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The effectiveness of hyperbaric oxygenation treatment on circadian rhythm and motor functioning in children with cerebral palsy

Medical Science

KEYWORDS: hyperbaric oxygenation, cerebral palsy, circadian rhythm, gross motor function

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ABSTRACT

Hyperbaric oxygenation treatment is an advanced therapeutic approach for the neural rehabilitation of children with cerebral palsy. The authors investigated the effects of HBO treatments on circadian rhythm, motor functions and spoken language production. Total scores of the Sleep Disturbance Scale for Children, the Gross Motor Function Measure–88 (GMFM-88) and verbal production with the largest change in the production of syllables and sentence were significantly better after 120 HBO treatments at 1.55 atm and 100% oxygen ($p < .000$). Furthermore, as opposed to children with severe form of cerebral palsy (GMFCS V) in group of children that have better motor functions (GMFCS II) improved sleep patterns were indentified already after 30 hyperbaric treatments.
Statistically significant improvements in different spheres of functioning with minimal side effects during study provide further investigations in this field and scientific support for the early intervention and neurological rehabilitation of young children with cerebral palsy.

Introduction

Cerebral palsy, as a complex development disorder, represents not only personal but also family and broad social issue. Disorders of perception, sensation, cognition, communication and behavior, with primary motor deficits indicate that apart from non progressive disorders of cerebellum units, exists dysfunction of other central nervous system structures that can represent significant part of the complex clinical picture which often stays out of primary treatment.

In that sense, existing traditional treatments even with considerable engagement and dedication produce limited results. Therefore, in this field, the application of various multidisciplinary procedures that in addition include molecular oxygen therapy under the conditions of higher ambient pressure (hyperbaric oxygenation, HBO) is more common.

The reason for the application of this type of treatment lies in the biological reasoning that for the normal functioning of each cell, nerve cells in particular and the preservation of cell homeostasis, the presence of adequate quantity of molecular oxygen is necessary. The presence of the available molecular oxygen is essential for normal mitochondrial activity, for maintaining a normal relation between mitochondrial and extra-mitochondrial activity, and to maintain the optimum pH for both the enzyme activity, and the excitability of cell membranes.

This was exactly the guiding idea for application of hyperbaric oxygen therapy as a part of standard restorative-rehabilitation procedure in these children.

As cerebral paralysis is not an isolated disorder of exclusively motor deficit, a number of studies have been dealing with a group of behavior disorders associated with the underlying condition, which as a rule remain separate but may have a considerable role in therapeutic effects of the entire disorder. Although sleep disorders in early childhood, with prevalence in children with normal physiological development, range from 5% to 40% [1,2,3,4,] several studies, focusing on the rhythm of sleep in children with the cerebral palsy, have reported that sleep disorders are more frequent in these children than in those with normal physiological development[5,6,7]. Newman et al. reported that 44% had at least one significant sleep disorder[5,6]. The reason of altered rhythm of sleep in this group is often associated with muscular spasm, pain and epileptic seizures[6]. Therefore, a number of authors indicate melatonin therapy as effective and safe treatment for improvement of circadian rhythm in children with different developmental disorders, including those with cerebral palsy[8,9].

Studies about effects of hyperbaric oxygenation in children with cerebral palsy bring out contradictory results about the motor progress of this group of children[10-14]. One of possible causes is application of different protocols as well as duration of treatment. Also, none of these studies have presented findings on matter of circadian rhythm before and after HBO treatment.

Having presented these facts, the purpose of this study was to investigate the effectiveness of hyperbaric oxygenation treatment on circadian rhythm and motor functioning in children with cerebral palsy and to assess the feasibility of incorporating hyperbaric oxygenation treatment as a part of the standard therapy management of this specific population.

METHOD

Design

The design was a prospective cohort study into circadian rhythm and motor functioning after using hyperbaric oxygenation therapy with follow-up of one year. The study was approved by the Ethical Committee of the Centre of Hyperbaric Medicine from Belgrade, and done without any financial support by parents or appropriate health funds.

