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Hyperbaric Oxygenation Therapy in the Treatment of Cerebral Palsy: A Review and Comparison to Currently Accepted Therapies

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ABSTRACT

Hyperbaric oxygenation therapy (HBOT) has shown promise in clinical trials and is sought by many parents of children with cerebral palsy (CP). There is unusual resistance to expanding the indications for this modality, which is the only treatment available for certain conditions, such as decompression sickness and air embolism, and which is effective in a number of others related to wound healing. A recent study that showed notable improvements in children with CP treated with slightly pressurized air, as well as those treated with a standard protocol for HBOT, is invoked to deny effectiveness of HBOT. Political and economic considerations, rather than purely scientific ones, play an important role in this controversy. Further systematic research is needed, but in the meantime children should not be denied access to HBOT.

Hyperbaric oxygenation therapy (HBOT) in the treatment of certain conditions (for example: decompression accidents, gas gangrene, burns) is supported by substantial clinical literature. Some other conditions (for example: skin or tissue grafts, specific cases of anemia) are also on the accepted indication list but with scant support from formal clinical trials. Its use in some conditions has proved ineffective, and in others, especially neurologic, it has been very controversial.

In 1994 Harch reported the first North American case of HBOT in a child with cerebral palsy (CP).¹ Around the year 2000, some researchers² affirmed that, following HBOT, some patients with CP experienced improvement in motor function, and decreased muscle spasms. Controversy soon developed in the newspapers. Political factors have impeded further research and the adoption of new clinical applications.³⁻⁸

What is HBOT?

In 1999 the drug definition of HBOT was refined and restated as the use of oxygen at greater than atmospheric pressure as a drug to treat basic pathophysiologic processes and the associated diseases.⁹ Under normal atmospheric pressure at sea level—760 mm Hg, 1 atmosphere absolute or 1 ATA—hemoglobin in the blood is already 97% saturated with oxygen, with very little capacity for increasing oxygen transport.¹⁰ Oxygen is also dissolved directly in the plasma in a more bioavailable form. According to Henry's Law, the absorption of a gas is directly related to the partial pressure of the gas. About 17 times as much oxygen can be carried in the plasma when the patient breathes 100% oxygen at a pressure of 3 ATA, compared with breathing room air at sea level (see Table 1). The added pressure can also reduce blood flow to the damaged areas, and hence reducing edema, without compromising oxygenation.¹¹

The pressure must be applied to the entire body. This is accomplished either in a single-person chamber, usually pressurized with 100% oxygen, or a multi-place chamber, which is pressurized with air while patients breathe oxygen through a mask or hood. Multi-place chambers have a reduced fire hazard, but there is some variability in the concentration of oxygen actually inhaled because of leakage around the mask. This is less true with the use of a hood.

In Canada, in the public system, there are fewer than a dozen hyperbaric chambers available to treat various medical conditions.

Risks of HBOT

HBOT, particularly at pressures lower than 1.75 ATA, involves little risk of any major complications. In fact, the risks of HBOT are minimal when technicians obey safety regulations and follow a specific protocol. They include rare decompression accidents.

Adverse effects of HBOT on the human body include barotrauma most commonly involving the middle ear, sinuses, or dental restorations. This is reported to occur in 2% of patients.¹² Most patients are able to prevent ear barotrauma by using simple self-inflation techniques. Reversible myopia may occur during high-pressure treatments. Some patients do not tolerate confinement in a small enclosed space.

There are only few absolute contraindications to HBOT (pneumothorax, and treatment with adriamycin, vincristine, and similar drugs). Conditions such as respiratory infection, chronic sinusitis, epilepsy, optic neuritis, certain lung diseases, and claustrophobia must be carefully evaluated before treatment is authorized.¹³ Significant adverse effects are very uncommon: see Table 2.

Rationale for HBOT in CP

CP is most often caused by an ischemic/hypoxic injury during the perinatal period. While hypoxia may cause cell death, there may sometimes be a zone called the "ischemic penumbra," in which brain cells receive just enough oxygen to survive, but not enough to function normally. Since that discovery, many have asked the question: to what extent can HBOT reactivate damaged neurons?

