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Hyperbaric oxygen therapy is safe and effective for the treatment of sleep disorders in children with cerebral palsy

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ABSTRACT

Objective: To observe the effects of hyperbaric oxygen (HBO_2) therapy on the treatment of sleep disorders and its safety in children with cerebral palsy (CP).

Methods: A total of 71 recruited children were divided into two groups based on age: group 1, aged between 2 and 4 years; and group 2, aged between 4 and 6 years. The effects of HBO_2 therapy on sleep quality were observed.

Results: The total sleep items (TSIs) were significantly different in the two groups between pre-HBO_2, post 10 HBO_2 sessions, and post 20 HBO_2 sessions ($p < 0.01$). A total of 15/38 (39.5%) participants in group 1 and 8/21 (38.0%) in group 2 presented difficulty in falling asleep; 17/38 (44.7%) in group 1 and 4/21 (19.0%) in group 2 had a short duration of sleep during the night; and 20/38 (52.6%) in group 1 and 11/21 (52.4%) in group 2 woke up easily in the night. No significant difference in the average TSIs in 59 participants was found after 10 HBO_2 sessions. Eight participants had insomnia after the first 5 sessions, and three in group 2 had nocturnal hyperkinesia after 15 sessions. A seizure during decompression was observed in 2/59 participants (2/419 sessions).

Discussion: These results indicate that HBO_2 therapy is beneficial to improve sleep and is safe for children with CP; however, further studies are necessary to explore the mechanisms of HBO_2 on sleep.

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Cerebral palsy; hyperbaric oxygen treatment/therapy; sleeping; excessive somnolence disorder

Introduction

The prevalence of sleep problems has been reported in 10–40% of children with cerebral palsy (CP) [1,2]. The parents complain that their children have difficulty in falling asleep, short sleep duration, and frequent awakenings during the night [3–5]. Sleep disturbances significantly impair and aggravate children's emotional, behavioral, and cognitive functions [6–8]. The lives of these children and their families are both deeply disturbed. Zucconi [9] speculated that the perception of "common zeitgeber" in brain-injured children changes, synchronization of circadian rhythms is disturbed, and endogenous hormone release is dysfunctional. Although the mechanisms of sleep problems have not been clarified, no specific studies using drug interventions have been carried out to combat sleep disturbances in children with CP, and only a few studies have focused on behavioral interventions and some secondary benefits of pharmacological interventions on sleep in children with cerebral diseases [10,11]. For example, flunitrazepam [12] and baclofen [13] have been reported to reduce seizure frequency, spasticity, and dystonia; and they could also reduce sleep disturbance.

Until now, little is known regarding specific medications to treat sleep disorders in younger children with CP. Although it has been shown that oral melatonin in short-term use in some countries [14] improved sleep latency; it did not decrease nocturnal awakenings in children. Moreover, these studies only included a small number of older children (4–12 years) and the outcome of short-term treatment. Thus, effective interventions for sleep problems in children with brain damage are a truly neglected area in clinical research. Exploring a safe and effective treatment for sleep disturbance in younger children with CP will help to improve their quality of life and the well-being of their families as well.

Hyperbaric oxygen (HBO_2) treatment involves breathing 100% oxygen in a hyperbaric chamber. The atmospheric pressure is elevated 2–3 times more than normal atmospheric pressure. HBO_2 increases the amount of oxygen physically dissolved in the blood, with the arterial oxygen partial pressure (PaO_2) being 1100 mm Hg under 1.6 ATA and elevating oxygen tension to 400 mm Hg in the tissue. The amount of dissolved oxygen meets resting cellular requirements without any hemoglobin. Such doses of oxygen have numerous

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Table 1. Medical history.