Participants

After voluntary sign up by the parents a convenience sample of 52 children with spastic form of cerebral palsy are included in HBO treatment. All children are fulfilled the criteria for inclusion in the study. The inclusion criteria were age 3-7 years, diagnosis of cerebral palsy according to the Gross Motor Function Classification System (GMFCS), changes of circadian rhythm, and absence of epileptic seizures and pulmonary dysfunction. Within the group, none of the children had never previously received HBO treatment or botulinum toxin A treatments within 6 months. Thirty children were classified as GMFCS level II and 22 as GMFCS level V (Table 1). Informed written consent was obtained and signed by the children's parents before participation.

Measures

Primary expected outcome was to restore physiological circadian rhythm in children as well as their motor functioning after the completed session of treatment. The changes of motor function were followed by Gross Motor Function Measure (GMFM-88), four-point ordinal scale, containing five dimensions of motor functioning[15]. Besides calculation of the total score of motor functions, the scale provides percentage calculation of each dimension of motor function, enabling more precise monitoring of changes developed during the hyperbaric oxygenation treatment.

Circadian rhythm is monitored by Sleep Disturbance Scale for Children (SDSC). This is a Likert-type scale, and as clinical tool it is suitable for evaluation of specific sleep disorders in children. The scale contains 26 questions rated from 1 to 5 points, divided into 6 categories for obtaining valid information on disturbances of falling asleep and maintaining sleep, transitory disturbances (wakefulness and sleep periods), on excessive somnolence, modified breathing rhythm during sleep, night sweats and night fears[16]. A total score ranges from 26 to 130, and circadian rhythm is considered pathological when the sum of scores is over 70.

Other outcome measures included changes in spontaneous verbal production, the emergence of vocalization, the first words and increase in the length of verbal statements. Testing of verbal production was an individualized criterion-referenced measure that can be used to evaluate individual changes of verbal expression. It is a five-graded, ordinal scale, ranging from 0-indicating without verbal expression, through 1-indicating vocalization and 2-syllable, 3-indicating words and 4-phrase.

Procedure

Evaluations were made 0–15 days before treatment and after each completed HBO treatment (after three, six, nine and 12 months from the beginning of first HBO treatment). All evaluations were performed in Centre for hyperbaric Medicine in Belgrade, by one physician and one speech and language pathologist not providing services to the children. All 52 had 120 HBO treatments according to the protocol which included a 60 minute-hyperbaric oxygen therapy with 100% oxygen at 1.55ATA, during thirty days, Monday to Friday, after which followed a pause of six weeks, and then the procedure is repeated. During HBO treatment (1.55 ATA), partial pressure of oxygen varied from 500 mmHg (10 minutes after the beginning of HBO therapy), 1000 mm Hg (after 30 minutes of HBO therapy), 1200 mmHg after 60 minutes of HBO therapy, which is average score of 160 mmHg after HBO therapy. All that indicates this protocol provides not only minimum of side effects but also optimal maturation of immature neural structures, needed for complex movement. Under same conditions, there is also recorded change of pressure in parents which followed their children (108 mmHg after 10 min., 130 mmHg after 30 min., 125 mmHg after 50 min. and 105 mmHg at the end). Those changes are not dangerous to parents and does not make any changes in hematological status.

Also, during an intervention, in addition to hyperbaric oxygenation children had standard physical and speech therapy, on average, four times a week by the child's local therapist.

Data analysis

Data analysis was performed in SPSS software (SPSS v. 17). Descriptive parametric statistics are presented as mean, SD and 95% CI. Within-group changes in GMFM scores, SDSC scores from baseline through 30, 60, 90 and 120 hyperbaric treatments of follow-up were analyzed with repeated measures analysis of variance (ANOVA). For effects involving the within-subjects factor, the F statistic test was based on the Huynh-Feldt adjustment for the degrees of freedom. For testing differences in verbal production before and after 120 hyperbaric oxygenation treatments was used paired simples t-test with confidence intervals of 95%. Age, gender and duration of standard physical therapy before children were included in HBO procedure were analyzed as the between-subjects factors.

