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Brain Stimulation Techniques in Cerebral Palsy

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Abstract

Cerebral palsy (CP) is presented as the most prevalent neurodevelopmental disorder which primarily damages the posture and motor function. Nowadays, major advances in brain imaging and brain stimulation techniques have been prepared the promising status in diagnostic and interventional processes. In this review study, a brief explanation is provided about several techniques of brain stimulation to remedy the children suffered CP; the potential and performance of these techniques in restoration of damaged motor neural circuits; clinical trials ever conducted in this area; safety and tolerability of these novel therapeutic approaches for CP patients. In summary, brain stimulation in various frameworks offers new insights into a novel therapeutic approach for pediatric CP, but efficacy and safety need to be further addressed.

Keywords: Brain stimulation; Cerebral palsy; TDCS; DBS; RTMS

Introduction

Cerebral palsy (CP) is presented as the most prevalent neurodevelopmental disorder which primarily damages the posture and motor function [1-4]. Clinical sings typically can be appeared at early childhood. The prevalence of CP is thought to be 3 to 4 children per 1000 and about 2-2.5 neonates in each 1000 live births [2,3,5,6]. This childhood disability strongly affects quality of life in these populations because it is often accompanied by another psychological and musculoskeletal disorder [1]. Cognitive deficits are seen in approximately 50% of CP population. Also, it is reported that seizure abnormality was appeared in third of children with CP [7,8]. Therefore lack of knowledge can exert a heavy load on their family. Nowadays, major advances in brain imaging and brain stimulation techniques have been prepared the promising status in diagnostic and interventional processes. Rehabilitative intervention, especially occupational therapy in the field of motor learning have been promoting aligned with these technologies and obviously can enhance the chances in the future a head [9-12]. In this review study, a brief explanation is provided about several techniques of brain stimulation to remedy the children suffered CP; the potential and performance of these techniques in restoration of damaged motor neural circuits; clinical trials ever conducted in this area; safety and tolerability of these novel therapeutic approaches for CP patients.

Deep Brain Stimulation

Deep brain stimulation (DBS) depicts the innovative interplay between externally applied electrical forces and the central nervous system for diagnostic or therapeutic targets. An electrochemical gird as the basis of the intracellular communication and a chemical reaction for the induction of a precise electrical impulse are fundamental elements of DBS. Impulse initially triggers the release of a specific neurotransmitter of the cell, which in turn activates or deactivates neurons at the stimulation site. This direct electrical stimulation of small cellular community modulates faulty neurochemical systems [13]. A common DBS system has 3 Components: a pulse generator, which is typically implanted in the sub-clavicular area; one or two leads, which are inserted into the target area in the brain; and an insulated extension wire passed subcutaneously. The role of wire is connecting the generator with the lead [14]. Thus, DBS system includes quadripolar electrode inserted into the brain that extends behind the ear, and an internal pulse generator (IPG) implanted either on top of or deep to the pectoralis fascia. IPG is programmed transcutaneously via a device [15]. Surgical process for implantation of DBS could perform awake or asleep [13]. The system produces short electrical pulses, similar to a cardiac pacemaker. It is substantially important that of patient's symptoms were monitored to adjust the applied setting to the pulse generator for resolving the likely medical problems. In order to, the DBS system must be programmed by a physician [14]. DBS has greatly substituted ablative procedures for the treatment of advanced Parkinson disease, essential tremor, and other movement disorders. In addition it is approved for obsessive compulsive disorder. Although DBS is not a completely curative procedure, it could improve symptoms and quality of life. It is promisingly considered that DBS safer than ablative surgery [14]. By the early 1970s, there were reports based on the chronic DBS systems implanted into the thalamus concerning to chronic pain [16,17]. In 1991, Both Benabid et al. [18] and Blond and Siegfried's groups [19] developed thalamic DBS system for tremor. Thereafter, Cooper and colleagues implemented to locate the electrodes over the cerebellum and into the deep thalamic nuclei in CP, epileptic and spastic paralytic patients [20]. There are a few evidences on the pallidal DBS system as an alternative to pallidotomy [21]. In 1994 sub thalamic nucleus (STN) DBS has been represented the effectiveness for bradykinesia, tremor and rigidity [22,23]. In epilepsy, open-label studies with a small sample size have been revealed the positive findings of DBS application on the hippocampus and STN [24]. Today, DBS is widely accepted as an effective treatment for children with primary generalized dystonia [25]. Katsakiori et al. explored patients with secondary dystonia who treated with DBS. They obtained useful results to improve the patients. Hence, DBS has been utilized successfully in various forms of dystonia [26]. Pallidal DBS is

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an established treatment for medically refractive dystonia [27]. Totally, pediatric application of DBS is still in its early stages and faces to some limitations. However, DBS has been utilized for both hypokinetic and hyper kinetic movement disorders. As mentioned above, Dystonia is the most common condition treated by DBS in pediatric population. CP is arguably the most common cause of dystonia in childhood. The use of DBS for secondary dystonia associated with CP is being investigated by Warren et al. [13]. Oral medications have few benefits in many patients as the side effects frequently exceed those benefits. Hence, motor function improvements cannot be expected in most patients. The stimulation of Globus pallidus internus in children with primary dystonia revealed the effect of BP-DBS in a small sub-group of CP patients with dyskinesia [28]. Therefore, Bilateral pallidal DBS could be an effective therapeutic approach for patients with dystonia-chorea and CP. Scientists even states that in these patients, the optimum therapeutic spot is the posterior lateroventral region of globus pallidus internus (GPi). Diffusion of the stimulation to adjacent structures (mainly Globus pallidus externus), may bring out the little improvement [29]. DBS can offer meaningful changes in multiple domains of general health, dysfunctions and disabilities. Thus, the sequential assessments to evaluate the clinical utilities following DBS via rating scales particularly in children with CP are obligatory [25,30,31]. Possible adverse event following DBS could be hemorrhage resulting in a superficial or deep hematoma. Infection and erosion are side effects of DBS that sometimes the removal of the hardware may require for antibiotic treatment and probable re-implantation. Other risks include those related to tunneling the wires from the head to the chest to implant the device in the chest, and serious medical complication after surgery [14].

