

## EDITORIAL

# Hyperbaric oxygen therapy and cerebral palsy – where to now?

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The administration of hyperbaric oxygen (HBO<sub>2</sub>) for the treatment of cerebral palsy (CP) has been advocated for some years. The first substantial account was given at the 1989 UHMS ASM, when Machado reported his experience over ten years treating 230 children in Sao Paulo (1). Subsequent reports including three randomized clinical trials, bring the total numbers to approximately 700 children, (2-8) yet controversy continues unabated about the role of hyperbaric therapy. The recent report in this journal examining the side effects experienced by children enrolled in the Quebec RCT has sparked spirited responses questioning both the motivation of the authors and their conclusions concerning the safety of HBO<sub>2</sub> (9). (See Letters to the Editor of Gottlieb, Neubauer, Marois and Vanasse and response by Muller-Bolla, Ducruet and Collet, UHM 2007; 34(1): 1-6).

Controversy surrounded the Quebec RCT even prior to publication (2). A Scientific Advisory Committee was asked to evaluate the scientific validity of the study and critically examine the hypotheses developed to explain

the results (10). The Committee concluded they had no reservations about the scientific validity of the results, but questioned the mechanism of action for HBO<sub>2</sub> and recommended that no further clinical trials in children should be undertaken ‘*unless there is more basic science data to guide the design of future trials*’. As the mechanisms by which HBO<sub>2</sub> might modify CP are not a high research priority for pediatric neurologists – no recent reviews give HBO<sub>2</sub> more than a passing mention – this seems most unlikely at present. In clinical practice, the question remains: is HBO<sub>2</sub> really a promising therapeutic option in CP, or merely another unproven use for an underemployed chamber?

Cerebral palsy is not a specific diagnosis, but an “umbrella term” describing the clinical presentation of non-progressive motor deficits in children during the first year of life, which can arise from a broad spectrum of etiologies (11). The inciting event occurs during the prenatal, natal, or postnatal period, when the developing brain and motor control system are immature and susceptible to various forms of injury. The world incidence of CP is approximately 1.5 to

2.5/1,000 live births, and has a strong correlation with the degree of prematurity at delivery (12). Despite reductions in the rate of birth asphyxia over the past 20 years, the prevalence of CP has actually increased from 1.9 to 2.3/1,000 live births. The most likely explanation for this trend is improvement in survival of very low birth weight premature infants (12). With current practice, 85% of babies born weighing under 1,500 grams survive, and up to 15% of these survivors are likely to exhibit significant spastic motor deficits (13,14). The estimated annual total cost of care for these patients in 2002 was \$US 8.2 billion (15).

Children with CP present with developmental delay and static (i.e., non-progressive) motor deficits (11). The motor deficits are variable and can include weakness, incoordination, spasticity, clonus, rigidity, and muscle spasms. Spasticity can be quite debilitating and, if left untreated, can lead to muscle fibrosis, musculoskeletal deformities and contractures. In addition, abnormal movements may be noted in some patients, including athetosis, chorea, and dystonia. The motor deficits are often classified as to their severity (i.e., mild, moderate, severe) and topographical distribution (e.g., diplegia, monoplegia, quadriplegia). Many children with CP have normal intelligence, especially those with spastic diplegia. However, there is a strong correlation between the severity of CP and the presence of mental retardation. Other clinical features that can be associated with CP include epilepsy, bowel and bladder dysfunction, hearing loss, visual impairment, and poor nutritional status due to pseudobulbar palsy. Overall, approximately 36% of CP patients develop epilepsy, with onset during the first year of life in over two thirds of the cohort (16).