Results

Applied analysis of variance with repeated measures (ANOVA) on motor functioning, sleep patterns and verbal production indicates a significant oxygenation effect in treated children with cerebral palsy.

In the group of children whose motor functioning belongs in GMFCS level V results after each completed series of treatments indicate significant effects of oxygenation on dimensions lying with rotating (30 HBO: p = .000; 60 HBO: p = .000; 90 HBO: p = .000; 120 HBO: p = .000) and sitting (30 HBO: p = .000; 60 HBO: p = .000; 90 HBO: p = .000; 120 HBO: p = .000).

Considerable differences on tested dimensions at the end of the study indicate a significant effect of prolonged continuous exposure to hyperbaric oxygenation (dimension lying with rotation F = 83.84, df = 4.00, 1.00, p = .000; sitting F = 101.92, df = 2.59, 649, p = .000)

Furthermore, the effect of molecular oxygen at repeated measures on a sleep disturbance scale first registered after 60 HBO exposure (30 HBO: p = .107; 60 HBO: p = .000; 90 HBO:

p = .000; 120 HBO: p = .000), and stay until the end of the study (F = 137.46 , df = 3.27, .819, p = .000) .

We also found major improvement of verbal production after 120 HBO exposures (t = -10.46; df = 21; p = .000), with the largest change indentified in the production of syllables. Before HBO treatment three children (13.6 %) used syllables, and after 120 hyperbaric treatments, 12 of them (54.5 %). In contrast, no significant interaction of gender, age and previous physical and speech and language therapies was found for any of measures.

In the group of children whose motor functions belongs GMFCS level II the effect of molecular oxygen in all tested categories was registered. In this group progress is not only evident after each completed series of HBO treatments (standing and walking: 30 HBO: p = .000; 60 HBO : p = .000 ; 90 HBO : p = .000 ; 120 HBO : p = .000), but the this effect was recorded at the end of the study (standing : F = 99.74 , df = 2.76 , .691 , p = .000 ; walking : F = 142.95 , df = 4 , 1.00 ; p = .000).

As opposed to children with severe cerebral palsy in group of children that have better motor functions improved sleep patterns were indentified already after 30 hyperbaric treatments and this result had preserved until the end of study (30 HBO: p = .000 ; 60 HBO: p = .000 ; 90 HBO : p = .000 ; 120 HBO : p = .000 ; F = 98.75 , df = 2.38 , .595 , p = .000) (Tables 2 and 3). Observed verbal production was statistically improved after 120 HBO exposures, not only within the group (F = 230.84, df = 1.00, 1.00, p = .000), but also for each individual child. In fact, before this study started, ten out of thirty children (33.3 %) were without verbal production, and none of them had ability to form sentences. At the end of the study all children were with some form of verbal expression, two of them (6.7%) formed vocalization, eight (26.7 %) syllable, also eight (26.7 %) form words and 12 (40%) of them a sentence.

Gender, age and earlier exposure to physical treatments in this group of children before inclusion to the study were not significantly influencing data that was obtained during exposure to molecular oxygen under conditions of high ambient pressure.

Trial limitation

The lack of professional information and wider knowledge of HBO effects in children with cerebral palsy affects a small number of doctors to include these children in the HBO treatment before completing the process of myelinzation, which greatly reduces the effectiveness of this intervention method. Also, the inability to expose children twice a day to HBO treatments with a time break of 10 to 12 hours as well as the occurrence of associated diseases such as epilepsy and obstructive lung diseases which in children with cerebral palsy are one of the main limiting factors to apply HBO therapy in this population.

