0	943.0	1901.0	898.0
GMFM global	57.3	28.5	66.3	26.1
	n	%	n	%
Sex				
Male	30	52.6	22	40.7
Female	27	47.4	32	59.3
Problems at birth				
Child				
Low birth weight	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 haemorrage	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	0.0
Placenta abruption	8	14.0	4	7.4
Bleeding	4	7.0	4	7.4
(Pre)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
Eyes, respiratory, nose disorders	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

HBO_2 = Hyperbaric oxygen. GMFM = Gross motor function measure

Table 2. Children with at least one event in each group

Events reported	Number of events		Number of children with at least one event	
	HBO_2 n	Control n	HBO_2 n (%)	Control n (%)
Middle ear barotrauma[1a*]	30	16	28 (50.0)	15 (27.8)
Myringotomy without barotrauma[1b]	3	0	3 (5.4)	0
Pharyngitis[2]	17	8	16 (28.6)	8 (14.8)
Ear pain[1a]	11	9	8 (14.3)	7 (13.0)
Otitis[2]	4	4	4 (7.1)	4 (7.4)
Fever[2]	4	3	3 (5.4)	3 (5.6)
Dyspepsia[2]	1	4	1 (1.8)	4 (7.4)
Myringotomy tube problems[1b]	3	1	3 (5.4)	1 (1.9)
Vomiting[2]	2	3	2 (3.6)	2 (3.7)
Agitation[2]	2	1	2 (3.6)	1 (1.9
Laryngitis[2]	2	1	2 (3.6)	1 (1.9)
Sinusitis[2]	2	1	2 (3.6)	1 (1.9)
Asthma[2]	1	1	1	1 (1.9)
Sinus barotrauma[1a]	3	0	2 (3.6)	0
Latex contact dermatitis[2]	1	1	1 (1.8)	1 (1.9)
Viral infection[2]	1	1	1 (1.8)	1 (1.9)
Insomnia[2]	2	0	2 (3.6)	0
Nausea[2]	0	2	0	2 (3.7)
Scarlet fever[2]	1	1	1 (1.8)	1 (1.9)
Mouth ulceration[2]	1	1	1 (1.8)	1 (1.9)
Urticaria[2]	1	1	1 (1.8)	1
Tooth barotrauma[1a]	0	2	0	1 (1.9)
Bronchitis[2]	1	0	1 (1.8)	0
Cough[2]	1	0	1 (1.8)	0
Conjunctivitis[2]	0	1	0	1 (1.9)
Herpes simplex[2]	0	1	0	1 (1.9)
Accidental injury (home)[2]	0	1	0	1 (1.9)
Rhinitis[2]	1	0	1 (1.8)	0

1a Side effects related to pressure/volume change: (p=0.1) RR was 1 (95% CI: 0.9-2.1)
1a*: (p=0.02) RR was 1.5 (95% CI:1.1-2.2)
1b Other events related to pressure/volume change
[2] Other events HBO_2 = Hyperbaric oxygen

Table 3. Children with at least one event of middle ear barotrauma according to their characteristics at baseline

		Middle ear barotrauma					
		Children with ≥ 1event		No events			
		n	%	n	%	p^a	p^b
Gender						0.13	0.11
	Male	24	46.2	28	53.9		
	Female	19	32.2	40	67.8		
Age (years)						0.72	0.73
	3-4	10	34.5	19	65.5		
	5-7	19	43.2	25	56.8		
	>7	14	36.8	24	63.2		
GMFM Global (baseline)						0.28	0.19
	< 40	16	48.5	17	51.5		
	40-70	11	40.7	16	59.3		
	> 70	16	31.4	35	68.6		
		m	SD	m	SD	p^a	p^b
Developmental age (months)		20.7	17.7	21.9	15.8	0.71	0.60

Logistic regression: [a] univariate analysis. [b] multivariate model adjusted for the variables
GMFM = Gross motor function measure

pressure in the ears (8, 20). Table 3 did not allow us to determine the subject who should be offered a prophylactic myringotomy because baseline characteristics of children with at least one event of middle ear barotrauma or none did not differ significantly from those who did not. Although not significant, the children with MEBT had a tendency to have a lower GMFM global score and developmental age at baseline than children without an event (Table3).

The second most common side effect related to pressure/volume changes was ear pain and not sinus barotrauma (Table 2) as indicated by Beuerlein et al. (18). The exclusion of children with a recent history of acute or chronic sinusitis could explain these results, i.e. only 3.6% in the HBO_2 therapy group, because the sinus squeeze is encountered especially when congestion is present (13, 16). It usually occurs in patients with allergic rhinitis or upper respiratory tract infections, which is a contra-indication to HBO_2 therapy (6, 21). Bleeding from the nose (7) was observed in two of these children.

Tooth barotrauma has been only rarely reported (17, 18) and our results confirm that this form of barotrauma is uncommon, with only one case observed (in control group).The child was probably affected by pulpitis where rapid pressure changes increase inflammation-related tooth pain. No neurological or pulmonary manifestations of oxygen toxicity were noted. This could be explained by the exclusion criteria that eliminated all children who had a health condition that could increase the risk of events due to oxygen toxicity. Lack of power because of small sample size is another issue. Finally, in our study we used low oxygen pressure (1.75 atm abs) compared to the pressures of 2.0 (20) or 2.8 atm abs (18) that were reported to be dangerous for the central nervous system (CNS). Two studies in children reported one case of CNS oxygen toxicity when exposed to higher pressures for longer exposure times (4, 6).

We did not observe any case of pulmonary toxicity in our study. However pulmonary symptoms have been reported after daily exposures to oxygen at 2.0 or 2.4 atm abs for 2.0 or 1.5 hours, respectively (22). Duration of exposure could be an important factor as mentioned by Nuthall (23) who showed pulmonary oxygen toxicity was due to prolonged exposure to low pressure such as

0.5 atm abs. Pulmonary manifestations seem more frequent than CNS symptoms in children: bronchospasm and hypoxemia were described in 35% and 6% of children respectively (6). Montgomery et al. reported shortly after HBO_2 therapy in children with CP (24), one case of severe respiratory distress and one case of acute respiratory failure (1.75 atm abs, 120 minutes and 1.5 atm abs, 90 minutes respectively). In all these cases, pulmonary oxygen toxicity was completely reversible (6, 24).

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The etiology of visual changes is debatable; it could be related to either direct oxygen toxicity on the lens (17) or more general "ocular effects" without any relation to oxygen toxicity (18). However, visual changes have never been noted in children (25) and were not observed in our study. Table 2 shows that the incidence of 'others events' was similar in both groups. Except for two cases of contact dermatitis related to latex allergy, the other events are more difficult to explain. They corresponded to general features usually associated to confinement anxiety (18) in children including nausea, vomiting and anxiety (14). This would explain why the rates are similar in each group.

CONCLUSION

Our study shows that exposure to low hyperbaric pressure (1.75 atm abs) is associated with minor signs of barotrauma compared to very low (1.3 atm abs) exposure. All other side effects due to change of pressure, oxygen toxicity or confinement anxiety were rare and similar in both groups.

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