	n
Age	
2–3 years (2.66 ± 0.65 years)	47
4–6 years (5.83 ± 1.69 years)	24
Gender	
Female	39
Male	32
Problems at birth	
Low birth weight	8
Prematurity	11
Hypoxic-ischemic brain	29
Respiratory distress	7
Brain bleeding	18
Infection	6
Neonatal jaundice	16
Congenital heart disease	7
Epilepsy	21
Pachygyria	1
Abnormal electroencephalogram	36
Computed tomography scans	
Intracranial hemorrhage	18
Hypoxic-ischemic brain	29
Infarction	19
Malacia	7
Widened subarachnoid	32
Reduction in white matter	32
Ventricular dilatation	7
Periventricular leukomalacia	3
Mother	
Gestational diabetes	15
Placenta previa	2
Type of CP	
Spastic	34
Atonia	12
Athetosis	15
Mixed-Type	10
Sessions of HBO_2 therapy (Mean ± SD)	Total
Group 1 (n = 38) 18.94 ± 8.65	722
Group 2 (n = 21) 16.67 ± 10.65	416

beneficial biochemical, cellular, and physiological effects [15]. HBO_2 therapy has been considered to be a treatment to improve both functional and cognitive abilities; for example, it has been shown to improve the functions of both arms in children with CP [16–21] and to improve sleep disturbances, headaches, memory, and cognitive difficulties in two airmen who suffered from 8-month concussive injuries [22]. Although Collet [23,24] first reported that HBO_2 therapy was not associated with any significant improvement in these areas, McDonagh *et al.* [19] have reviewed that there was some bias in the participants' samples and that an unusual HBO_2 treatment protocol was used in these studies. All neuropsychological assessments depend on enhanced motivation for the parents and their children, and most of the children in McDonagh's study were not enthusiastic or cooperative. More recently, insomnia of patients who suffered from type III osteoradionecrosis and chronic sequelae after brain injury has been reported to be significantly improved by HBO_2 treatment [25,26]. This discrepancy might be due to different HBO_2 treatment protocols and nonrigorous methodology.

Although 13 indications for HBO_2 therapy are accepted by the Undersea and Hyperbaric Medical Society (UHMS) [27], CP is not accepted by the UHMS in the USA. In some countries, especially in China [28], HBO_2 is applied as an important treatment to ameliorate some symptoms of CP [16–21,29] and to improve the effect of other interventions [18,19]. HBO_2 for children is generally considered to be relatively safe below 2 ATA for less than 2 h [16–21]. The common side effects of HBO_2 therapy [30,31] are middle ear barotraumas and oxygen seizures induced at a middle level of pressure (1.75 ATA). They can be prevented almost completely by informing these parents during the first doctor visit, e.g. if the patients have a stuffy nose or fever, they are forbidden to enter the chamber.

After some sessions of HBO_2 therapy in our department, the parents stated that their children had a longer sleep duration, more comfortable sleep, less frequent night waking, and less crying after 1–3 sessions of HBO_2 therapy than prior to HBO_2 therapy. They had a good appetite and mood during the day following HBO_2. In 2005, in our Department of HBO_2 Therapy, the Sleep Disturbance Scale for Children (SDSC) was used to evaluate the effect of HBO_2 on sleep in children with neurological disorders (e.g. hypoxic-ischemic encephalopathy (HIE), CP, traumatic brain injury, and attention deficit hyperactivity disorder. In the present study, we aimed to assess prospectively the effects of HBO_2 in young children with CP and the safety of HBO_2. Bruni [32,33] developed the questionnaire items of the SDSC to evaluate sleep-related behaviors in children and adolescents [32–35] with neurological disorders. Because the focus of this study aimed at initiation and maintenance of sleep, 3 items of total sleep and 13 questionnaire items from the SDSC were adapted to compare these parameters between baseline (1 month pre-HBO_2) and after 10 and 20 HBO_2 sessions.

Methods

Participants and groups

A total of 71 children (aged 2–6 years, see Table 1) with CP diagnosed in the Department of Pediatrics [*TBA-blinded for review*] Hospitals were enrolled as outpatients from February 2005 to February 2013 in the Department of HBO_2 Therapy at [*TBA-blinded for review*] and the [*TBA-blinded for review*].

In the present study, all situations, parental intervention, and habits for sleeping at home were kept the same as those in pre-HBO_2 to eliminate the influences of sleep ecology.

The inclusion criteria [36] were set as follows: The participants (1) were 2–6 years old and had a documented diagnosis of CP with a history of hypoxia in the perinatal period; and (2) had a motor development delay of more than 3 months and abnormal signs on magnetic resonance imaging or computed tomography (CT) scans, showing periventricular leukomalacia, intracranial hemorrhage, infarction, malacia, widened subarachnoid, reduction in white matter, or ventricular dilatation.

Table 2. Contraindications of HBO_2 therapy.

