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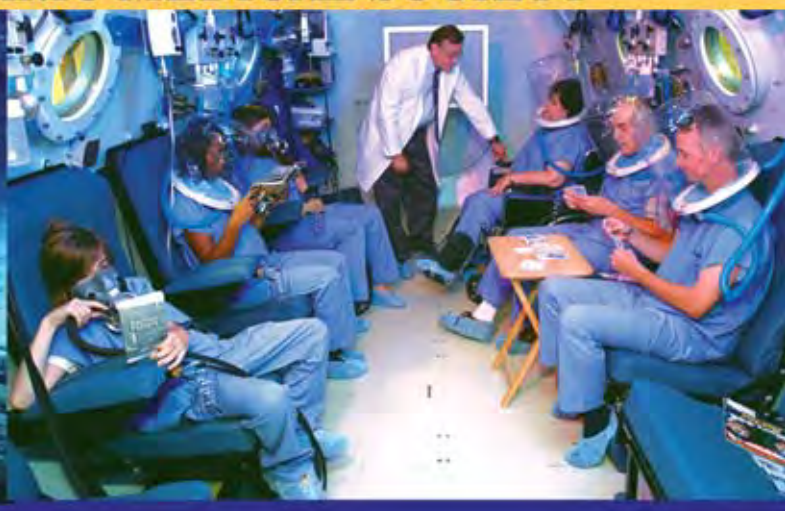

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How and why hyperbaric oxygen therapy can bring new hope for children suffering from cerebral palsy – *An editorial perspective*

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Cerebral palsy (CP) is generally considered a non-progressive condition resulting from neurological injury in the antenatal or perinatal period. The increased survival rates of premature infants due to advances in neonatal intensive care has led to increased incidence of CP, which is now higher than three in 1,000 births. Perinatal hypoxic-ischemic (HI) events resulting in cellular necrosis, neuronal inactivation and cerebral white matter injury are the most common causes of severe neurological handicaps in children with CP.

The challenge

Physiologically, hypoxic-ischemic brain injury could be defined as acute oxygen and nutrient deprivation to the brain caused by faulty cerebral circulation, resulting in cellular bioenergetics failure and neurological dysfunction. As in stroke, traumatic brain injury (TBI) and age-related metabolic brain disorders, there is no effective treatment/metabolic intervention in routine clinical practice for children with CP. Intensive therapy and rehabilitation programs are valuable tools for improving the quality of life for these unfortunate children, but they offer, at best, only partial relief.

New results

In this current issue of *UHM*, Mukherjee *et al.* present convincing evidence that hyperbaric oxygen (HBO_2) therapy in combination with standard intensive rehabilitation (SIR) could be the coveted neurotherapeutic method for children suffering from neurological dysfunctions due to CP [1]. The idea that HBO_2 therapy can provide a valuable brain repair tool for CP is not new and has been investigated in several earlier clinical trials, but the results were conflicting [2-6]. What makes the current findings persuasive is the methodical, multifaceted comparison: The short-term and long-term outcomes of SIR in conjunction with normal air (21% oxygen) HBO_2 sessions at 1.3 atmospheres absolute (atm abs) were compared with those of SIR in conjunction with:

(a) 100% oxygen HBO_2 sessions at 1.5 atm abs and
(b) 100% oxygen HBO_2 sessions at 1.75 atm abs.

For long-term follow-up, patients were evaluated two and eight months after the beginning of treatment. Interestingly, significant long-term beneficial effects were observed for all combined treatments, including the case of normal oxygen at 1.3 atm abs, compared to SIR alone.

A call for consensus

While the findings support the idea that "low-dose" HBO_2 can provide new hope for children with cerebral palsy, additional, larger-scale clinical studies are needed to further confirm the findings and determine the most effective and personalized treatment protocols. Furthermore, before initiating future clinical trials, some issues associated with the optimal practice of HBO_2 therapy for children with CP should be explored:

- proper sham control;
- the optimal dose-response curve (oxygen and pressure levels);
- the optimal treatment duration/number of HBO_2 sessions; and
- the proper selection criteria of the study cohort.

Further below we reflect on the optimal HBO_2 therapy practice in light of the recent findings by Mukherjee *et al.* – of new understanding of the brain damage

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associated with CP and of new understanding regarding the neurotherapeutic effects of hyperbaric oxygen. We hope that our reflections will ignite in-depth discussions within the hyperbaric medicine community, to help reach consensus on whether, why and how HBO_2 therapy can give hope to children with cerebral palsy.

Underlying repair mechanisms

It is now understood that the recently observed restoration of neuronal activity in the metabolically dysfunctional stunned areas following HBO_2 treatments is accomplished via an assortment of intricate mechanisms. The combined action of hyperoxia and hyperbaric pressure leads to significant improvement in tissue oxygenation and affects both oxygen-sensitive and pressure-sensitive genes. HBO_2 therapy can initiate vascular repair and improve cerebral vascular flow, induce regeneration of axonal white matter, stimulate axonal growth, promote blood-brain barrier integrity, and reduce inflammatory reactions as well as brain edema [7-12].