Discussion

Based on literature data and broad knowledge of hyperbaric medicine, this study is the first prospective cohort study of the effect of hyperbaric oxygenation on circadian rhythm and motor functions of children with the cerebral palsy.

Published results of studies, focused on sleep disorders and therapy in children with neurodevelopmental disturbances, suggest the correlation of inadequate time of melatonin secretion and difficulty falling asleep and sleep maintenance (DSPS and ISM)[17-19], with parallel emphasis on melatonin therapy as efficient treatment for

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reduction of latency of falling asleep[20]. However, none of published studies reported the effect of melatonin on the improvement of a total time of sleeping[21] or reduction of a number of awakenings during night[20,21]. Although these studies provided data on the effect of melatonin on circadian rhythm, it should be mentioned that the study by *McArthur and Budden* (1998) involved children with Rett syndrome, while two other studies [20,21] included children with broad spectrum of neurodevelopmental disorders and different pathological patterns of sleep. Therefore, one of possible reasons for such results may be that dosage and time of melatonin administration is not always completely controlled, given the fact that the action of oral melatonin starts from 30 minutes to 2 hours from the time of its ingestion. In addition, worth is mentioning that the basic mechanism of action of melatonin to falling asleep has not been fully clarified yet, although there are some assumptions of its effect on lowering body temperature and/or direct effect on endogenous brain structures consequently causing somnolence [22]. Given the fact that children with cerebral palsy have modified and immature anatomic and physiological cerebral structures, resulting from inadequate oligodendroglial activities and fetal myelinization occurred in 70% of children with the cerebral palsy born before gestational week 32 and in 30% of term children with the cerebral palsy [23], we consider that hyperbaric oxygenation not only has effect on maturation of corticostriatal (CS) and corticocerebral (CC) connections, and mediotemporal lobe responsible for motor learning but it also has effect on maturation of complex hippocampal connections that are included in circadian system, providing an adequate quantity of molecular oxygen necessary for normal mitochondrial activity, translating it into the status of dominantly normal in distinction from earlier dominantly extra mitochondrial activity with resulting altered pH value of the intracellular space and its noxious metabolites, what all together affect the process of myelinization and establishment of normal functions. In this way, not only physiological rhythm of sleep and awakening but also other endocrine functions that are the basis of social behavior are regulated.

Our study has shown the improvement of sleep in the treated children. The presence of statistically significant difference of circadian rhythm in these children after every completed session of hyperbaric treatments confirms the importance of introduction of hyperbaric oxygenation in primary restorative-rehabilitation treatment of children with the cerebral palsy.

Out of 12 published studies addressing the effect of hyperbaric oxygenation on different functioning aspects in children with the cerebral palsy, the empirical data of 11 have underscored the efficiency of this interventional method. On the other hand, only 5 studies were focused on the analysis of the hyperbaric oxygenation effect on changes of motor function in this group of children [10-14]. In their pilot study including 25 children with the spastic diplegia, *Montgomery et al.* reported progress in gross motor functions in three of five dimensions of motor functioning as well as improvement in fine motor functions with parallel reduction of spasticity after 20 hyperbaric treatments in duration of 60 minutes with 95% oxygen at 1.75 ATA pressure. Positive results of hyperbaric oxygenation was also reported by *Collet et al.* in 2001, in their randomized, controlled study involving 111 children with the cerebral palsy. During this study, both groups of children underwent 40 treatments, where the treated children were exposed to 100% oxygen at pressure of 1.75 ATA and the controls were breathing 21% oxygen at 1.3 ATA. Upon the completion of hyperbaric treatments, both groups of children were recorded to have a significant improvement in gross motor functions, attention, memory, functional abilities and language without significant difference between the compared groups (p=.544). Although the authors believed that the obtained results might be associated with the equal effectiveness of these two therapies and positive motivation of the children's parents[11], the US Agency of Healthcare Research and Quality, which had also analyzed this study, considered that "one should not rule out the possibility of effectiveness of pressurized 'room air' on the improvement of motor functions" [24,25]. In addition, a significant improvement of 3.96% was recorded on the motor function scale after 40 HBO treatments in children included in study by *Marua* and *Vanas* in 2006 [11]. *Mukherjee* et al. (2014) published first open, independent, longitudinal study reporting data on improvement in 150 children with cerebral palsy. Although the study recorded the improved GMFM scores in all four groups of children (three groups of children differently treated by hyperbaric oxygenation and intensive rehabilitation: group I – 21% O_2 at 1.3 ATA; group II - 100% O_2 at 1.5 ATA; group III - 100% O_2 at 1.75 ATA; and the controls – only rehabilitation), the authors emphasized that these three different HBO treatments were equally effective for achieving significant improvement of gross motor function in children with cerebral palsy[14]. Besides the aforementioned studies, it is worth to point at evidence on the improvement of brain neuroplasticity in patients with chronic brain injury after the application of hyperbaric oxygenation with 100% oxygen at 1.5 ATA [26].