Absolute contraindications	
UHMS	China
Untreated tension pneumothorax	Untreated tension pneumothorax Active bleeding *in vivo* Untreated malignancy Bronchopulmonary dysplasia
Relative contraindications	
	1. Untreated severely complicated congenital heart disease 2. Upper respiratory tract infection with stuffy nose and fever 3. Epileptic seizures while taking antiepileptic drugs (every day within a week before HBO_2) 4. Bulla 5. Acute asthma (within 1 month before HBO_2) 6. Convulsions (within 1 month before HBO_2) 7. Acute throat inflammation

Note: UHMS, Undersea and Hyperbaric Medical Society.

Table 3. Scales and indications of items with the modified SDSC.

Item	Indication	Scale
1. Sleep hours/night on most nights	9–11 h	1
	8–9 h	2
	7–8 h	3
	5–7 h	4
	<5 h	5
2. How long after going to bed does your child usually fall asleep?	<15 min	1
	15–30 min	2
	31–45 min	3
	46–60 min	4
	>60 min	5
3. Going to bed reluctantly	Never	1
4. Difficulty in falling asleep 5. Falling asleep anxiety 9. Falling asleep sweating 10. Night awakenings	Occasionally (1–2 times/mo)	2
11. Difficulty in falling asleep after awakenings 16. Night sweating	Sometimes (1–2 times/wk)	3
23. Difficulty in waking up 24. Tired when waking up 25. Sleep paralysis	Often (3–5 times/wk)	4
26. Daytime somnolence	Always (daily)	5

The exclusion criteria were set as follows [23]: The subjects (1) had hereditary cerebral disorders; (2) had a recent episode (within 1 month) of acute otitis or chronic otitis (three episodes or more within the previous year); (3) had been treated with botulinum toxin, orthopedic surgery, or dorsal rhizotomy; (4) received HBO_2 treatment previously; (5) underwent fewer than eight HBO_2 sessions; or (6) had caregivers or parents who failed to complete the sleep data questionnaire.

The medical histories of the participants are listed in Table 1. The contraindications of HBO_2 therapy indicated from the UHMS [27] and China [37] [*TBA-blinded for review*] were excluded from recruitment (Table 2). According to the HBO_2 treatment protocol in [*TBA-blinded for review*], the participants underwent 20 sessions for a course. The study was approved by the Ethics Committee of the two hospitals mentioned above. Questionnaires of sleep disturbance and consent for data use and HBO_2 treatment were requested and approved by their parents after describing the study design and their cooperation at the first doctor consultation.

The children were divided into two groups based on age: group 1, aged between 2 and 4 years; group 2, aged between 4 and 6 years. The participants were further divided into four subgroups based on the type of motor developmental delay: spastic, atonia, athetosis, and mixed-type (different types of CP have different sleep disorders).

Outcome parameters

The total sleep items (TSIs) for initiation and maintenance of sleep was applied to evaluate the therapeutic response of sleep in children with CP [2] as follows: (1) the average time to fall asleep; (2) the average hours of sleep per 24 h; and (3) the average number of night awakenings during 1 month pre-HBO_2 as well as post 10 and 20 HBO_2 sessions.

The SDSC questionnaire has been described and validated for sleep disturbance in children with neurological disorders [33] and was used in this study. The SDSC scale included 26 items in a 5-value Likert-type scale. In the present study, the difficulty of initiation and maintenance of sleep (DIMS) disorders were examined. Factor 1 (DIMS; items 1–5, 10, and 11) was also applied to evaluate sleep in these children (see Table 3). Furthermore, Factor 5: Disorders of excessive somnolence (DOES, items 23–26) and Factor 6: Sleep hyperhidrosis (SHY, items 9 and 16) were investigated.

Safety criteria of HBO_2 therapy

Indications for ear discomfort or pain in children were judged based on the child crying and simultaneously grabbing his/her ear(s) during compression. If the participants or attendants complained of ear discomfort or ear pain during compression, the ear drum should be checked from outside the chamber after decompression. Otoscopic findings were categorized according to the modified Teed classification system of middle ear barotraumas [38]. The occurrence of seizures during HBO_2 therapy was diagnosed according to the UHMS Guidelines of HBO_2 Therapy [27,37].

Follow-up period

HBO_2 therapy had a continuous effect on sleep for approximately 1–3 months. All children examined were followed up for more than 1 year. Ten of these children were going to be followed up for more than 3 years; at present, we are still undergoing follow-up exams.