At the cellular level, HBO_2 can improve cellular metabolism, reduce apoptosis, alleviate oxidative stress and increase levels of neurotrophins and nitric oxide through enhancement of mitochondrial function in both neurons and glial cells, and may even promote neurogenesis of endogenous neural stem cells [7-13]. It is important to note that, as in stroke and TBI, the hypoxic-ischemic conditions following cerebral palsy engender depolarization of the mitochondria membrane and induction of mPTP (mitochondrial permeability transition pore), which reduces the efficiency of energy production and elevates the level of reactive oxygen species (ROS).

Tissue oxygenation via HBO_2 can inhibit mPTP and thus has the potential to reverse this abnormality [8]. However, it must be applied carefully to ensure that the increased tissue oxygen does not cause cellular toxicity due to overly high ROS levels.

The control group dilemma

There are inherent ethical and logistic difficulties in handling the sham-control in HBO_2 therapy trials. The standard requirement for proper sham-control is: *"Medically ineffectual treatment for medical conditions intended to deceive the recipient from knowing which treatment is given."*

Hyperbaric oxygen therapy includes two active ingredients: pressure and oxygen. The pressure is being utilized for increasing plasma oxygen, but the pressure change by itself may have significant effects on the cellular level. The pressure effect may be of greater significance in human tissues that are under tight autoregulation pressure control, such as the brain and kidneys [14-18]. The intracranial pressure, the pressure within the skull and thus in the brain tissue and cerebrospinal fluid (CSF), is normally 0.0092-0.0197 atm (7–15 mm Hg). Any increase in cranial pressure may have a significant effect on neurons, glial cells and the function of endothelial cells [14,15, 18].

A classical example that highlights the significance of small changes in pressure is acute mountain sickness (AMS) and high-altitude cerebral edema (HACE). In AMS and HACE, even a small increase in ambient air pressure – less than a sixth of an atmosphere – may reverse the pathology [19]. Put together, the observations imply that any increase in pressure, even with reduced oxygen percentage, cannot serve as a placebo since it exerts at least one of the two active ingredients of HBO_2 therapy.

Elevated pressure with low oxygen can be an effectual treatment

To generate the sensation of pressure, the chamber pressure must be 1.3 atm abs or higher. However, breathing normal air, even at 1.3 atm abs, cannot serve as a proper sham-control since it is not an *"ineffectual treatment,"* as required by the placebo definition; it leads to significant physiological effects resulting from the elevated pressure and the tissue oxygenation. Therefore, as we discuss below, such doses should be regarded as a dose-comparison study, as was correctly done by Mukherjee *et al.*, who demonstrated that it is effective in the treatment of children with CP [1]. Other clinical trials also found that patients treated with low oxygen showed improvements similar to patients treated with higher dosages [2,4,20,21]. However, in those trials, the low-dose treatments were mistakenly regarded as sham-control, leading to incorrect conclusions. In studies 4, 20 and 22, room (21% oxygen) air at 1.3 atm abs was used as a sham-control to test the HBO_2 effect on CP and patients with mild TBI (mTBI) treated with 100% oxygen at 2.4 atm abs. Another study used lower-than-normal (14% oxygen) air at 1.5 atm abs to test the effect of hyperbaric

oxygen on children with cerebral palsy who were treated with 100% air at 1.5 atm abs [2]. In all of those studies, the treated group and the low-oxygen group, which the authors mistakenly considered to be sham-control, show similar improvements [2,4, 20,21]. Consequently, the authors in both studies concluded that the observed improvements were merely placebo effects and therefore that HBO_2 therapy had no neurotherapeutic effects on mTBI and CP.

Their conclusions are clearly challenged by the findings of Mukherjee *et al.* published in this volume and by recent clinical trials testing the effect of HBO_2 on post-stroke and mTBI patients [1,23,24]. Changes in brain activity that were assessed by SPECT imaging, as described next, further support this understanding [23,24].

HBO_2 therapy can activate neuroplasticity and revitalize brain functions: New trials provide convincing evidence that hyperbaric oxygen can induce neuroplasticity, leading to repair of chronically impaired brain functions and improved quality of life in post-stroke and mTBI patients with prolonged post-concusssion syndrome, even years after the brain insult [23,24].

These trials adopted the crossover approach in order to overcome the inherent sham-control constraints of HBO_2 therapy. In this approach, the participants are randomly divided into two groups. One, the trial group, receives two months of HBO_2 treatment while the other, the control group, goes without treatment during that time. The latter are then given the same treatment two months later. The advantage of the crossover approach is the option for a triple comparison:

- between treatments of two groups,
- between treatment and non-treatment periods of the same group, and
- between treatment and non-treatment periods in different groups.

The study endpoint included blinded detailed computerized clinical evaluations that were blindly compared for all patients, with single-photon emission computed tomography (SPECT) scans. HBO_2 sessions led to similar significant improvements in tests of cognitive function and quality of life in both groups. No significant improvements occurred by the end of the non-treatment period in the control group. What made the results particularly persuasive was that the results of SPECT imaging were well correlated with clinical improvements and revealed restored activity mostly in metabolically dysfunctional stunned areas. Those observations indicate hyperbaric oxygen as a potent means of delivering to the brain sufficient oxygen to activate neuroplasticty and restore impaired functions that are accomplished via an assortment of intricate mechanisms, some of which were mentioned earlier.