It is generally admitted that the cells to which the blood flow is dramatically reduced for 10 minutes or so (less than 10 ml of blood per 100 g of brain tissue per minute)¹⁵ undergo necrosis and form the core of a lesion. With less severe hypoxia, some researchers believe that cells can survive for a long time in an "idling" state, and might be reactivated if blood flow is restored. Those who observed a decrease in spasticity and functional improvements with HBOT hypothesized that neurons might be viable but inactive much longer than previously believed.^{16,17}

Table 1. Quantity of Oxygen Dissolved in the Blood Owing to Pressure³⁷

Pressure	Percentage of O ₂ inhaled	Quantity of O ₂ (in ml) dissolved in 100 ml of blood
1 ATA	21% (normal air)	0.32
1 ATA	100%	1.7
2 ATA	100%	3.7
3 ATA	100%	5.6

Table 2. Type and Occurrence of Complications and Side Effects of HBOT in 782 Patients¹⁴

Complications	Occurrences	Comments
Problem in equalizing pressure in the middle ear	1: 5.7 patients, 1: 52.7 exposures	In most cases, this complication occurs only once per patient.
Barotrauma in the middle ear	1: 26.1 patients	No effects noted.
Ruptures of the eardrum	1: 260.7 patients	Affects only patients who present sensory deficits in their auditory system.
Use of tubes in the ears	1: 65.2 patients	
Barotrauma of the sinuses	1: 86.9 patients	
Claustrophobic anxiety	1: 23 patients	Varied symptoms.
Toxicity of oxygen in the central nervous system	1: 195.5 patients, 1: 2,844 treatments	The literature assesses the risk at between 1:10,000 patients and 1:20,000 treatments.
Effects on vision	Unverified	In contradiction with the literature.
Toxicity of oxygen or barotraumas of the lungs/or the inner ear	No occurrences	
Treatments interrupted following complications	1: 55.9 patients	
Treatments interrupted following complications due to claustrophobic disturbances	1: 78.2 patients	
Total of treatments interrupted	1: 290.0 patients	

Depending on the pressure used during treatment and on the speed of compression, the rate of incidence may vary greatly. Mean number of treatments per patient: 11.4.

Table 3. Studies of HBOT in Children with Cerebral Palsy

Author	Place	No. of subjects	No. of treatments	Conclusion
Machado (1989) ¹⁶	Sao Paulo, Brazil	230	20	Decrease in spasticity in 95% of the cases. 6 months post-treatments: improvement in cognitive functioning or in level of spasticity among 75.6% of the children.
Cordoba-Cabeza (1998) ³⁸	Las Tunas, Cuba	14	20	A satisfactory response was observed among patients treated in the first year following the lesion, with more significant and more rapidly obtained results.
Montgomery et al. (1999) ⁷	Montreal, Canada	25	20	The results show an increase in gross motor functions in 3 of the 5 items of the Gross Motor Function Measure (GMFM), an increase in fine motor functions, and a decrease in spasticity.
Barrett (1999) ³⁹	University of Texas at Galveston, Texas, USA	14	60	Hyperbaric oxygen therapy produced increases in the assessment of gross and fine motor functions, and decreased spasticity among patients with cerebral palsy.
Packard (2000) ⁴⁰	Cornell University, USA	26	40	Among some children with moderate to severe cerebral palsy, there is evidence that HBOT improves motor skills, attention, language, and play. For some children, an improvement in vision was noted. While the treatment is not curative nor miraculous, the changes are often substantial.
Collet et al. (2001) ³⁴	Montreal, Canada	111 (1 group tested at 1.3 ATA and 21% O ₂ and 1 group tested at 1.75 ATA and 100% O ₂)	40	The two participating groups improved substantially (with no difference between the two groups) with respect to gross motor functions, language, attention, memory, and functional abilities. The authors hypothesized that either the two treatments were equally effective, or the simple fact of participating in research that allowed communication with other children had a positive effect.
Waalkes et al. (2002) ⁴¹	U.S Army	8	80	The assessments compared pre- and post-treatments using several functional measures. HBOT demonstrated an increase in gross motor functions and a decrease in total time of necessary care for the children with cerebral palsy.
Sethi and Mukherjee (2003) ³²	New-Delhi, India	30 (15: HBOT + occupational therapy 15: occupational therapy alone)	40	Rate of progress in gross motor functions of the test group (<i>HBOT + occupational therapy</i>) is much more rapid than that of the control group (<i>occupational therapy alone</i>).
Marois and Vanasse. (2006) ⁴³	Montreal, Canada	118	40	Significant increases in the GMFM of 3.96% for the entire group of subjects.
Mukherjee (2006) ³¹	New-Delhi, India	84	40	Rate of progress in gross motor functions of the test group (<i>HBOT + therapy</i>) is much more rapid than in the control group (<i>therapy only</i>).

