

Cerebral Palsy Update - Focusing on the Treatments and Interventions

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Cerebral palsy (CP), known as “Little’s disease” is the most common neurologic disorder in pediatric patients. The core problem of CP is the abnormal movement and posture which manifests very early in the development. The cornerstone to treat the children with CP is the conventional rehabilitation program based on neurodevelopmental approach that has been done for decades. Recently, various translational research has emerged, and focused on the changing therapeutic paradigm using high technologic equipment such as computer- or robotic-approach, botulinum toxin, or stem cell use with potential therapeutic effect. Many other trials using newly developed devices, or combination of old and new therapies are ongoing to demonstrate the evidence, however obstacles still remain. Regarding rehabilitative therapy, the use of exercise-based treatment such as early intervention, gross motor task training, hippotherapy, reactive balance training, treadmill training with/without body weight support, and trunk-targeted training are promising. Virtual reality, robot-assisted and computer-enhanced therapies are very potent therapeutic tools for CP under way of mass commercialization. Regarding medical therapy, botulinum toxin injection showed the most concrete benefit for CP children. Stem cell therapy is just beginning, performing experimental studies *in vivo*. The author reviewed the current research, expanding therapeutic options to improve the posture and movement control in children with CP.

Key Words: Cerebral Palsy; Therapeutics; Rehabilitation; Exercise

INTRODUCTION

Cerebral palsy (CP) is the most common neurological disease in children with an incidence of 1 to 2.3 per 1,000 live births. After CP was firstly introduced by William John Little in 1843, it has been used as an umbrella term to describe a group of permanent disorders related to brain insults occurring in the growing brain. Currently, CP is defined as a persistent but not a progressive disorder of posture and movement system, associated with functional activity limitations and sensorial, cognitive, communication problems, epilepsy, and musculoskeletal system problems [1]. Gross and fine motor activities of CP result from the summation of various deficits such as abnormal muscle tone, joint contracture, abnormal muscle co-contraction and timing, and asynchronous recruitments of related muscles. Postural impairments are driven

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Received 7 December 2015

Revised 29 January 2016

Accepted 31 January 2016

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from brain lesions, which cause insufficiencies in postural networks. Common problems in postural control of CP are scarcities in anticipatory and reactive postural regulations, as well as sensory and/or musculoskeletal inefficiencies of postural control.

Despite of development in modern medicine and sciences in the 21st century, the incidence of CP was not decreased in western countries. As a result, CP is the most common disability in childhood with prevalence unchanged for the last 60 years. Similar to the unchanged incidence and prevalence, the management of CP also didn’t make a breakthrough so far. Fortunately, new treatment regimens with evidence have been continuously introduced, and debates for the effects of interventions are ongoing. This review will discuss about the therapeutic interventions for the rehabilitation of CP and their clinical usefulness until now.

REHABILITATIVE INTERVENTION

1. Early intervention

Early intervention means a process of providing services to children from birth to 36 months of age who have delays in one or more area of physical, cognitive, social, emotional, or adaptive development [1]. Early intervention programs include various areas such as therapy, family training, health, psychology, vision and assistive technology, social work, and care coordination services. Spittle A. et al., reviewed the effect of early developmental intervention to the preterm infants from 1966 to 2015, and concluded that early intervention programs for preterm infants have a positive influence on cognitive and motor outcomes during infancy, with cognitive benefits persisting into preschool age. But, further studies to determine which early developmental interventions are the most effective in improving cognitive and motor outcomes, and on the long term effects of these programs will be the challenge faced [1,2].

