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Analysis of the results of a randomized study of hyperbaric oxygen therapy in the treatment of children with cerebral palsy: Placebo or physiological effect?

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Introduction

The results of the study of the effects of hyperbaric oxygen therapy (HBO study) in the treatment of children with cerebral palsy have been known for over six months. However, these results are still controversial. The directors of the "Fonds de la recherche en sant du Quebec" (FRSQ), the organization responsible for overseeing this study and some researchers, including the principal researcher, Dr. Jean-Paul Collet, are convinced that the improvements observed in both groups of children involved in the study was due solely to a placebo effect. Others, the authors included, believe that the cause or causes of this improvement were not clearly identified by this study and suggest the need to pursue further research of HBO treatment.

We have voiced our opinions on several occasions and are now compelled to document our position in order to enable those interested in this debate to familiarize themselves with our argument, weighing the pros and the cons. We would like to demonstrate that we are not merely presenting an empathetic attitude towards desperate parents faced with the unfortunate condition of their child. Recognizing our limitations in the area of research,

we associated ourselves with and collaborated with a team of researchers, clinicians and methodologists possessing the competence required to write the original version of this study, which was left practically unchanged by Dr. Collet. However without prejudice, we feel that our twenty years of experience in paediatric rehabilitation and our involvement in numerous research projects often dealing with experimental treatments gives us the right to voice our opinion. We invite the readers to judge these objective arguments on their own merit.

A.HBO Study: The uncontested facts

The consensus of the research group was that the randomized HBO study for children with cerebral palsy demonstrated that:

-Both groups of children that participated in the study showed improvements in mobility as measured by the Gross Motor Function Measure (GMFM), in language skills and in auditory and visual memory.

-The results did not show that the treatment at 1.75 ATA and 100% O₂ were superior to the so-called "placebo" at 1.3 atmospheres with ambient air. As often pointed out while the research protocol was being developed and in the discussion of the results, the "placebo" was in fact not an inert treatment. We had recommended a true control group that would not have received any treatment.

Furthermore:

-The research group and the scientific advisory committee were of the unanimous opinion that the improvements observed were clinically significant.

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-The improvements in the GMFM scores in both groups were observed during the retest three months posttreatment.

-There were no serious side effects in the course of the 2,500 HBO treatments administered during the pilotstudy and the double blind study.

-All who evaluated this study acknowledged its scientific merit.

B. The reasons for the improvement

During three long plenary sessions and several other meetings in small groups, the researchers debated the possible explanations for the improvements observed in both groups of children We feel it is appropriate to convey the researchers conclusions with respect to the possible reasons for the observed improvements.

1. A placebo and/or participation effect. According to many researchers the apparent cause of observed improvements is the fact that the individual participated in a study. Without being able to clearly identify the mechanism, studies have shown that the involvement in a research study resulted in improvements in the parameters being evaluated. To explain the observed changes, we have made reference to the placebo effect, the Hawthorne effect, the increased amount of time the parents spent with their children or the increase in the social interaction of the parents and children.

2. The effect of the HBO therapy. As mentioned above, the placebo referred to in this study was not a true placebo. It was a HBO treatment at 1.3 atmospheres of pressure with ambient air. This treatment has an effect on the partial pressure of blood gases and perhaps other physiological effects. It is therefore possible that this treatment could have a beneficial effect at the cerebral level.

Hypotheses not retained by the research team

The team of researchers evaluated the possibility that the improvements were due to the natural evolution in the neurological condition of the subjects or the effect of learning in the tests used.

These hypotheses were not

retained as the children's development was stable or had shown only slight improvement. The improvement

was much greater following the HBO treatment. We also consider that there was no learning effect in the tests

used, especially with the GMFM, which was the principal variable.

C. Our Position

Our opinion is based on the following points that we will elaborate:

-The placebo was not in fact inert and it would be more appropriate to claim that these children received a reduced dose of HBO, in other words an exposure to a pressure of 1.3 atmospheres of ambient air.

-Without denying the existence of a placebo effect, or the possibility that the observed improvements are due

to the placebo effect, we maintain that there has been no scientific proof that:

-a placebo can significantly improve mobility, language and memory of children with cerebral palsy clinically

or statistically. If the results were due to a placebo, then it was as effective on motor performance as the

conventional therapy currently considered the most effective treatment (intensive physical therapy) and in a shorter amount of time.