Other mechanisms have also been suggested to explain the sometimes astonishing improvements described both by researchers and by the parents of children submitted to HBOT. Increased oxygenation is known to enhance neovascularization in wounds, burns, and other types of lesions; perhaps the same could occur in cerebral lesions. Additionally, increased oxygen might improve the metabolism and function of the remaining normal cells.¹⁸ It has been shown that low-pressure hyperbaric oxygen therapy (LPHBOT) can induce cerebrovascular changes and improve cognitive function in a rat traumatic brain injury (TBI) model.¹⁹

One recent addition to the neovascularization and metabolic hypotheses involves stem cells. One study conducted at the University of Pennsylvania School of Medicine²⁰ demonstrated that HBOT can cause up to an 8-fold increase in the quantity of stem cells circulating in the human body.

Many researchers have demonstrated, using cerebral single photon emission computerized tomography (SPECT scans), increased vascular activity in the brain following treatments in a hyperbaric chamber.²¹⁻²³

Empirical Results with HBOT in CP

The first pilot study was conducted by Montgomery et al.² and showed that 25 patients with CP presented a significant increase in their gross motor functions (5.3%) and fine motor functions, along with a decrease in spasticity, following 20 sessions of HBOT (95% oxygen at 1.75 ATA for 60 minutes). The video exams of the children before and after HBOT were blindly evaluated and the post-HBOT exams were picked as the better exam about 65% of the time. Later studies also demonstrated positive results: see Table 3.

Collet et al. conducted a study²⁴ intended to fill in the gaps of the study by Montgomery et al. Collet et al. studied 111 children: The "study" group of 57 received 40 sessions of HBOT with 100% oxygen at 1.75 ATA. The "control" group of 54 received air at 1.3 ATA, also in a hyperbaric chamber. Both groups had 60-minute sessions 5 days a week for 8 weeks. Of the 111 children, 107 completed the treatment series, and 101 had a 3-month follow-up.

Gross motor function was assessed using the GMFM (Gross Motor Functional Measure),²⁵ a standardized tool that is considered the most reliable and objective way to measure gross motor function in children. The children stopped all other interventions while they underwent HBOT, so the improvement in GMFM occurred in

Table 4. Comparison of Changes in Gross Motor Functional Measurement (GMFM) Observed among Children with Cerebral Palsy According to the Type of Intervention.

Study	Type of intervention	N	Age (years)	Changes	Rate of progress
Montgomery et al. (1999) ²	HBOT	25	5.6 ± 1.6	4.9/1 mo	4.9/mo
Collet et al. (2001) ²⁴	HBOT	57	7.2 ± 2.6	2.9/2 mo	1.45/mo
	HBA (hyperbaric air)	54	7.2 ± 2.6	3.0/2 mo	1.5/mo
Marois and Vanasse (2006) ⁴³	HBOT	118	6.28	3.96/3.9 mo	1.01/mo
Russell et al. (1989) ⁴⁵	Intensive PT	88	4.9	3.7/6 mo	.61/mo
Trahan et al. (1999) ⁴⁶	Intensive PT	50	3.7 ± 1.6	5.7/8 mo	.71/mo
Hays et al. (1998) ⁴⁷	Dorsal rhizotomy ± PT	92	7.5 ± 3.98	5.2 ± 1.8/1 y	.43/mo
Nordmark et al. (2000) ²⁵	Dorsal rhizotomy ± PT	18	2.5 - 6	9.6/1 y	.8/mo
Wright et al. (1998) ⁴⁸	Dorsal rhizotomy ± PT	24	4.8 ± 1.1	11.8/1 y	.98/mo
McLaughlin et al. (1994) ⁴⁹	Dorsal rhizotomy ± PT	34	7.6 ± 3.65	9.6 ± 6.9/1 y	.8/mo
Steinbok, Reiner and Kestle (1997) ⁵⁰	Dorsal rhizotomy ± PT	30	4.1	11.3/9 mo	1.25/mo
McLaughlin et al. (1998) ⁵¹	Dorsal rhizotomy ± PT	43	6.45 ± 3.6	7.2/2 y	.3/mo
Damiano and Abel (1998) ⁵²	Strength Training	11	8.8 ± 2.3	1.1/1.5 mo	.74/mo
Steinbok, Reiner and Kestle (1997) ⁵⁰	Electrical stimulation	44	7.3	5.9/1 y	.49/mo
Almeida et al. (1997) ⁵³	Intrathecal baclofen	1	11	6.4/2 y	.26/mo
Law et al. (1997) ⁵⁴	Family Centered Functional Therapy	5	Under 4	17.7 /3 mo (Goal area only)*	--
McGibbon et al. (1998) ⁵⁵	Equine therapy	5	9.6	7.4 /2 mo (E only)*	--
Knox and Evans (2002) ⁵⁶	PT (Bobath)	15	7.4±2.8	2.24/3 mo	.75/mo
Tsorlakis, Evaggelidou, Grouios and Tsorbatzoudis (2004) ⁵⁷	PT (NDT)	34	7.3±3.6	2.63/4 mo	.66/mo
Sterba, Rogers, France and Vokes (2002) ⁵⁸	Equine therapy	17	9.10±0.10	0	0/mo