Data collection

The three items of therapeutic response and the SDSC questionnaire from parents evaluated each child's quality of sleep and was recorded at the baseline (pre-HBO_2)

Table 4. Basic medical data of the two age groups.

	Group 1, *n*	Group 2, *n*
GMFCS level		
I	10	6
II	17	5
III	6	7
IV	3	1
V	11	5
Total	47	24
Type of epilepsy		
Generalized tonic-clonic seizures	9	4
Complex partial seizures	2	1
Simple partial seizures	0	2
Muscle twitching seizures	2	1
Total	13	8
Abnormal electroencephalogram	23	13
Type of cerebral palsy		
Spastic	26	15
Atonic	5	0
Athetosis	3	2
Mixed	4	4
Total	38	21
Difficulty in falling asleep (going to bed or after awaking)	15	8
Short time sleeping <5–7 h	17	4
Easily waking up	20	11

as well as post 10 and 20 HBO_2 sessions. The data were reviewed and entered into the research database by the two doctors on duty for HBO_2 treatment, separately.

Protocol of HBO_2 therapy

HBO_2 therapy was administered in a multi-place chamber with compressed air, and the children inhaled 100% O_2 with a hood covering their head (See-long, USA). There were three phases for HBO_2 (Liu et al. 2006): compression for 10 min, isobaric pressure of 1.6 ATA for 50 min, and decompression for 10 min. The duration of inspired oxygen for one session was 60 min (during isobaric and decompression phases), once daily for 5 days per week. All children and attendants (caregivers) drank or ate fruits during compression. A total of 15–20 sessions of HBO_2 were given to the participants.

The price for one session of HBO_2 was 65 RMB, which was paid by the family. For [*TBA-blinded for review*] residents, 80% of the costs of HBO_2 were paid by the Social Security Medical Fund of [*TBA*].

Statistical analysis

All data were analyzed by computer using the Statistical Package for the Social Sciences (SPSS 13.0). The parameter differences for the SDSC items before and after HBO_2 therapy were analyzed by a paired *t*-test. The differences in the SDSC items between 10 and 20 sessions of HBO_2 therapy were analyzed by analysis of variance (ANOVA). To account for the number of subscales within the measurements, statistical significance was set to $p < 0.01$.

Results

Data were analyzed from 71 of the original participants, including 39 girls and 32 boys. All participants had motor and mental retardation because of cerebral problems during the perinatal period (see Table 1). A total of 35/71 participants had more than two factors causing disease during the perinatal and/or postnatal period. Brain CT scans showed intracranial hemorrhage, HIE, infarction, malacia, widened subarachnoid reduction in the white matter, or ventricular dilatation. A total of 43/71 participants had more than two signs on the CT scans. Twenty-one participants had epilepsy (see Table 1). A total of 12/21 children with epilepsy took valproate, 6/21 took clonazepam, and 3/21 took carbamazepine (according to a prescription by a specialist for epilepsy). In total, 55/71 could not walk and 52/71 had no verbal speech. The motor function levels in the two groups are listed in Table 4.

Pre- and post-HBO_2 TSIs

Seven of the participants who underwent fewer than eight sessions were excluded from this study due to a fever, severe crying in the chamber, or family factors. Five of the participants were excluded from the analysis because their caregivers and parents failed to complete three total sleep scores (TSSs) and the sleep data on the SDSC questionnaire. The remaining 59 participants underwent 1138 sessions (10–20 sessions, Table 5). The TSIs were significantly different in the two groups between pre-HBO_2 and post 10 and 20 HBO_2 sessions (Table 5, $p < 0.01$). A total of 15/38 (39.5%) participants in group 1 and 8/21 (38.0%) participants in group 2 presented difficulty in falling asleep (going to bed or after waking up in the night). A total of 17/38 (44.7%) in group 1 and 4/21 (19.0%) in group 2 had a short duration of sleep in the night. A total of 20/38 (52.6%) in group 1 and 11/21 (52.4%) in group 2 woke up easily during the night (Table 6). The pre- and post-HBO_2 TSIs were improved to some extent by 10 and 20 sessions (Table 5, $p < 0.01$). The sleep latency time was shortened, the average hours of sleep duration each day were prolonged, and the average number of night awakenings per week decreased significantly.