On the other hand, in 2012 study involving 46 children with the cerebral paralysis (24 children from HBO group received 100% oxygen at 1.5 ATA and 22 controls were exposed to 14% oxygen at 1.5 ATA), there was no GMFM scale records of improvement in either group of children after 40 treatments. The changes by Pediatric evaluation of disability inventory (PEDI) were recorded in both groups without significant difference between the compared groups. That is why these authors concluded that hyperbaric treatment had no effect on the improvement of gross motor functions (GMFM scores), and considered that hyperbaric oxygenation was not an adequate therapy for children with the cerebral palsy and without the history of neonatal hypoxic-ischemic encephalopathy [13].

With clear observation on a series of drawbacks noted in the previous study, including its preparation and realization, which produced as dubious data as possible, our study, although not including children with neonatal hypoxic-ischemic encephalopathy, showed significant improvement in gross motor scores in all four tested dimensions in the cohort group of children. We consider that statistically significant improvement, achieved in different spheres of functioning in the treated children with the cerebral palsy with minimal side effects during study, opens the possibility of further investigations in this field with introduction of hyperbaric oxygenation into standard process of management of these children. Performed therapeutical molecular oxygen procedures under conditions of the increased ambient pressure (HBO therapy) have produced completely expected results and justified all theoretical assumptions that have been a guiding idea for the beginning of this study. First, the obtained results show the improvement of general children's condition. Significant improvement of head and trunk control, rotation in lying and sitting position as well as improved head-arms coordination within dimensions of lying with rotation and sitting was recorded after 30 HBO expositions in GMFCS level V children. Expected improvement of motor coordination in dimensions of standing and walking were recorded after 30 hyperbaric expositions in GMFCS level II children. In addition, verbal expression (vocalization and verbal production) was recorded as improved after 120 HBO treatments. Introduction to circadian rhythm, primary normal rhythm of sleep and wakefulness (earlier falling asleep without awakenings during night, with length of sleep continuity matching the age) in these children, beginning from the seventh hyperbaric oxygenation treatment, as well as the rhythm of nourishment (fullness, hunger, thirst) and emptying of the colon are the results of special significance. These results directly confirm that the structures of the central nervous system other than cerebellum are included, as dysfunctional, into the complex clinical picture, which is often over-simplified in clinical practice by the term cerebral paralysis.

Our results unquestionably demonstrate that a significant role, in the clinical picture, is ascribed to nervous structures, which either maturate much slower or are phylogenetically younger, such as hippocampus, parts of amygdala system and hypothalamus. Imbalance of their functions that is primarily manifested by disturbed rhythm of sleep and wakefulness as well as other

dysfunctions based on inadequate molecular oxygen quantity in some earlier period, causes the impairment of mitochondrial and extramitochondrial activities in these cells, what is all of a special significance. Therefore, besides direct effects of molecular oxygen on cellular functions of the cerebellar functional units, the study results clearly indicate that cerebral palsy is a complex functional disorder of a number of nervous structures, and that the restoration of circadian rhythm directly affects the function of cerebellum; moreover, it has effect, via hippocampus, on a number of higher and lower structures of the nervous system with evident hypothalamic effects on biological rhythms, including necessary normal rhythm of secretion of not only hypothalamic hormones.