Rethinking the HBO_2 dose-response curve

The aforementioned recent trials provide convincing evidence that HBO_2 can repair brain damage in post-stroke and mTBI patients. These results, and in particular the remarkable agreement between clinical improvements and SPECT imaging, imply that the observed improvements following HBO_2 therapy in the earlier studies on mTBI patients and children with CP were due to the neurotherapeutic effect of hyperbaric oxygen rather than being a placebo effect.

By the same token, the observed improvements following either normal air at 1.3 atm abs (on patients with mTBI) or 14% air at 1.5 atm abs (on children with CP) imply that HBO_2 sessions can have significant neurotherapeutic effects even at low dosage, provided there is pressure elevation. Therefore, as we mentioned earlier, such doses should be considered as dose-comparison studies rather than sham-control, as was correctly done by Mukherjee *et al.*, who demonstrated normal air at 1.3 atm abs to be an effective treatment for children with CP rather than a placebo effect [1]. These results are also in agreement with the earlier findings by Collet *et al.* [4] that were perceived as puzzling for more than a decade. Yet, as stated by Collet *et al.* (Collet *et al.* 2001): *"The improvement seen in both groups for all dimensions tested deserves further consideration."* The results by Mukherjee *et al.* clearly responded to this suggestion by considering room air at 1.3 atm abs as dose-comparison. Their findings could have been even more persuasive had they included metabolic imaging as part of their evaluations. Since they did not, this issue should be further addressed in future studies.

Clearly, large-scale, well-controlled, pressure dose-response studies are required to determine the optimal HBO_2 therapy protocol for different conditions. Until such information is available, any treatment involving change in the environmental pressure should be considered as a dose-comparison rather than a sham-control study. Moreover, since at a young age, brain protection is stronger (reflected by high ROS levels associated with CP) and neuroplasticity is more potent, it is reasonable to expect that optimal efficacy will be achieved by lower

tissue oxygenation. Along such line of reasoning, the previously described trials used 2.0 atm abs for post-stroke patients and 1.5 atm abs for patient with mTBI with an intact macrovascular bed [23,24]. Due to the high diversity in the manifestation of cerebral palsy and in its severity, future efforts should also be directed towards a personalized dose-response curve. For example, it is likely that higher tissue oxygenation will be the practice of choice for children with a high expression of ApoE4, which is an inhibitor of mitochondrial respiration.

Treatment duration and monitoring protocols:

Treatment duration is another elusive issue that needs to be resolved by future studies. It is quite clear that weeks to months would be necessary for brain tissue r egeneration and angiogenesis, but the upper time limit from which no further improvements are expected remains unknown. The first clinical evaluation (not metabolic/physiological evaluation) should be done after a sufficient number of HBO_2 sessions and should expect sizable changes. One must bear in mind that children with CP suffer neurological deficiency since birth, so it will take time for the brain repair to become clinically apparent. For example, it is not reasonable to administer 20 daily HBO_2 sessions to children with pervasive developmental disorders (PDD) and expect to see significant clinical progress within a time frame of less than a month [25].

On the other hand, it is important to perform frequent metabolic/physiological evaluations, which may provide valuable information for adjusting the dose-response curve. More studies are needed to determine the minimal effective dosage and the treatment duration for specific brain injuries. Non-invasive, in-chamber measurements that are currently being developed, specifically EEG and DTI, may shed some light on this important question.

It is also crucial to perform long-term post-treatment evaluation, as done by Mukherjee *et al.*, who performed evaluations after two and eight months [1]. Especially, when children are concerned, one expects that HBO_2 therapy will ignite the brain's innate repair system so that improvements will continue long after the treatment. As Mukherjee *et al.* have found, different doses may generate similar short-term improvements but can lead to different long-term post-treatment effects. In other words, dose-response curves should be assessed based on long-term effects. Clearly, there is an urgent need for larger-scale, prospective studies with long-term follow-up.

Optimal candidates for HBO_2 therapy

Brain insults may result in a variety of brain injuries. The most severe is necrosis, which cannot be reversed. However, as was mentioned earlier, necrotic foci are often surrounded by metabolically dysfunctional, stunned areas, which manifest as regions of high anatomy-physiology mismatch. Current imaging technologies reveal that the stunned brain areas may persist for months and years after an acute brain event [24, 26-28] and this is where metabolic intervention can be most effective [23,24]. For this reason, the optimal candidate for hyperbaric oxygen is a patient with unrecovered brain injury where tissue hypoxia is the limiting factor for the regeneration processes. In this patient, HBO2 may induce neuroplasticity in the stunned regions where there is a brain anatomy/physiology (e.g., SPECT/CT) mismatch [23, 24]. Unfortunately, in many – if not most – clinical studies done with hyperbaric oxygen on brain-injured patients, including those with cerebral palsy, the stunned areas have not been assessed by imaging. The anatomical/physiological imaging should be incorporated as an essential part of the basic evaluation of every candidate for hyperbaric oxygen therapy. In a similar manner, transcutaneous oximetry at the ulcer bed serves as a basic evaluation for patients suffering from peripheral non-healing wounds [29,30}.

An urgent call

In conclusion, we call on the hyperbaric community to rethink the neurotherapeutic effects of HBO_2 therapy and to agree on common and scientifically sound guidelines to best conduct prospective, controlled HBO_2 clinical trials. Reaching a consensus on the way to handle the control group, dose *vs.* efficacy, selection criteria of the study cohort and duration of treatment will pave the way for future studies that will explore the full potential of neurotherapeutic HBO_2.