-a placebo can produce long-lasting effects. The improvements were still observed three

months post-treatment

in the retest of the subjects involved in this study. Without being able to scientifically confirm, the impression of both parents and health care professionals following these children is that the improvements persisted, (one year and more).

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-a placebo can result in reproducible improvements from one study to another. The mobility improvements measured by the GMFM in both groups involved in the randomized study were identical to the results of three pilot studies and one case study. We are in agreement with the experts on the scientific advisory committee that there is no irrefutable scientific proof demonstrating any therapeutic benefit of low-pressure hyperbaric therapy. This however does not imply that a beneficial effect does not exist. Some clinical and experimental data allows us to defend this hypothesis.

D. The "placebo" group received a reduced hyperbaric treatment

That the placebo was not inert was not only a concern upon completion of the study, but had been pointed out

and discussed during the development of the research protocol. The initial versions of the protocol (versions

that were submitted and approved by the ethical committees of Hopital St. Justine, Centre hospitalier regional

de Rimouski and Institut en readaptation en deficiance physique de Quebec in May 1999) read as follows:

"Since a pressure of 1.3 atmospheres could eventually produce an effect (it is not an inert placebo), we had

proposed the introduction of a third group in the study that would not receive any treatment. The children in

the control group would be evaluated, with the awareness that they didn't receive the treatment, initially, one

month later and at the end of the study. This group of subjects would allow us to verify the natural evolution of

the condition and the effect of repeating the evaluation on the measured performance."

On Dr. Collet's recommendation (eventually approved by the majority of researchers) the inclusion of this

third control group was discarded in order to include more subjects in the other two groups thus obtaining more

significant statistics.

We were not the only ones to have raised this methodological problem. The results of this study were

presented at the Underwater and Hyperbaric Medical Society Conference by

Dr. Stephane Tremblay in June 2000. The report of Dr. Tremblay's presentation states:

"many individuals

recommend verifying in future studies whether in fact the placebo was inert (28% O₂=placebo) as well as the effect of oxygen at partial pressure, seeing as the improvement in both groups was clinically significant." This point was also raised during the presentation of the results of this study at the American Academy of Cerebral Palsy and Developmental Medicine in Toronto, September 2000, given in part by Dr. Michel Vanasse.

A letter addressed to Dr. Collet from Dr. Butcher, the senior editor of the journal The Lancet, accepting the text of the results of our study stated:

"I am very pleased to be able to tell you that The Lancet's editorial team had decided to accept your paper for publication provided that all references to "placebo" are changed to "slightly pressurized room air (or something similar)"."

Evidently these comments do not allow us to conclude that the treatment was responsible for improvements observed in the group that received the attenuated hyperbaric therapy. However, it does indicate that many scientists feel this possibility cannot be excluded and should be the focus of further investigation. It was the conclusion in the resume of the paper written by Dr. Collet, on the results of our study that has been accepted for publication in The Lancet:

"The important improvement observed in both groups for all three dimensions tested deserves further considerations."

E. Comments regarding the "placebo" effect or the effect of participation

1. Placebo effect, effect of participation (inclusion benefit) and "Hawthorne effect"

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Without intending to do a complete analysis of the placebo effect, we feel it is important to comment on the subject. During the discussions pertaining to the possible causes of the improvements noted in both groups of subjects, many of the researchers maintained that it was due to a placebo effect, inclusion benefit or "Hawthorne effect" or a combination of the three. The designated committee of experts chosen by the FRSQ concluded that this was the most probable explanation of the reported improvements. Some reproached us for attempting to deny the obvious, that these effects are well known and well documented. If this is in fact the case, it is surprising to report that the paper

reporting the results of our study only includes one very general reference to this subject. We do not in any way deny the existence of the placebo effect, however, we have always maintained that there is no scientific proof that such an effect could explain the improvements reported in the children that received either the complete or reduced hyperbaric therapy. The placebo effect is a well-known phenomenon to health care professionals that has rarely been studied. The titles of certain papers cited by the experts of the scientific committee refer to these studies: "The Mysterious Placebo Effect", "The Uncontrollable Placebo Effect".

The effect of participating in a study as possibly being the sole factor resulting in an improvement in the subjects involved was also postulated. It is a fascinating hypothesis and remains just that, a hypothesis. The effect of participating in a study, also referred to as the inclusion benefit, is not well known. Remarks made by

Dr. Lantos suggesting this phenomenon remains hypothetical in an editorial in the Journal of Pediatrics 1999,

"The "inclusion benefit" in clinical trials":

"As a thought experiment, let us suppose that it is really true that participants in randomized clinical trials do have better outcomes than similar patients with similar diseases treated in the same institution at the same

time". In the same editorial he adds: "The phenomenon of inclusion benefit, if real".