Naturally, the progress of technology, primarily noninvasive nanotechnological procedures, and technologies for defining the activities of a group and individual nerve cells, may significantly contribute to diagnosis of this condition and therapeutical effects, for which the results of our study clearly indicate that molecular oxygen has a key role in pathogenesis and treatment of this disorder.

Multiple etiological factors of this condition, and evidence on disorders of a number of structures, not only corroborate our results but also clearly pinpoint the place of this medical procedure in multidisciplinary approach to restorative-rehabilitation procedure in these children, with apparently significant results before the process of myelinization is completed.

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Potential Conflicts of Interest:
Nothing to report.

TABLE1. Descriptive Statistics of the Participants at the Study, Presented as Percentage (n=52)

Variable	**N**	**%**
	52	
Gender		
Male	28	53.84%
Female	24	46.15%
Age		
3-4 yrs	25	48.07%
5-6 yrs	27	51.92%
GMFCS level		
GMFCS level II	22	42.30%
GMFCS level V	30	57.69%
Earlier exposure to physical treatments		
1-2 yrs	26	50%
3-5 yrs	26	50%
Verbal production		
Whitout production	21	40,38%
Vocalisation	14	26,92%
Syllable	10	19,23%
Word	7	13,46%
Sentence	0	0%

GMFCS, Gross Motor Function Classification System

TABLE 2. Within subjects effect on tested measures after 120 HBO treatments

Within subjects effect	F	df	Huynh-Feldt	Sig.
GMFCS level V lying with rotating	83.84	4	1.00	.000
GMFCS level V sitting	101.92	2,59	.649	.000
SDSC	137.46	3,27	.819	.000
Verbal production	150.54	1	1.00	.000
GMFCS level II standing	99.74	2,76	.691	.000
GMFCS level II valking	142.95	4	1.00	.000
SDSC	98.75	2,38	.595	.000
Verbal production	230.84	1	1.00	.000

GMFCS, Gross Motor Function Classification System; SDSC, Sleep Disturbance Scale for Children

TABLE 3. Pairwise comparisons for tested dimensions

	Pairwise Comparisons (before) factor1 (after) factor1		Mean Difference (before factor1-after factor 1)	SD	Sig.
GMFM level V					
lying and rotation	30 HBO th	60 HBO th	-2,95	.67	.000
	60 HBO th	90 HBO th	-4,5	.53	.000
	90 HBO th	120 HBO th	-5,77	.91	.000
sitting	30 HBO th	60 HBO th	-2,04	.41	.000
	60 HBO th	90 HBO th	-2,95	.41	.000
	90 HBO th	120 HBO th	-4,77	.44	.000
SDSC	30 HBO th	60 HBO th	1,09	.37	.107
	60 HBO th	90 HBO th	5,36	.59	.000
	90 HBO th	120 HBO th	4,81	.63	.000
GMFM level II					
Standing	30 HBO th	60 HBO th	-2,04	.39	.000
	60 HBO th	90 HBO th	-1,62	.26	.000
	90 HBO th	120 HBO th	-2,92	.39	.000
Walking	30 HBO th	60 HBO th	-1,82	.36	.000
	60 HBO th	90 HBO th	-1,7	.30	.000
	90 HBO th	120 HBO th	-2,64	.38	.000
SDSC	30 HBO th	60 HBO th	2,16	.40	.000
	60 HBO th	90 HBO th	3,37	.48	.000
	90 HBO th	120 HBO th	3,19	.48	.000

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GMFCS, Gross Motor Function Classification System; SDSC, Sleep Disturbance Scale for Children; HBO, hyperbaric oxygenation; th, therapy;

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