We envision future studies that will demonstrate the effectiveness of HBO_2 therspy for a wide spectrum of syndromes that currently have partial or no solutions, such as central sensitization (fibromyalgia), radiation damage, vascular dementia and other metabolic aging effects.

The authors report that no conflict of interest exists with this submission.

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Intensive rehabilitation combined with HBO_2 therapy in children with cerebral palsy: A controlled longitudinal study

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ABSTRACT

Objective: The present study aimed to assess the effect of intensive rehabilitation combined with hyperbaric oxygen (HBO_2) therapy on gross motor function in children with cerebral palsy (CP).

Methods: We carried out an open, observational, platform-independent study in 150 children with cerebral palsy with follow-up over eight months to compare the effects of standard intensive rehabilitation only (control group $n = 20$) to standard intensive rehabilitation combined with one of three different hyperbaric treatments. The three hyperbaric treatments used were:

- air ($FiO_2 = 21\%$) pressurized to 1.3 atmospheres absolute/atm abs ($n = 40$);
- 100% oxygen pressurized at 1.5 atm abs ($n = 32$); and
- 100% oxygen, pressurized at 1.75 atm abs ($n = 58$).

Each subject assigned to a hyperbaric arm was treated one hour per day, six days per week during seven weeks (40 sessions). Gross motor function measure (GMFM) was evaluated before the treatments and at two, four, six and eight months after beginning the treatments.

Results: All four groups showed improvements over the course of the treatments in the follow-up evaluations ($p < 0.001$). However, GMFM improvement in the three hyperbaric groups was significantly superior to the GMFM improvement in the control group ($p < 0.001$). There was no significant difference between the three hyperbaric groups.

Conclusion: The eight-month-long benefits we have observed with combined treatments *vs.* rehabilitation can only have been due to a beneficial effect of hyperbaric treatment.

INTRODUCTION

Cerebral palsy (CP) is due to a lesion of the developing brain, characterized by inadequate muscle tone and control, often associated with other types of neurodevelopmental delay involving cognitive, communication and psychosocial skills. Treatments are mainly focused on exploiting residual cerebral function, and intensive rehabilitation is recognized to have demonstrated its efficacy in achieving better function and autonomy, thus creating a better quality of life [1].

The leading causes for cerebral palsy stem from a critical reduction of oxygen (O_2) delivery to a part of the developing brain in the perinatal period [2]. The site of the brain lesion can be localized with cerebral blood flow measurements using brain single-photon emission computerized tomography (SPECT) [3,4] because impaired brain cell nutrition and oxygen delivery are related to inadequate blood flow. While hypoxia may cause neuronal death, there is a well-known phenomenon called the "ischemic penumbra," which defines a volume of tissue surrounding a zone of infarction where cells receive enough oxygen to survive in an "idling state," but not enough to function normally [5]. It has been suggested that these neurons might be viable much longer than previously believed [6,7,8], and this is where regenerative medicine is trying to play a role. Hyperbaric oxygen (HBO_2) treatment has shown reproducible benefits for more than two decades in hundreds of

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children with CP around the world [9]. Using high-quality SPECT imagery, several studies of children with CP and of adults after a stroke have shown that HBO_2 therapy may regenerate or revive cells in the ischemic penumbra in the brain [7,10,11]. This increased vascular activity would allow the reactivation of "idling" neurons [6,10,11, 12], as HBO_2 therapy is known to increase neovascularization in wound healing. The higher tissue oxygen levels provided by HBO_2 therapy might also favor better metabolism and function of unaffected cells [13,14].

To date, despite several reports of benefit, the use of HBO_2 therapy for CP has met opposition, which has even polarized the field of clinical HBO_2 therapy [15-18]. The first pilot study [19] reported the positive effects of HBO_2 therapy on 25 carefully selected children with the form of CP known as spastic diplegia. The improvements were measured both on gross and fine motor function. Based on the results of this pilot study, a double-blind randomized multicenter trial (n = 111) of HBO_2 therapy for children with CP was conducted by Collet *et al.* [20]. This study included only two groups of children: one treated at 1.75 atmospheres absolute (atm abs) with 100% O_2, while the other breathed air at 1.3 atm abs. Some involved in the statistical analysis of the results regarded the use of compressed air at 1.3 atm abs to be an inactive placebo, although this was opposed by the clinicians.

The controversy required the appointment of an independent adjudicator by the *Lancet*, who agreed that such a change in pressure and increase in the level of oxygen could not be referred to as a "sham" treatment. In fact, exposure to 1.3 atm abs increases the arterial plasma oxygen concentration (PaO_2) by nearly 50% [21]. It was little recognized at the time that blood flow in the physiological range of oxygen concentrations is controlled by the interaction between nitric oxide and hemoglobin [22]. Changes in oxygen levels also regulate genes involved in angiogenesis and neutrophil activity in inflammation [23]. As the best dosage of oxygen for the treatment of children with CP is not known, a sham control group should have been included to ensure an adequate experimental design. The controversy was highlighted by an editorial comment entitled "Hype or hope" published in the same issue of the *Lancet* journal [24].