* Law et al. and McGibbon et al. considered only part of the GMFM, the goal area or one of the five dimensions, the E group (running and jumping), respectively. Most children evaluated on the E group have already achieved nearly 100% on other functions. The degree of improvement on the entire GMFM would probably have been only 20% as great as the reported numerical results suggest.

the absence of other therapies. Both groups, receiving two different dosages of hyperbaric treatments, improved very significantly following the interventions. The progress persisted after 3 months. During the 2 months of treatment the rate of progress was 15 times faster than during the 3 months follow-up when all usual therapies were reintroduced. No significant differences were noted between the two groups. Scores improved by 2.9 units in the HBOT group and 3.0 in the pressurized air (“control”) group, $P = .544$. Other assessments included performance in daily activities, attention, memory, and language. Both groups improved significantly in these areas, with no significant difference between them.

The researchers postulated that either the two treatments were equally effective or that the mere act of participating in a trial that promoted communication with other motivated children and parents had a positive effect.

Discussion

The introduction of the Internet has brought scientific and medical information to the lay public. While this situation prevents significant discoveries from going unnoticed or from being pushed aside by overly conservative scientists, there is also the risk of rendering too popular those treatments for which the proof of effectiveness is clearly insufficient. Not all readers possess the scientific background necessary to evaluate studies properly. All they feel they need to know is that “it works” in certain cases. Thus,

with increasing frequency, patients bring their doctor material that questions their previous prescription or suggests the use of a new approach.²⁶ This tendency might become widespread if the creators of a new approach follow the example of drug companies and launch “awareness” (marketing) campaigns aimed directly at their consumers (direct-to-consumer advertising), as proposed by Wicker in 2001.²⁷

The criteria for acceptable proof of effectiveness of HBOT are inconsistent. For example, the use of HBOT was accepted by the Undersea and Hyperbaric Medical Society in 1996²⁸ for treating intracranial abscesses on the basis of only 19 cases (13 cases in Germany and six in the United States). On the other hand, HBOT for CP has not yet been recognized by the UHMS despite the publication or the presentation in international meetings of more than 650 positive cases.

Broadening the applications of HBOT since the 1980s in the absence of the unequivocal demonstration of a pathophysiologic mechanism, in cases of neurological problems among others, has led to HBOT being labeled as “alternative” or “experimental.” Proponents of “evidence-based medicine” have been reticent about acknowledging new indications.

The 10 studies on the treatment of CP with HBOT presented in Table 3, even though some have a small number of participants, have all demonstrated significant and often impressive improvements compared with what is seen from the majority of known and accepted therapeutic approaches for this condition. In fact,

depending on the age and the severity of the condition of children with CP, the rate of progress (see Table 4) measured with the GMFM can be up to five times higher than the one obtained with intensive physiotherapy (PT) or even after rhizotomy followed by intensive PT. So far, no recognized approaches in the treatment of CP have shown faster or more impressive positive changes in gross motor function. Moreover, most recognized approaches like PT or rhizotomy do not improve cognition or communication. HBOT has an effect on global function of the brain and, besides the very important changes in motor function, the most common improvements reported by more than 80% of the parents are in cognition and language.

Lack of rigor in certain research, such as weaknesses in the selection of patients and/or nonstandard protocols, is responsible for the lack of acknowledgement of HBOT, according to Locklear.²⁹ However, if this argument were the only reason for the neglect of or opposition to HBOT, how could one explain that several approaches (e.g. botulinum toxin) used with the same population, and which had not been the subject of double-blind research, are nonetheless widely accepted and have been paid for by the health care systems in Canada for more than 10 years?

Although the study was designed in a way meant to minimize possible criticism, the significant results of Collet et al. have been interpreted in such a way that they refuel the debate instead of contributing to its resolution, even among the authors of this study.

The funding organization, the Fonds de Recherche en Santé du Québec (FRSQ), minimized the fact that significant improvement in the state of the participants did indeed take place and attempted to make everyone believe that the treatment at 1.3 ATA was simply a placebo. This misinformation has since been repeated several times.⁴⁶ We know that pressurized air at 1.3 ATA increases the plasma oxygen concentration by more than 30%. This effect, delivered by a "Gamow bag," saves lives endangered by "mountain sickness" during high-altitude trips every year.³⁰ The study by Collet et al. has measured and documented the substantial effect of a small increase in pressure, even without supplemental oxygen.