2. Neurodevelopmental treatment (NDT)

After the introduction of NDT from Berta and Karel Bobath, NDT - also known as the Bobath approach - has been the major therapeutic approach practiced by experienced therapists for the rehabilitation of CP, and has been an evolving concept since the 1940s. According to the Bobaths at the beginning period, the major problems of CP originate from central nervous system dysfunction, which interferes with the normal postural control and motor development against gravity. And the goal of treatment is the establishment of normal motor development and function without contractures or deformities. NDT focused on sensorimotor components of muscle tone, reflexes and abnormal movement patterns, and postural control. Therapeutic handling using sensory stimuli was used to inhibit abnormal reflexes, spasticity, and abnormal movement patterns, and to facilitate normal muscle tone and equilibrium reaction [3]. The child was a relatively passive recipient of NDT treatment. The normal sequence of development was recognized as a basic frame for treatment. With the development of neuroscience, the emphasis of NDT has been changing and the idea of 'key points of control' was introduced and more active participation of children was also encouraged. Systemic preparation of specific functional tasks was instituted in the actual daily living setting. According to the research, NDT alone or NDT combined with 'conventional rehabilitation' therapies (range of motion exercise, muscle strengthening, and locomotor activities), improved

postural balance over 6 weeks in children with diplegic CP. Eight hours (two 40 min sessions/week for 6 weeks) of NDT for the control of trunk balance enhanced postural control of children with spastic diplegia, aged 3 to 10 years, especially in the sitting posture [4,5]. But the result of NDT was conflicting for relatively good functional CP with the gross motor function classification system (GMFCS) I-II [6].

3. Progressive resistance exercise (PRE)

Until recently, strengthening exercise such as PRE was not recommended because it would increase spasticity of cerebral palsy patients. But, recent clinical trials showed strength training such as PRE can improve lower-limb muscle strength in children with CP without increasing spasticity. The background principle of PRE is 'the overload principle', that is, to build the muscle bulk and strength, progressively increasing in intensity exercise is obligatory. For successful PRE, training should be tailored, and organized with progressive increase in intensity, thereby stimulating strength gains that are greater than those associated with normal growth and development. PRE includes resisted motion or lifting tasks, with structured increases in training loads, to increase muscle strength and coordination. But, execution of resisted ankle and knee exercises for a total of 6 hours (two 15 min sessions/week for 12 weeks), joined with rehabilitation (12 hours), did not improve standing balance or gait kinematics in well walking children with CP, aged 5 to 14 years [7].

4. Gross motor task training (GMTT)

A task-specific program like GMTT is a more appropriate training program for motor learning, which includes practice of functional movements in activities of daily living. GMTT was conducted by replication of simple functional gross motor exercises (e.g. roll over, come to sit, sit to stand, standing and walking). Six weeks (five 1hour sessions/week, total 30 hours) of sit-to-stand and step-up exercises improved standing balance and dynamic postural stability during gait in children with CP aged between 5- and 12-year-olds [8]. A lower dose (total 10 hours) of GMTT such as sit-to-stand, standing, walking, and object pick-up activities also improved dynamic balance during gait in 4- to 11-year-old children with CP [9]. As a point of exercise specificity and functional training, GMTT has higher clinical utility because it can be performed in most therapeutic settings without specialized devices.

5. Hippotherapy and/or hippotherapy simulators

Except one study, the data using a real horse revealed relatively uniform beneficial effects on the function of CP [10-23]. With specialized programs using horseback riding and horse care, the delivery of motor and sensory stimulation has shown improvement in sitting and standing balance for ambulant, school-aged CP children. But, the beneficial effects of hippotherapy significantly differed according to the level of GMFCS or functional status of cerebral palsy. There were no balance gains in younger (2-5 years), wheelchair-dependent (gross motor GMFCS V) children after lower-dose hippotherapy (one 1 hour session/week for 8 weeks) in sitting balance [14]. Of importance, children with mild spastic CP were more likely to have improvement in postural control after hippotherapy compared with severe spastic CP children. For postural control with hippotherapy, at least 16 hours were needed.

But, the data using hippotherapy simulators has shown more or less conflicting data according to the dose of simulator uses and severity of CP until recently. When compared with hippotherapy, simulator studies had several limitations such as the heterogeneity of subject (GMFCS I-V), varying therapy dose (2.5-8 hours), etc. [15].

6. Reactive balance training (RBT)

RBT contains repetitive exercise of balance recovery, when erect on a supporting surface that is disturbed without warning in various directions. After exercise on a force platform for 2 hours (one 20-25 min session/day for 5 days, 100 perturbations/ session), standing balance was improved in walking children with CP (GMFCS I-II) [4].