After the courses of treatment, the improvements on gross motor function were impressive and equivalent in both groups. Improvements in language and neuropsychological functions were also recorded in both treatment groups. There are two ways of interpreting the results: either the two treatments were equally effective, or the improvements were all caused by a "participation effect." Based on the major improvements reported, the latter interpretation is inappropriate [25] but has, unfortunately, been promoted as evidence that hyperbaric treatment is ineffective in CP children [26] restricting further research on the subject. The aim of this present study is to answer the questions raised by the study by Collet *et al.* [20] by assessing the effect of different dosages of hyperbaric treatment combined with intensive rehabilitation on motor function in children with CP.

METHODS

Participants

A total of 150 children with CP were selected for the study among those attending rehabilitation at the Foundation for Spastic and Mentally Handicapped Persons-UDAAN (FSMHP-UDAAN) center in Delhi, India. All participants had to meet the following inclusion criteria: children up to teen age of either sex with all types of CP, any cognitive and motor development level.

Children were excluded if there were other developmental or genetic disorders, uncontrolled epilepsy or asthma, as well as ear, nose or throat disorders. Forty percent of all of our participants had minor to moderate epilepsy due to their injured brain. Half of them were significant enough to be on antiepileptic medication. It was the parents' decision to include their children in the HBO_2 therapy groups. Participants who were not assigned to HBO_2 therapy groups were assigned to the control group. All participants were engaged in the same intensive rehabilitation program at FSMHP-UDAAN. Only the children who did not default on at least six months of standard therapies were assessed. Quality, magnitude and type of care were uniform across all four groups. Participants' characteristics are described in Table 1. The study was approved by the ethics committee of Apollo Hospital, Delhi, and the parents' informed voluntary written consent was required after medical clearance.

Treatments

The study covers a 10-year span of treatments during which the three different dosages of hyperbaric oxygen were used. The different dosages were not implemented at the same time, and the children were offered the HBO_2 therapy available at the time of their inclusion in the protocol, which means that no selection bias occurred in the choice of dosage.

Table 1: Participants' characteristics

Groups	Diagnostics	Gender (M/F)	Age (yrs) Mean (range)	GMFM baseline score Mean (SD)
Control (*n*=20)	Athetoid CP, *n*=2 Hemiplegic CP, *n*=2 Diplegic CP, *n*=4 Quadriplegic CP, *n*=12	13/7	3.5 (1 to 17)	29.6 (13.0)
1.3 atm abs (*n*=40)	Athetoid CP, *n*=3 Hemiplegic CP, *n*=0 Diplegic CP, *n*=16 Quadriplegic CP, *n*=12	29/11	4.9 (1 to 11)	29.6 (14.8)
1.5 atm abs (*n*=32)	Athetoid CP, *n*=3 Hemiplegic CP, *n*=1 Diplegic CP, *n*=15 Quadriplegic CP, *n*=13	23/9	4.3 (1 to 12)	34.3 (15.6)
1.75 atm abs (*n*=58)	Athetoid CP, *n*=6 Hemiplegic CP, *n*=2 Diplegic CP, *n*=19 Quadriplegic CP, *n*=31	40/18	4.3 (1 to 13)	32.5 (11.8)

atm abs = atmosphere absolute; CP = cerebral palsy; F = female;
GMFM = gross motor function measurement; M = male.

Every child received the same intensive rehabilitation care by the same therapist team, at the same center, using the same protocol, and the same duration of follow-up. The rehabilitation program was applied for two hours/day, six days/week over six months, and consisted of a half-hour of individual therapies of physical therapy, occupational therapy, speech therapy and special education.

For hyperbaric therapy, the children were assigned to four groups:

A- No hyperbaric treatments, rehabilitation only (control group), *n*=20;
B- 40 sessions, one hour/day, six days/week at 1.3 atm abs air, 21% O_2 (room air), *n*=40;
C- 40 sessions, one hour/day, six days/week at 1.5 atm abs HBO_2, 100% O_2, *n*=32;
D- 40 sessions, one hour/day, six days/week at 1.75 atm abs HBO_2, 100% O_2, *n*=58.

All hyperbaric treatments were given six days/week during seven weeks. In all treatment sessions, the total amount of time spent in the hyperbaric chambers was 90 minutes, as 15 minutes for either compression and decompression was taken. HBO_2 using 100% oxygen was delivered through a hood inside a multiplace hyperbaric chamber at a local tertiary care hospital, using pressures of 1.75 or 1.5 atm abs. Hyperbaric air treatment at 1.3 atm abs using room air at 21% oxygen was carried out using a soft chamber. We carried out initial and periodic assessment of lung and ENT passages and temporarily stopped hyperbaric therapy whenever there was any air passage obstruction or inflammation. Children with a previous history of epilepsy were referred to a pediatric neurologist, and the anti-epileptic dosages were increased marginally during the hyperbaric treatments period.

Evaluation procedures

In all children, gross motor function was systematically evaluated before the treatments and at four and six months after the beginning of the treatments by the same therapists, who were accustomed to undertaking the evaluations. To have more data, and when possible, we were often able to evaluate the children at two and eight months after the beginning of treatments. The gross motor function measure (GMFM66) [27] was applied to every child. It is a criterion-based observational measure (66 items) that assesses motor function in five dimensions: A-lying and rolling, B-sitting, C-crawling and kneeling, D-standing and E-walking, running and jumping.