Disagreement among researchers is a common occurrence in the scientific world. However, in this case, it appears that Collet and the FRSQ⁴⁶ wanted to save their hypothesis instead of submitting to the verdict established by the facts. Indeed, when the results proved positive for the two groups, whereas quite obviously one expected either insignificant results or a significant difference between the two groups, Collet and the FRSQ preferred to minimize the results of HBOT, instead of acknowledging an effect of the air treatment at 1.3 ATA.

Controversy about the study began even before publication. The editor requested that there should not be any reference to the treatment of the control group as "inert" or "placebo" rather, it should be called precisely what it was: slightly pressurized air. Following publication, a disagreement among the authors of this study with regard to the "official" interpretation of the results spread to several scientific journals. The "official" conclusion was that HBOT was ineffective for CP, without considering the improvements, which were indeed noteworthy, and even impressive, for both groups.³¹

Misinformation about this research reached its peak when, following its publication in the *Lancet*, an official communiqué published by FRSQ in 2001 changed the title and the conclusion. The title of the published paper was: "Hyperbaric Oxygen for Children with Cerebral Palsy: A Randomised Multicentre Trial," but in the communiqué the FRSQ entitled it: "No Advantage of High-Pressure Oxygen for Treating Children with Cerebral Palsy." Despite the significant results reported in the study, the communiqué stated: "hyperbaric oxygen therapy produces no therapeutic effect in children with cerebral palsy."⁴ This

communiqué gave rise to anger and indignation among many researchers as well as among the families who participated in the research and who had noted significant progress in their children.

More recently, the U.S. Agency for Healthcare Research and Quality (AHRQ) concluded that the presence of pressurized air during the research might have had a beneficial effect on motor functions. It stated: "The results of the only truly randomized trial were difficult to interpret because of the use of pressurized room air in the control group. As both groups improved, the benefit of pressurized air and of HBOT at 1.3 to 1.5 atm should both be examined in future studies.... The authors of the trial thought that the children in both groups improved because participation in the study provided an opportunity for more stimulating interaction with their parents.... This is speculative, however, because there was no evidence to suggest that the parents and their children had less time together, or less stimulating interaction, before the study began.... The possibility that pressurized room air had a beneficial effect on motor function should be considered the leading explanation."³²

Despite controversy about the results, the study of Collet et al. paved the way for further research in HBOT for CP. The question about what did produce the improvements in participants demands an answer. It would certainly be beneficial to repeat the study, this time with one group with pressurized 100% oxygen, one group with pressurized air at 1.3 ATA, one group at 27% of O₂ at 1 ATA, and one group with unpressurized air, the last serving as the true control group. Those results might even demonstrate that HBOT as defined by the UHMS in 2006³³ (100% O₂ at a minimum of 1.4 ATA) is not necessary for treating children with CP if an attenuated treatment, slightly pressurized air (21% O₂ at 1.3 ATA) or even 27% O₂ at 1 ATA, can do the job.

Until very recently, the Quebecois Government's position was not very favorable toward any additional research on the effects of this treatment on children with CP. Adopting that position, it aligned itself with the position adopted by Health Canada in 2006, which recognizes the effectiveness of HBOT in the treatment of certain conditions but formally challenges its effectiveness for CP, by stating: "right now, nothing has demonstrated the usefulness of this treatment."³⁴

Nevertheless, a law enacted in March 2005 authorizes the Department of Revenue of Quebec to grant tax credits to Quebecois families to treat children with CP with HBOT.³⁵ Moreover, in May 2006, the Department of Health of Quebec entrusted to the Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) the mandate to examine the effectiveness of HBOT in CP.³⁶ The AETMIS report concluded there was enough evidence to recommend further investigation on the effect of HBOT in CP.

A number of questions need to be addressed, including the effect of participation in an organized trial; the optimal or minimum necessary pressure and oxygen concentration; and the number and frequency of treatments needed to produce a maximal result.

Conclusions

Previous studies of HBOT in CP have shown noteworthy favorable results, but to produce conclusive evidence, additional, more systematic trials are needed.

Much is at stake. Improvement in the function, independence, and comfort of persons with a severely disabling neurologic condition could lead to significant improvements in health and quality of life as well as to significant cost savings in the long term. While other treatment modalities are paid for by government programs, parents must bear the cost of HBOT as the controversies continue.

In the meantime, given the very low risk of adverse effects and the promising results, children should be allowed access to HBOT.

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