7. Treadmill training (TT) with (no-, partial-, full-) body weight support

TT involves walking or running on a treadmill with full-, or partial-, or no-body weight support. In several studies, TT without body weight support for 7 hours (two 30 min. sessions/week for 7 weeks) for ambulant CP (GMFCS I-II) showed improvement in standing balance [24]. Robot assisted partial- or full- body weight support TT also showed improvement in standing balance, and in foot loading symmetry with eye open for partial ambulant children (GMFCS II-III) [25]. Contrary to the effectiveness in partial weight bearing TT with robotics, further research with randomized controlled study designs still need to determine the efficacy of TT for children with poor mobility (GMFCS IV-V).

8. Functional electrical stimulation (FES)

Of five randomized trials, three trials reported statistical significance between-group differences in favor of FES compared with those without FES. But, two trials reported no statistically significant results between-group differences of FES compared with activity training alone [26]. FES along with rehabilitation exercise applied to back and abdominal muscles concurrently showed a more marked improvement in postural alignment than rehabilitative therapy alone. The protocol of FES application was an order of 10 seconds 'on' followed by 12 seconds 'off', frequency of 25 to 35 Hz, pulse width of 250 μ s, and intensity of 20 to 30 mA. Total time was 10 to 18 hours (five or six 30 min. sessions/week for 4-6 weeks), with the same procedure as in common with rehabilitation. There was no specific discomfort with children receiving FES [27].

9. Trunk-targeted training (TTT)

TTT consists of exercises focused on trunk muscle strengthening and control. Trunk-strengthening exercises using a vibrating platform from between 1.5 and 2.5 hours over 4 weeks demonstrated the improvement in postural alignment and functional muscle strength. A few studies showed vibration training itself can induce gross motor function and bone mineral density for cerebral palsy. But, further studies are required to prove the real benefits of vibration therapy on balance and postural alignment of CP [28].

10. Visual biofeedback (VB)

VB is a standing training on a balance platform in a laboratory while maintaining the center of pressure, symbolized as a red dot on a computer screen, static, or shifting it to a target. VB training for 9 hours (three 30 min. sessions/week during 6 weeks) improved the performances on the tasks that were trained in ambulant hemiplegic school-age children with CP, GMFCS I. And furthermore, the results for gait showed that the walking pattern became more symmetrical after the training [29].

11. Virtual reality (VR)

VR can be specifically tailored for individualized rehabilitation while the game-based nature appeals to motivation and engagement with the intervention and is particularly relevant for children with CP. Conflicting results were obtained on the impact of virtual reality. Five hours (four 25 min. sessions/week for 3 weeks) of supervised Wii Fit training, in a physiotherapy clinic, playing games aimed at improving standing balance and weight shift, re-

sulted in improved standing balance for children with spastic hemiplegia, GMFCS I-II. However, stair climbing was unchanged or, in some cases, deteriorated. Snider et al. [30], reviewed the VR as a therapeutic option for CP and concluded that VR has potential benefits for children with CP. However, the current level of evidence is poor and empirical data is lacking. Future methodologically rigorous studies are required.

12. Robot-assisted and computer-enhanced therapy

Robot-assisted rehabilitation in combination with virtual reality has rapidly evolved with technological advancements over recent years. Robot therapy can complement conventional therapies and provide a task-specific functional training, with a high number of repetitions over a prolonged time period. Novel technologies, like robotic-assisted gait training (RAGT) and other computer-assisted systems to improve upper extremity function, are increasingly implemented in the pediatric field [31]. The advantage of virtual reality is that it can provide real time feedback about the patient's performance, and motivate young patients to continue exercises with challenging virtual scenarios. Preliminary findings until recently indicate that robot-assisted training in children with central motor impairment could be beneficial, but conclusive evidence about its efficacy is still lacking. But, therapeutic potential may be enormous for the future.

13. Constraint-induced movement therapy (CIMT) for upper limb interventions

CIMT is to restrict the use of the less-affected hand and arm to encourage the use of the more-affected upper limb [32]. For CIMT, a variety of restraints, including non-removable/bi-valve casts, slings, splints, and gloves/mitts are used [33]. A significant treatment effect favoring CIMT was reported by many authors. Suggested impacts of CIMT on the developing brain are true recovery in the damaged brain, or compensation of neighboring undamaged brain, or acquiring bilateral organization of unlesioned hemisphere, or CIMT might influence inter-hemispheric inhibition by reducing cortical activity in the unlesioned hemisphere. But, the optimal type and duration of CIMT is yet undetermined.