The incidence of patients with a short sleep latency time, short sleep disturbance, and easily waking up in the night significantly decreased in group 1 ($p < 0.05$) but was not different in group 2 ($p > 0.05$) between pre-HBO_2 and post 10 HBO_2 sessions (see Table 6). After treatment, these patients in the two groups were calm and had no difficulty in falling asleep at bedtime. The number of cases with short sleep duration (less than 5–7 h) in the two groups was reduced from 21 to 6.

Modified TSS

Characterization of all the participants was as follows: 69.5% (41/59) had spastic CP, 8% (5/59) had athetosis and atonic seizures, respectively, and 13.6% (8/59) had mixed CP. The items of Factor 1 (DIMS) were significantly improved in 76.1% (35/46) of the participants with spastic CP and athetosis (the sleep hours/night on

Table 5. Total sleep items: pre-HBO_2 and post 10 and 20 HBO_2 sessions.

Group	*n*		Average time to fall asleep (min)	Average hours of sleep duration one day per week (h)	Average number of night awakenings per week	*t*	*p*
1	38	Pre-HBO_2	31.52 ± 8.87	10.50 ± 2.51	2.65 ± 1.46		
		Post 10 HBO_2 sessions	19.02 ± 4.45*	13.69 ± 3.89	1.74 ± 0.96	6.4896	0.0080*
		Post 20 HBO_2 sessions	18.10 ± 3.73	12.01 ± 4.15	1.58 ± 0.63	7.3687	0.0072*
2	21	Pre-HBO_2	37.28 ± 10.56	11.04 ± 3.81	1.19 ± 0.85		
		Post 10 HBO_2 sessions	20.77 ± 9.22	13.91 ± 4.01	0.90 ± 0.68	6.1879	0.0001*
		Post 20 HBO_2 sessions	21.81 ± 10.32	13.81 ± 2.89	0.86 ± 0.57	6.3528	0.00014*

Table 6. Numbers of total sleep items: pre-HBO_2 and post 10 HBO_2 sessions.

Groups	*n*		Numbers of difficulty in falling asleep (ratio)	Numbers of short sleep duration (<5–7 h) (ratio)	Numbers of easily wake up (ratio)
1	38	Pre-HBO_2	15 (39.5%)	17 (44.5%)	20 (52.6%)
		Post 10 HBO_2 sessions	Δ7 (18.4%)	Δ8 (21.1%)	Δ11 (28.9)
2	21	Pre-HBO_2	8 (38.1%)	4 (19.0%)	11 (54.4%)
		Post 10 HBO_2 sessions	☆5 (23.8%)	☆2 (10.0%)	☆7 (36.8%)
Total	59	*p*	Δ$p < 0.05$	☆$p > 0.05$	

Table 7. ANOVA post 10 and 20 HBO_2 sessions.

	Sum of squares	Mean square	*F*	*p*
Between groups	56.357	28.045	2.301	0.826
Within groups	8024.31	27.385		
Total	8153.247			

most nights was prolonged by 1–2 h/day, falling asleep became easier, the awakening frequency in the night decreased, and the likelihood of being in a good mood when waking up in the morning increased) after 10 sessions of HBO_2. Moreover, the items of DOES changed. In particular, tiredness in 51.3% (7/13) of the participants with atonia and mixed CP was improved when waking up, they had a good mood in the daytime, and they more actively moved their limbs after 10 sessions; however, the SHY items did not change markedly after 10 sessions of HBO_2.

The average modified TSS of the 59 participants was not significantly different (Table 7) between after 10 and 20 sessions. Moreover, eight participants had a short sleep duration and difficulty in falling sleep at night after the first five HBO_2 sessions; however, these sleep problems were relieved following 5–7 sessions. Three of the 59 participants older than 4 years had nocturnal hyperkinesia after more than 15 sessions. Hyperkinesia and excitement in the night was relieved within 3–5 days after stopping HBO_2 treatment.