In up to 50% of CP cases, no definitive causal etiology can be delineated (11,12). Of the remaining, a wide variety of perinatal

etiologies have been identified, including hypoxia/ischemia, stroke, trauma, infections, and chromosomal and genetic syndromes (17-20). The neuropathology is also variable, but usually includes one or more of the following: periventricular leukomalacia (PVL; strongest risk factor), germinal matrix hemorrhage (often associated with PVL), cerebral artery-distribution infarcts, and gray-matter ischemic lesions of the thalamus and basal ganglia (21). Recent research suggests that the immature oligodendrocytes of the developing white matter are very susceptible to injury from free radicals, excitotoxic over-stimulation, and pro-inflammatory cytokines (21), any or all of which may be associated with hypoxic/ischemic events (22-24). Immature cells are susceptible to free radical damage because they have lower concentrations of the antioxidant superoxide dismutase (22), while excitotoxic injury can occur more easily because developing oligodendrocytes overexpress AMPA-kainate receptors, which are stimulated by kainate released during hypoxic-ischemic events (23). Pro-inflammatory cytokines, including interferon- $\gamma$ , tumor necrosis factor- $\alpha$ , and interleukins-2 and -6, are generated during hypoxia and ischemia and have been demonstrated in regions of PVL (21). Both interferon- $\gamma$  and tumor necrosis factor- $\alpha$  have toxic effects on developing oligodendrocytes (25).

The clinical diagnosis of CP requires an extensive work-up, including neuro-imaging with magnetic resonance imaging (MRI) (22). MRI is very sensitive to the damage in the fetal and infant brain that may result in CP (e.g., PVL).

Therapy may be directed to prevent or ameliorate the injury in the acute phase, or to improve function in an established case. In neonates, there is typically a latent period of six to 48 hours between a clinical hypoxic insult and development of clinical manifestations,

suggesting there may be a short window of therapeutic opportunity available to ameliorate or even reverse the cerebral damage (13, 26). While HBOT has been advocated in both situations, clinical reports have almost exclusively involved HBO<sub>2</sub> for children between the ages of 3 and 12 years.

Conventional treatment options will include physical and occupational therapy, drug therapy for spasticity, orthopedic procedures (e.g., orthotic devices, tendon lengthening), and neurosurgical intervention in selected cases (e.g., dorsal rhizotomy, peripheral neurotomy) (11, 27,28). Spasticity should be treated (i.e., tone reduction) when there is unequivocal evidence for interference with function, positioning, care, or comfort level. Drug therapy includes baclofen (most commonly used), diazepam, dantrolene, and tizanidine. Children that are intolerant of or refractory to oral medications can be considered for intrathecal baclofen therapy.

HBO<sub>2</sub> has been advocated for the improvement of both functional and cognitive ability. In the Quebec study, both the HBOT and 'control' (1.3 ATA breathing air) subjects showed improvements in gross motor function of about 3% at three months. This compares well to the 5 to 10% improvement in 12 months reported following dorsal rhizotomy (29, 30) Cognitive improvements were noted in visual working memory, auditory attention and self-control in both groups. In general, improvements in both arms were similar to those reported in other clinical investigations using HBO<sub>2</sub> (3,6).

Surprisingly little has been written concerning how HBO<sub>2</sub> might produce benefit. Most justification for therapy has been based on clinical results of the controlled and uncontrolled studies referred to above, rather than the development of a clear scientific rationale. Neubauer has reported changes on single photon emission computed tomography

(SPECT) images before and after therapy that demonstrate improved regional blood flow. These findings imply improved function and therefore clinical status, and are associated with improvements noted by parents (7). The 'idling neuron' hypothesis is suggested to explain these case series findings, with the assumption that HBO<sub>2</sub> can improve blood flow to inactive but viable neurons.

Some of Collet's co-authors have suggested that pressure might have a therapeutic benefit unrelated to hyperoxia. They cite in support a rat model of acute cerebrovascular injury and a case series of 11 patients treated for 'chronic toxic encephalopathy' with 10 exposures to 24% oxygen at 1.3 ATA (31,32).

Those who doubt the true therapeutic effect of both HBO<sub>2</sub> and low pressure air suggest the results are most likely due to a form of participation effect, or a state of cognitive dissonance, where a highly motivated group of parents and researchers have positively influenced both function and cognitive ability equally in both blinded arms of the Quebec trial. The same effect might operate in any unblinded clinical trial in this area (10,33). There is evidence for the association between participation in clinical trials and improved outcome across a broad range of patients, including children (34,35). A positive influence may arise from a selection effect (the most motivated group are entered into trials), a placebo effect, an increased compliance with therapy or a combination of all three. The inclusion of a highly motivated group in an intensive protocol involving repeated compression over several weeks and sustained contact with other motivated families seems a likely scenario for positive reinforcement of any perceived improvement.