The "Hawthorne " effect was also proposed as a possible cause for the reported improvements of the subjects

in our study. This effect is defined as: the effect of being conscious of being observed can cause a modification

in the behavior of an individual. In a recent study of the "Hawthorne" effect and the sensation of feeling better

after anesthesia, De Amici et al. (2000) concluded: "Whereas this study answers the question concerning the

importance of the Hawthorne effect in a field where subjective perception is predominant, the impact of this

phenomenon on more "objective " parameters remains open. However, the improvements reported in the

children treated were based on objective data, not on a sensation of feeling better.

These remarks can explain

our reluctance to believe that the placebo, the participation or Hawthorne effects be the cause of the reported

improvements.

Furthermore:

2. A placebo as effective or even more so than conventional treatment?

We have often mentioned that there are few effective treatments for children with cerebral palsy, and thus the importance of not neglecting a treatment as promising as hyperbaric therapy. In the past few years there have been several papers investigating therapeutic modalities available for children with cerebral palsy, which have concluded that there is no scientific evidence to support the effectiveness of these treatments. (Turnbull 1993, Graves 1995, Majnemer 1998). Dr. Majnemer wrote in her paper: "there is a lack of evidence to support the efficacy of rehabilitation interventions in children with cerebral palsy". Some open or pilot studies have reported that intensive physical therapy (6 to 8 months, two times a week) result in a functional improvement measured by the GMFM (Gross Motor Function Measure, the evaluation tool used in our pilot and randomized studies). However, for comparable populations, children with spastic diplegia, we observed a 5.3% improvement on the global score of the GMFM in our pilot study (after 20 treatments, after one month) compared to an improvement of 4% reported by Russell et al. (after 6 months of intensive therapy). Furthermore, in the subjects involved in the randomized study, a generalized improvement was reported, including attention and communication.

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We can therefore establish that the hyperbaric therapy resulted in functional improvements more rapidly and more generalized than conventional treatment. If we accept that the improvement observed in the children having received HBO therapy is due to a placebo, must we then conclude the improvements resulting from the 6-8 months of intensive physical therapy were also due to placebo because the results were identical?

3. A reproducible and persisting placebo effect?

Another interesting and, in our opinion, very important element that was highlighted by our research was that the improvements persisted at least three months post treatment. The children were systematically re-evaluated three months later and we were able to document beyond doubt the persistence of the gains observed after 40 hyperbaric treatments (and even a slight improvement which was not statistically significant). In a pilot study Dr. Maurine Packard of Cornell University evaluated 26 children that had received 40 HBO treatments (each

lasting one hour at 1.5 ATA). She noted that the improvements in the areas of attention, language and ability to play that were observed immediately after the treatments were still present six months later.

Our clinical experience leads us to believe that the improvements reported persist even in the long term, in other words for at least one year after the treatment. To our knowledge, no scientific proof exists confirming the persistence of a placebo for that period of time.

We are aware that there does not exist, other than our research study, a randomized, double blind study

conducted to analyze the effect of this therapy. However, there have been some credible case studies and pilot

studies on children with cerebral palsy (Paleg 1998, Barrett 1999, Montgomery et al. 1999, Packard 2000),

published or presented at conferences. We may have reservations about the conclusions of these studies, but

one thing does remain unchanged, they all showed similar improvements.

F. Is a low-pressure hyperbaric treatment effective?

We would like to restate that we are in agreement with the report of scientific advisory committee that there is

no irrefutable proof illustrating that a HBO treatment at low pressure is effective on humans. Equally, there is

no scientific proof showing that it is ineffective as there has never been any research on humans to evaluate

this hypothesis. In our opinion, some of the clinical and experimental data deserve consideration.

-a recent study evaluating hyperbaric treatment with and without oxygen therapy in the treatment of cerebral

vascular accidents in rats showed that: " Hyperbaric oxygen and, to some extent, hyperbaric pressure

reduced ischemic brain damage and behavioral dysfunction."(Chang et al. 2000)

-A low-pressure hyperbaric treatment (without oxygen) , the Gammow bag, is effectively used to treat cerebral

edema suffered by some individuals when at high altitude, a condition known as "acute mountain sickness".