Safety issues of HBO_2 therapy

Ear discomfort and pain occurred in 12 of the children and 21 of their parents/caregivers, especially on first exposure in the chamber. It is possible that they purposely did not reveal their medical conditions such as catching a cold or having a stuffy nose or throat inflammation to achieve a quicker outcome. Middle ear barotraumas did not occur in any of the 71 children checked using otoscopy by the same doctors in the ENT Department [*TBA-blinded for review*]. None of the children or their parents/caregivers experienced pulmonary barotraumas, gas embolism, or claustrophobia. There was no occurrence of fire. Two of the 59 children (2/419 sessions) experienced a seizure during decompression at 10–15 kPa. During decompression, if a child experienced a seizure, decompression was immediately stopped (the pressure in the chamber was maintained at the current pressure to prevent lung damage). Meanwhile, the tent was immediately removed from the child, who then breathed air in the chamber to relieve the seizures (to alleviate convulsions due to oxygen toxicity). One or two minutes later, the seizures stopped and the participants went safely out of the chamber by following the decompression procedure. After stopping HBO_2 therapy for more than 2 weeks and taking anti-convulsants, the participants were safe to undergo HBO_2 treatment again, and no more seizure attacks occurred.

Discussion

In the present study, we showed sleep improvement such as reduced irritability, easy awakening, and prolonged sleeping in young children with CP after 10 sessions of HBO_2 therapy. The modified TSS in these patients was markedly improved as well. The average modified TSS of the 59 participants was not significantly different between 10 sessions and 20 sessions.

Cerebral disorders [1–4] may cause sleep-wake rhythm disorders and various sleep problems such as a short duration of sleep, difficulty in falling asleep, easily awakened in the night, and sweating during sleeping, which could further aggravate brain injuries and might worsen their mental and motor retardation. In the present study, a modified TSS and DIMS were applied to evaluate bedtime resistance, sleep duration and latency, night awakenings, and childhood sleep disorder [4,33]. We found that the incidence recorded was similar to that in previous reports [1,2]. Sleep disturbance occurred

in 69.5% (41/59) of the participants with spastic CP and in 13.6% (8/59) of the participants with mixed CP. These findings might be due to the fact that children with severe athetoid CP had decreased twitching movements during rapid eye movement sleeping [39,40] and that certain physical factors such as spastic quadriplegia and dystonic/dyskinetic CP are more common in these patients [2,39,40].

Interestingly, the items of the DIMS were significantly improved in the participants with spastic CP and athetosis after 10 sessions. Moreover, the items of the DOES were improved in the participants with atonia and mixed CP, and their tiredness was improved; however, the SHY items were not significantly influenced, indicating that HBO_2 therapy was beneficial to improve sleep quality. However, the incidence of modified TSS pre- and post HBO_2 therapy in group 2 was not significantly different, possibly due to the small sample and the fact that the children were older in group 2. Similarly, the effects of HBO_2 therapy on sleep disturbance in children with CP have the same efficacy as on sleep disturbance in adults (1.5 ATA, 100% oxygen for 1 h each day, 40 sessions for a course) [22,25,26]. Moreover, HBO_2 therapy contributes to enhancing mitochondrial recovery and reducing apoptosis in neuronal cells subjected to hypoxia [19,41,42]. HBO_2 has been gradually used in traumatic brain injury and stroke victims in Asia to alleviate hypoxia-induced myelin damage [42] and to improve cognitive and motor function. Since the consensus at the 7th International Congress of Hyperbaric Medicine in Moscow in 1981 was that HBO_2 therapy reduces post-hypoxic sequelae for infants with asphyxia in intensive care, HBO_2 therapy has been gradually employed for HIE [43,44] and CP for more than 30 years in China [37]. In this study, 59 participants accepted HBO_2 treatment and achieved a good outcome. It is possible that HBO_2 therapy improves hypoxia and ischemic cerebral cells and promotes activation, growth, and migration of neural stem cells [45–47]. Furthermore, HBO_2 therapy interferes directly with polymorphonuclear neutrophil adhesion, improves several markers of microvascular dysfunction after ischemia-perfusion, and promotes the formation of the collagen matrix [15]. It may help to salvage the penumbra in stroke patients and improves the clinical outcome [15,28,48]. Altogether, these findings provide us good evidence to understand the mechanisms of HBO_2 on CP with hypoxia/ischemia.