14. Hand-arm intensive bimanual therapy (HABIT or BIT) for upper limb interventions

HABIT was developed by Charles J. and Gordon A.M. in 2006 focusing on structured practice of functional activities that neces-

sitate bimanual hand use. Children practice bimanual activities 6 hours/day for 10 weekdays (60 hours). According to Dong et al., CIMT and BIT both produced similar improvements in the bimanual and unimanual capacities of the affected arm and overall functional performance. But, CIMT yields more improvements in the unimanual capacity of the impaired arm compared with BIT [34].

MEDICAL INTERVENTION

1. Botox injection

Injection of botulinum toxin has been a major advance in the care of children with CP during the last two decades [35]. The effects of botulinum toxin are seen in patients with all levels of GMFCS. Botox has been shown in multiple studies to reduce spasticity in the upper and lower extremities with a low incidence of side effects. The common sites of injections are the adductors, hamstrings, gastrocnemius, and soleus in lower extremity, and flexors of the arm, wrist, and fingers in the upper extremity. Botulinum toxin also may be used with other treatments, such as oral medication or intrathecal baclofen. To guide injection, electromyography or ultrasonography can be used. Clinical effect is usually visible within a week, and the peak at about a month. After that, the effect gradually declines, and reinjection is required in a three or four month interval.

According to Albavera-Hern et al. [36], flu-like feeling and fever, pharyngitis, nonspecific pain, falls, respiratory tract infection, bronchitis, vomiting, seizures, urinary incontinence, asthma, and infections were reported as adverse events. But, most of them are described as localized and minor.

Special warning for botulinum toxin is that there may be a distant spread of toxin effect beyond the treatment area, with the possibility of breathing and swallowing difficulties, and the risk of death. Adverse events could occur within hours of injection, or weeks later. The incidence of adverse events varies by toxin type. Overall rate of side effect for botulinum Type A was between 6.2% and 10%. It was 29.8% in type B and included bowel and bladder incontinence, dry mouth, swallowing difficulty, weakness, hypotonia, and increased seizures. Naidu et al. [37] recommended caution in patients at levels IV and V with a history of aspiration and respiratory disease. Patients with oropharyngeal dysfunction, pseudobulbar palsy and a high GMFCS level were considered as a high risk group of complication. But, the relationship between dosing

and adverse events has continued to be debated and further delineation is needed.

2. Stem cell-based intervention

Until now, the main theme of umbilical cord blood (UCB) stem cells targeting cerebral palsy was the safety and feasibility of UCB stem cells. Exceptionally, Romanov et al. [38], published the data using Human allogeneic ABO/Rh-identical UCB cells for treatment of CP recently. Patients were followed for 3-36 months, and they reported that multiple cell infusions did not cause any adverse effects. In contrast, in most patients who received four or more UCB cell infusions, positive dynamics related to significant improvements in neurological status and/or cognitive functions were observed. As a conclusion, multiple intravenous infusions of allogeneic ABO/Rh-identical UCB cells may be a safe and effective procedure and could be included in treatment and rehabilitation programs for juvenile patients with cerebral palsy. But, the research using UCB stem cells are still sparse and need further studies.

CONCLUSION

To treat the movement and posture abnormalities in the children with CP, translational research has been emerged recently. Based on the basic rehabilitative approaches using neurodevelopmental techniques, various exercise treatments such as early intervention, gross motor task training, hippotherapy, reactive balance training, treadmill training with/without body weight support, trunk-targeted training, and combination of these exercises have been developed and showed more promising results than the conventional therapy. FES, NDT, visual biofeedback, virtual reality, CIMT, HABIT, robot-assisted and computer-enhanced therapies are also expanding the horizon of treatment regimen in children with CP. Botox injection is world widely used, and stem cell therapy is introducing a change in the basic therapeutic paradigm. But, to treat the children with CP still has a long way to go.

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