Table 2: GMFM observed mean before and after HBO_2 therapy

	GMFM observed mean (SD)				
	Before HBO_2	**2 months after beginning HBO_2**	**4 months after beginning HBO_2**	**6 months after beginning HBO_2**	**8 months after beginning HBO_2**
Control	29.6 (13.0)		31.0 (12.8)	32.4 (12.8)	
1.3 atm abs 21% O_2	29.6 (14.8)	33.4 (13.1)	36.2 (13.6)	38.6 (14.3)	40.8 (14.2)
1.5 atm abs 100% O_2	34.3 (15.6)		39.3 (15.4)	42.5 (15.3)	46.4 (17.0)
1.7 atm abs 100% O_2	32.5 (11.8)		37.2 (10.8)	42.1 (10.4)	46.7 (9.7)

atm abs = atmosphere absolute; GMFM = gross motor function measurement

Each item is scored on a four-point scale, and the test gives numeric results for each dimensions as well as a total score. The score is reported as a percentage of the maximum score (100%) generally obtained in a normal 5-year-old child.

Data analysis

Linear mixed models were used to analyze the GMFM data. Such models permit the data to exhibit correlations and non-constant variances. These models, therefore, provide the flexibility of modeling not only the means of the data but also their variances and co-variances. Treatments were considered as fixed factors, and month and age were considered as co-variables. Month was time-dependent, while age was time-independent. Random components were introduced to depict individual trajectories over months with separate intercepts and slopes. A maximum likelihood approach was used to estimate the coefficients, and an unstructured random effect covariance matrix was utilized. Linearity for month and interactions (treatment *x* month) were tested. Information criteria (such as the Akaike criterion and the -2ln (likelihood)) and residual values were used to verify the quality of adjustment. Pearson product-moment correlation coefficient (r) was calculated to quantify the interrelationship among the GMFM variation and GMFM level before HBO_2 therapy.

RESULTS

As expected, groups were similar on the GMFM level at baseline ($p = 0.429$) and each group, including the control group, showed improvement in the GMFM scores over the course of the treatments ($p < 0.001$). As depicted in Table 3, there were statistically significant interactions between group and month ($p < 0.001$) and a statistically significant age effect ($p = 0.003$). To better understand these results, fixed-effect linear models are presented in Table 4 for each group. We observe that the GMFM score increases by 0.46 unit per month in the control group as compared to values ranging from 1.36 to 1.50 unit per month in the experimental groups; and these slopes are significantly different from the control group slope ($p < 0.001$). These results are visualized in Figure 1. GMFM variation, which is the average monthly improvement in the GMFM results over the course of the follow-up, was correlated with GMFM level before HBO_2 therapy ($r = -0.33$, $p < 0.001$).

DISCUSSION

This is the first study that has compared the effects of different hyperbaric dosages combined with rehabilitation in children with CP to a control group receiving only rehabilitation. As expected with intensive therapies, all four groups improved substantially. However, our findings demonstrate that the three groups treated with different dosages of HBO_2 improved much more than the control group, as their GMFM variations were on average three times higher.

In the present study, the three treatments were equally effective in producing gross motor improvement. This reproduces the impressive results obtained in the two groups (1.5 atm abs HBO_2, 100% O_2 and 1.3 atm abs air) in the study of hyperbaric treatment for CP children by Collet *et al.* [20]. Mychaskiw has pointed out in a UHM editorial that children treated with compressed air at 1.3 atm abs cannot be regarded as a control group [28]. It is obvious that giving more oxygen for neurologic conditions is not an all-or-none phenomenon. We find it disconcerting that such a flawed study has been used to claim a lack of efficacy of hyperbaric treatment in cerebral palsy when Collet *et al.* [20] actually stated: "The improvements in GMFM scores in both groups are

Table 3: Fixed effects estimation for GMFM

Variable	Coefficient (B)	SE(B)	T	*p*-value
Constant	24.65	3.31	7.45	0.000
1.3 atm abs	-1.91	3.65	-0.52	0.602
1.5 atm abs	2.91	3.73	0.78	0.437
1.75 atm abs	1.42	3.39	0.42	0.675
Month	0.46	0.18	2.52	0.013
LnAge	4.96	1.66	2.99	0.003
1.3 atm abs* month	0.90	0.22	4.14	0.000
1.5 atm abs* month	0.94	0.23	4.16	0.000
1.75 atm abs* month	1.04	0.210	4.95	0.000

atm abs = atmospheres absolute; GMFM = gross motor function measurement

Table 4: Predicted GMFM from fixed effects models in each group

Group	Model
Control group	GMFM = 24.65 + 0.46 Month + 4.96 LnAge
1.3 atm abs group	GMFM = 22.75 + 1.36 Month + 4.96 LnAge
1.5 atm abs group	GMFM = 27.56 + 1.40 Month + 4.96 LnAge
1.75 atm abs group	GMFM = 26.07 + 1.50 Month + 4.96 LnAge

atm abs = atmospheres absolute; GMFM = gross motor function measurement

clinically important… The improvement seen in all other outcomes is also striking." Moreover, the U.S. Agency for Healthcare Research and Quality (AHRQ) analyzed the results of the study and arrived at the same conclusions [25]. The AHRQ report mentioned that "The possibility that pressurized room air had a beneficial effect on motor function should be considered the leading explanation."