Nevertheless, in the current study, 8 participants had a short duration of night sleep and had difficulty in falling asleep at night after the first 5–7 HBO_2 sessions, and 3/21 participants (3/416 sessions) older than 4 years had nocturnal hyperkinesia after more than 15 HBO_2 sessions but were relieved within 3–5 days after stopping HBO_2 therapy. Taken together, HBO_2 therapy might have a double-edged sword effect on sleep in children with CP. It is assumed that HBO_2 has an inhibitory effect on the hyperexcitability of brain cells but exhibits an excitatory effect. The exact mechanism on sleep by HBO_2 is unclear; however, HBO_2 therapy is believed to help to restore the neural pathways injured by hypoxia and trauma as shown by single-photon emission computed tomography brain imaging [49–51]. It is possible that HBO_2 reduces the spasticity with CP [52] and alleviates various chronic pains through producing analgesia [53,54]; in addition, some reports suggest an association between pain and sleep [55]. Therefore, further studies are necessary to explore the mechanism of HBO_2 treatment on sleep in children with CP.

A few studies on sleep interventions in children have been reported, and some medications cannot be taken for a long term. Therefore, interventions for sleep disorders are important to be considered for improving the effects of rehabilitation. These interventions should have few side effects and be easily carried out in the clinic. Recently, the interaction between sleep disorders and neurological diseases has been reported [10]. Meanwhile, sleep improvement may also decrease muscle spasms and be helpful to improve motor function as well [39,40]. This new therapeutic intervention for CP could save time and reduce the economic burden for their families.

Some studies have shown that HBO_2 therapy is inefficacious for HIE or CP and that it has some side effects [30,31], such as middle ear barotraumas, oxygen seizures, and retinopathy of prematurity (ROP). In contrast, other studies have shown that HBO_2 therapy is beneficial to repair ischemia-induced neuronal cell damage [45–47] and that transient and interrupted HBO_2 treatment cannot cause ROP [56]. In the present study, ear discomfort and pain occurred in 12 children and 21 of their parents/caregivers at the first exposure; however, middle ear barotraumas did not occur because of the special anatomy of the tympanic membrane (round tympanic membrane and less than a 30° angle with the external auditory canal) and Eustachian tubes (short, wide, and approximately horizontal position) in infants and young children [57]. Our experience is that it is very important to educate patients and caregivers of children how to adjust the Eustachian tubes correctly, and patients should be forbidden into the chamber when they have a cold, a stuffy nose, throat inflammation, or tonsillitis.

At the first consultation, children and caregivers (who accompanied the children in the chamber) must be examined by chest X-ray to exclude the possibility of a giant cyst/bullae, severe emphysema, or pneumothorax to ensure that no pulmonary barotrauma occurs. Two children out of 419 sessions (0.5%) (2/59 children who suffered from epilepsy before HBO_2) had seizures during decompression. After stopping HBO_2 treatment and having no seizures for more than 2 weeks, these children could receive HBO_2 safely again. The incidence of seizures was 0.5%, far less than the 3% reported previously [58]. The oxygen concentration must be consistently kept less than 23% and monitored carefully during HBO_2 therapy in the multi-person chamber. Fires in the

chamber can be prevented by following the rules of safe operation for HBO_2 therapy.

It is worthwhile to note that the main side effect of hyperbaric treatment is convulsions due to oxygen toxicity. However, the rate of their occurrence is relatively low, and the occurrence is associated with a higher oxygen partial pressure and a longer time to breath oxygen [59]. The results of the present study showed that the incidence of oxygen convulsions was higher than that reported by Heyber [58], which might be due to the fact that the subjects in the present study were only limited to children with CP and that the child brain is at the developmental stage and is sensitive to some factors (such as a high fever, drugs, and oxygen). Determining how to reduce the incidence of convulsions/seizures due to oxygen toxicity should be further studied in the future.

The limitations of the present study were that it was a pilot clinical observation without a control group and that no independent measures such as polysomnographic data were obtained. In addition, this study had a small sample size. Furthermore, the effects of age on the results were not sufficiently examined. It would be interesting to study the differences in the effects of HBO_2 therapy between the two age groups in our next clinical trial. Nevertheless, the mechanism of sleep disorders in children with cerebral injuries treated with HBO_2 should be investigated further. Moreover, the appropriate HBO_2 treatment protocol should be optimized for a large sample of children in different age groups.

In summary, HBO_2 therapy is a safe and effective treatment for initiation and maintenance of sleep in children with CP, and it has minimal side effects, which can be prevented by obeying the rules of operation for HBO_2 therapy. This pilot study provides evidence of the effect of HBO_2 treatment on sleep for children with CP.

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