We cannot be certain of the real explanation for these results until we have more data. It does seem more likely that a participation effect is operating than a putative pressure effect

or one related to the administration of oxygen at 28% 1ATA equivalent. Even if either of the latter were true, the proper interpretation of the data would seem to be the administration of the safer and cheaper alternatives of 1.3 ATA air, or 28% oxygen at 1 ATA, than 100% oxygen at 1.75 ATA. As far as we are aware, no-one has adopted the practice of administering 28% oxygen outside the chamber environment – perhaps because this practice does not require a compression vessel.

Muller-Bolla is criticized for exaggerating the importance of middle-ear barotrauma (MEBT) during the conduct of the Quebec RCT. We agree the search for MEBT was very thorough with daily pre and post compression examination. It does not surprise any hyperbaric practitioner that the rate of asymptomatic MEBT was high. We agree with Drs. Gottlieb, Neubauer, Marois and Vanasse that the clinical importance of these findings is low, but also with Muller-Bolla that there is potential for significant MEBT *outside the context of this trial*. The report demonstrates what we assume to be true – that higher compression at faster compression rates is likely to produce more MEBT. The authors themselves conclude they have found only ‘minor signs of barotrauma’<sup>(9)</sup>, so we do not think there is a serious difference of opinion on this point.

Where do we go from here? All concede the need for further research, but the most appropriate directions are difficult. We do not believe there is more to be gained from further open series, but suggest two productive avenues. First, it is important to all chronic brain-injury patients that work continues at the basic science level in order to establish a reasonable mechanism of action for HBO<sub>2</sub> (or indeed pressure alone). This is critically important in children because of the potential for greater gain in the young and developing brain. Animal models continue to be generally

supportive of the use of HBO<sub>2</sub> for acute hypoxic/ischaemic brain injury in the adult, but there is little work on chronic or neonatal/pediatric injury. Moreover, the concept of the ischaemic penumbra remains debatable and the correct interpretation of SPECT scans in this context is unclear. Although animal models specific for CP are not as yet available, they are under development<sup>(21)</sup>. As models for CP become available, they should be studied in detail with HBO<sub>2</sub>, using neuropathological, physiological (e.g., SPECT, PET), MRI, and molecular (e.g., anti-oxidant enzymes, excitotoxic injury, cytokines) outcomes for a range of oxygen and pressure schedules.

Second, clinical studies of the highest possible methodological rigor are needed. The experiences following the publication of the Quebec study illustrate the intensity with which any future trials will be examined. We believe the most pertinent trial would compare the efficacy of HBO<sub>2</sub> (1.3 to 2.0 ATA, 1 hour daily for 4 to 6 weeks) to a sham air therapy and a sham using 100% oxygen therapy (both with transitory trivial compression to preserve blinding). Any future trials would need to consider appropriate, effective randomisation and blinding of all participants and investigators; appropriate sample sizes with power to detect clinically important differences; appropriate and carefully defined comparator therapy; appropriate outcome measures, including those previously reported; careful elucidation of any adverse effects and the cost-utility of the therapy. In addition, the types of CP patients allowed into the study would need to be carefully defined and regulated, to ensure that as homogeneous a group as possible were accrued. CP patients with a hypoxic/ischemic mechanism of neural damage might be the most favourable sub-group to consider for HBO<sub>2</sub> therapy.

This is a considerable challenge for any research group, particularly for clinical

hyperbaric facilities, and cannot be mounted in the absence of support from the pediatric neurology community. The onus is on enthusiasts who are already convinced of the efficacy of HBO<sub>2</sub> for CP to encourage and prosecute these trials if they wish to persuade the skeptical. The skeptical in turn should be willing to assist in the interests of rational and cost-effective use of scarce resources, but cannot be expected to drive an agenda for which they have little expectation of success.

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