However, our study has, like that of Collet *et al.* [20], clearly demonstrated the benefit of treatment with compressed-air at 1.3 atm abs, because we included a control group; thus the effect of hyperbaric conditions cannot be attributed to a participation or placebo effect. In fact, the placebo effect is a temporary phenomenon that lasts for a few weeks [29] and not for the eight months we have found benefit in our follow-up. Human physiology works within a narrow band for optimal activity. In this context, the increase of almost 50% in plasma oxygenation achieved by compressed air at 1.3 atm abs was of significance.

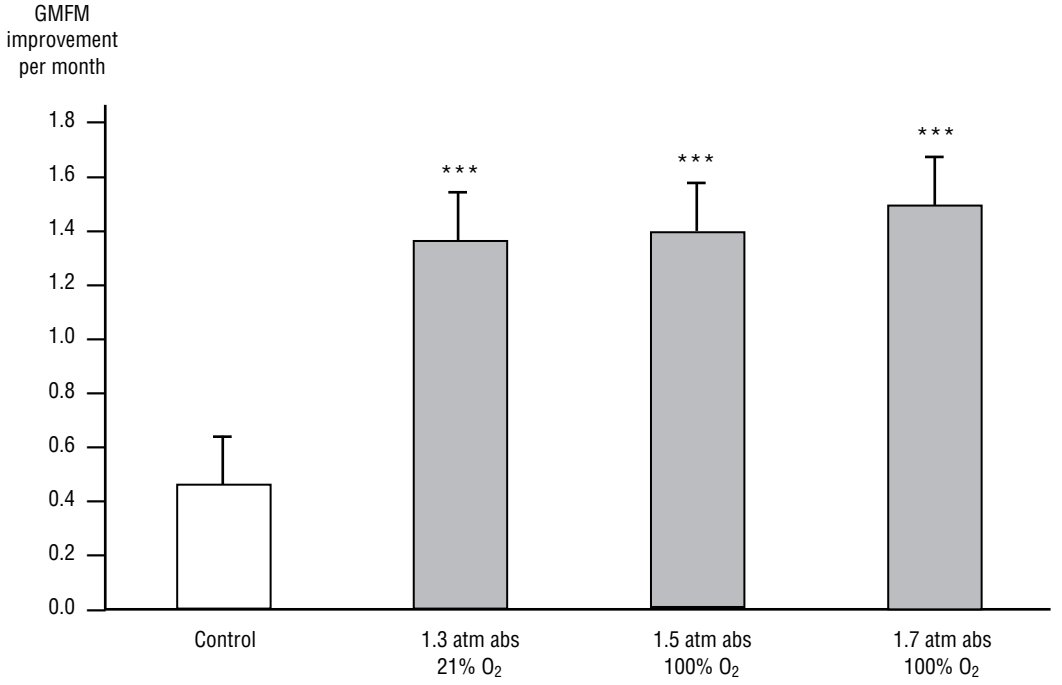
A study on patients with advanced lung disease has been undertaken in Jerusalem. While maintained on supplemental oxygen, they were taken down to the Dead Sea, where they breathed only ambient air. A statistically significant increase in walking distance was recorded, which persisted for a month after returning to Jerusalem. The increase in pressure achieved by descending to the Dead Sea was just 0.06 atm abs [30]. Compressed air at a pressure 0.3 atm abs over ambient cannot be considered a placebo; and a recent paper discussed the osmotic effects of a sudden increase in pressure [31]. In addition, most of the children included in our series were barely in a position to have the mental maturity to understand what was being done for them.

The results of the present study strongly support the fact that HBO_2 therapy, even in small dosage, can improve motor function and increase the effects of standard rehabilitation. The amount and quality of changes observed in our study are also in accordance with the results obtained in other studies on HBO_2 therapy in CP [10,19,20]. The authors are aware that Lacey *et al.* [32] have recently conducted a randomized control study in which they compared two different hyperbaric treatments, one of which (14% O_2 at 1.5 atm abs) has never been used on CP children before, and was considered by these authors as a control group. These authors present their study as a definitive answer to hyperbaric therapy inefficacy in children with CP even if major concerns can be addressed and explain the discrepancy with the present study.

First, despite the fact that in the control group, the condition simulated 21% oxygen at room air, this treatment must not be considered as a placebo treatment because no one knows exactly the potential physiologic effects of this hyperbaric treatment. Secondly, the change in GMFM in the HBO_2 group was 1.5 in two months, which is more than most changes measured with recognized treatments in CP [9]. Thirdly, Lacey *et al.* included only 20 participants per group and stopped the study prematurely, which avoided possibility of the results reaching a threshold for significance. These concerns have been addressed in a letter to the Annals of Neurology [33].