(Austin 1998) It is estimated that the pressure reached with this bag is approximately .2 ATA. Recently,

Heuser et al. reported a clinical improvement after ten hyperbaric treatments at a pressure of 1.3 ATA and in

the cerebral SPECT scan in six patients presenting a toxic encephalopathy.

-Two double-blind studies were conducted on humans to evaluate the effectiveness of HBO therapy in the

treatment of CVA in the acute phase. (Anderson et al. 1991, Nighoghossian and Trouillas 1995) The scientific

advisory committee did not cite these studies. In both studies, the experimental group received a treatment of hyperbaric oxygen therapy at 1,5 ATA with 100% oxygen and the placebo group 1.5 ATA without oxygen.

The study by Nighoghossian and Trouillas reported an improvement in both groups of subjects, with a greater improvement (however not statistically significant) in the group of patients that received the hyperbaric treatment with oxygen. In the study conducted by Anderson et al. improvement was reported in both groups, however the greater improvement was noted in the group that received hyperbaric therapy without oxygen (the difference was not significant statistically between the two groups). These patients were evaluated with a quantified neurological evaluation and a measurement of the volume of the cerebral infarct using repeated cerebral scans. The patients in the "placebo" group experienced more favorable results in these two

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measurements, suggesting that improbability of a placebo effect.

It is not up to us to evaluate in hindsight the results of these two studies. However, it would have been very

interesting to compare the evolution of both groups with a control group without treatment. In our opinion, the

results of both of these studies, especially the one by Anderson et al., support the possibility that a hyperbaric treatment at low pressure (1.5 ATA in that study) can have a therapeutic effect.

Furthermore, the physiological

effects of hyperbaric treatment are certainly more complex than solely the increase in partial pressure of

oxygen (Buras 2000). It would be interesting to study the physiology of hyperbaric therapy with and without

oxygen therapy.

G. Conclusion

The conclusion and the subsequent proposals are taken verbatim from what was proposed in May 2000. Our

position remains unchanged with regard to the follow-up of our research project.

We are convinced that our work on this therapeutic approach must be pursued in order to identify the cause or

causes of the reported improvements. It would be difficult to accept shelving the results of this study. We base

our convictions on the fact that the improvement in mobility reported in these children after two months of

hyperbaric treatment is similar to that measured after six months of intensive physical therapy (twice a week).

Furthermore the children involved in this study showed improvements in language and neuropsychological evaluations as well as mobility. Finally, the improvements persisted for at least three months post-treatment (as verified scientifically).

It is our opinion that in order to properly investigate the different hypotheses raised, a double-blind study must be conducted where a true placebo would be compared to different treatments (oxygen alone, hyperbaric treatment alone and hyperbaric oxygen). It is clear that we could not recruit enough subjects for such a thorough study in Quebec. A multi-center Canadian or international study would have to be considered . This study would require many months or years to plan, finance and realize. Furthermore it would require hyperbaric chambers that are not available at the present time in the Quebec's public health care system. Finally, even though we did not definitively identify the cause or causes of the improvements, we are convinced that these results will encourage parents to continue to pursue hyperbaric treatments for their children. For these reasons, we recommend that at least one or more hyperbaric treatment centers remain open in Quebec.

H. Proposal to maintain one or more hyperbaric treatment centers in operation

For the above mentioned reasons we propose:

- to maintain one or more hyperbaric treatment centers in operation
- to make these centers readily available to treat patients presenting a chronic, non-progressive encephalopathy , at their own expense

These centers should assume, in part, the responsibility of systematically evaluating the patients undergoing hyperbaric treatment with a validated detailed questionnaire such as the PEDI. Depending on their means, they should also evaluate mobility, language and cognition with as many subjects as possible. These centers should also agree to participate with any efforts to conduct a multi-centre Canadian or international study.

If one or more centers continue to operate and administer treatments in Quebec it would:

- avoid the need for parents to travel to Ontario or elsewhere (with all of the expenses and hardship it entails) in order to receive treatments often administered without any medical supervision nor pre and post treatment evaluation.

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-allow us to continue to study the effects of this treatment. Although we are well aware that it would not be a double-blind study, it seems clear that the systematic evaluation process that we recommend is better than no evaluation at all.

-maintain the centers best prepared to participate in a multi-centre study due to their geographic location and their ability to treat many subjects at once.

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