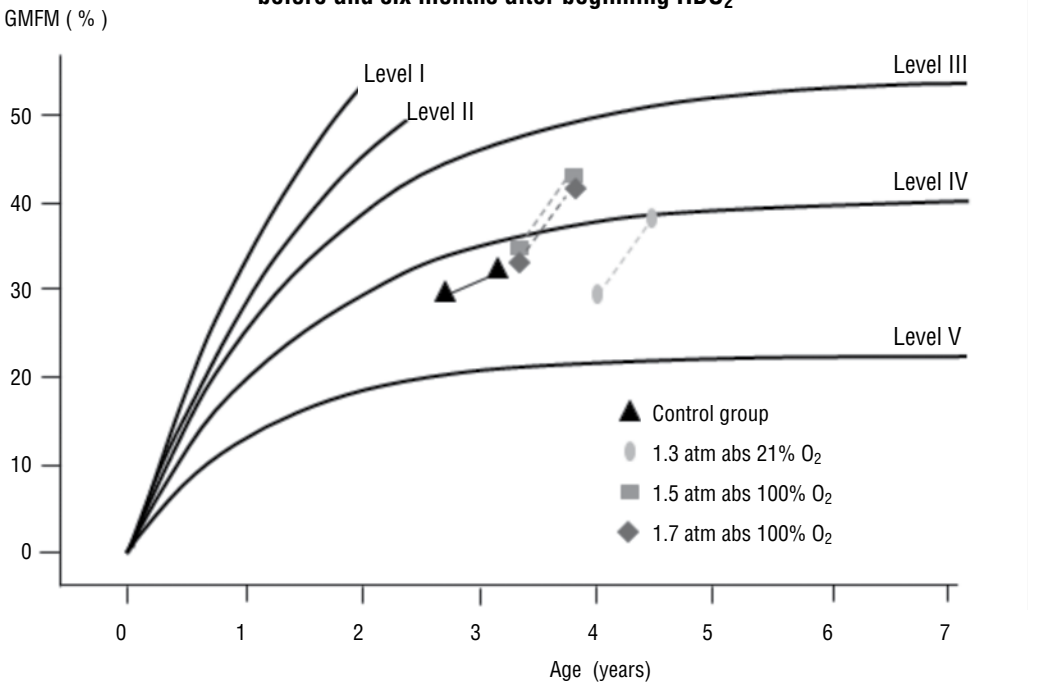
The Gross Motor Function Classification Scale (GMFCS) classifies CP disabilities into five levels based on the GMFM measurement at a given age. The natural gross motor progression of children with CP usually

Figure 1: Rate of gross motor function measurement improvement



*** = significantly different from the control group, $p<0.001$; atm abs = atmospheres absolute

Figure 2: Gross motor function classification scale values before and six months after beginning HBO_2



atm abs = atmosphere absolute; GMFM = gross motor function measurement

follows a curve similar to a logarithmic curve [27]. The children with the highest level of abilities are classified in Level 1, while Level 5 regroups the children with the most severe form of motor disability (Figure 2). The progression of children with CP should naturally follow the curves corresponding to their level of disabilities [27]. Figure 2 shows that the mean initial GMFM values of the four groups would classify them between Level 4 and Level 5 of the GMFCS. By end of six months of therapy, all three hyperbaric groups had improved to Level 4, whereas the control group did not change its disability level.

There are risks associated with the high oxygen pressures used in diving, but they are not relevant to the much lower pressures used in this study. The rate of change of pressure was slow, as the pressurization took 15 minutes, and only three children were excluded because of ear pain on compression. None of the participants needed ear canal grommet use. There were no other side effects.

Our study shows that HBO_2 therapy, when combined with rehabilitation, has many more positive effects than rehabilitation alone. As seen on SPECT imaging, hyperbaric treatment appears to reactivate certain damaged areas of the brain. It is, however, obvious that the recovering brain must be trained to work to its full potential to gain the best results. This highlights the importance of rehabilitation after or during HBO_2 therapy. Further research is needed to explore the cerebral plasticity processes that follow hyperbaric treatment. Improvement in function, comfort and the independence of children with disabling neurological conditions could lead to better health and quality of life as well as important cost savings in the long term.

LIMITATIONS

There were several limitations inherent to this study. First, participant repartition between groups was not randomized. It was the parents' decision to include their children in HBO_2 therapy groups, and participants who were not assigned to HBO_2 groups were automatically assigned to the control group. The different dosages of HBO_2 were not implemented at the same time over a 10-year period, which means that no selection bias occurred in the treatment or dosage choice.

Secondly, the evaluations were not blinded. We certainly recognize that it was not ideal, but it was difficult for us, in a longitudinal study conducted in a relatively small center and involving human interaction and evaluation by the same therapists, for blinded evaluations to have been undertaken.

CONCLUSION

A longitudinal study in children with cerebral palsy has been conducted. The study compared three different dosages of hyperbaric oxygen, combined with intensive rehabilitation with a control group receiving only rehabilitation. The rate of improvement in GMFM score was significantly superior in the three hyperbaric groups compared to the control group, There was no difference between the three HBO_2 therapy groups. The amount of changes are similar to the results obtained in the multiple studies on HBO_2 therapy in CP that have been published and are more important than the improvements measured with standard recognized therapies alone in CP. The very important difference observed in treated *vs.* controlled children can only be a genuine beneficial effect of HBO_2 therapy. Based on the results of this and other studies of HBO_2 therapy in CP children, HBO_2 combined with rehabilitation should be recommended for children with CP.

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The authors report that no conflict of interest exists with this submission. ■

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