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (TDCS) is a kind of brain stimulation therapies that have attracted much attention these days. In the past decade, several studies have provided insight into the mechanism of action and it's feasibility in rehabilitative interventions [32,33]. TDCS has some advantages than the other brain stimulation techniques. It's noninvasive and only uses two electrodes (anode and cathode) to induce weak direct currents (1-2 mA) in the scalp surface [34]. In TDCS, anodal stimulation causes an enhancement of cortical excitability, whereas cathodal stimulation acts inhibitory. The new TDCS systems are painless, safe, inexpensive and portable, allowing clinicians to accomplish exercise therapy and brain stimulation both together in rehabilitation centers [35-38]. The aim of TDCS is the induction of regional synaptic efficacy and modulating the cortical excitability. This local modulation of electrical activity is impermanent and is induced via weak direct electrical currents to the scalp simply through placement of two electrodes [34,36,39]. TDCS as a new tool of noninvasive brain stimulation has been widely applied and investigated in patients with neurological disorders [39]. There have been some studies which have addressed safety and efficacy aspects in pediatric TDCS. Here we mention them briefly. Auvichayapat et al. reported erythematous rash only in one participant in their experimental group. However, they demonstrated that the active TDCS condition was tolerated well by all participants without any dangerous side effects [40]. Andrade et al. conducted a naturalistic study of fourteen children aged from 5 to 12 who participated in TDCS treatment (10 sessions). The anodal transcranial direct current stimulation consisted of 2 mA for 30 min over the verbal cortex. The primary adverse events that were detected by children's parents included: tingling occurred in 28.6% of children and itching in the same percentage, some acute changes in mood for 42.9% of children and reported irritability was about 36%. In conclusion, this study introduced TDCS as a feasible and tolerable treatment in children [41]. Moliadze et al. investigated the adjustment of stimulation intensities in children and adolescents for TDCS. The study highlighted age-specific considerations of this technique on electrical activity modulation of cortex for the first time, and underlined the optimization significance of stimulation protocols in TDCS according to age with planning future studies in children [42]. Gillick et al. aimed to construct child-specific TDCS protocols based on dosing parameters. A ten year old child who suffered from presumed perinatal ischemic stroke and hemiparesis was included in the study. In this trial, to determine the current flow and electrode position, researchers used T1 magnetic resonance imaging (MRI) scans. They also incorporated the using method with previous trials. All the parameters including electrode size, electrode placement, dose intensity and time period were precisely checked. The results suggest that improvement in pediatric stroke TDCS guidance needs computational modeling to establish an informed dose customization [43]. The potential ability of this technique to improve motor learning in adults has been shown in many published studies, and multiple clinical trials have provided hopeful results on motor recovery and restoring the balance of the activation between two hemispheres in the sensory and motor systems [44-52]. The approach for applying TDCS in motor function is based on stimulating the lesioned hemisphere and suppressing the intact one over the motor cortex. Through this basic principle, ipsilesional anodal or contralesional cathodal stimulation have been used in studies to assess the motor learning improvement and neuroplasticity mechanisms behind, which is more highlighted in developing brain [49,53-55]. Grecco et al. assessed the combined effect of anodal TDCS and virtual reality for promoting gait in children with spastic diparetic CP. The study designed as a pilot, double-blind randomized clinical trial in rehabilitation centers in 10 sessions. Twenty participants were randomly assigned to the experimental group (with anodal stimulation and virtual reality) and the control group (with sham stimulation and virtual reality). This study demonstrated a significant improvement in experimental group for all measured parameters than another group. So the authors suggested that anodal stimulation combined with virtual reality can improve gait in children with spastic diparetic CP [25]. One study suggested that the combination of TDCS and treadmill training have a positive effect on motor function of children with spastic diparetic cerebral palsy [56]. Grecco et al. investigated the effect of TDCS during treadmill training on the temporal function mobility and gait variables in 24 children with spastic diparetic in a randomized double-blind controlled trial. Experimental group received anodal stimulation with 1 mA intensity over the conquering primary motor cortex during the treadmill training for ten 20 min sessions. TDCS led to improve the mobility and gait and induction of cortical excitability that were constant one month after ending the treatment [10]. Duarte et al. also revealed that TDCS combined with treadmill training ameliorated anterior-posterior sway, mediolateral sway and the parameters at pediatric balance scale in CP children. This study also confirmed the influences of anodal TDCS over primary motor cortex during gait training task on functional performance in this population [27]. Young et al. studied the effect of cathodal TDCS to improve voluntary movement in children with dystonia once in a pilot open-label and once in a sham- controlled study. Patients controlled the overflow in hand muscles better when the cathode electrode was placed on opposite hemisphere [57-59]. Bhanpuri et al. postulated that TDCS cannot be clinically applicable for decreasing childhood dystonia. They conducted a double-blind sham-controlled crossover study to survey the effect of TDCS on dystonia. The stimulation protocol consisted of 2 mA current over the motor cortex for 9 minutes in every session. They

found that cathodal stimulation resulted in the symptoms reduction in some children which was not clinically significant and anodal stimulation worsened symptoms [60]. Gillick et al. demonstrated some benefits of TDCS and constraint induced movement therapy (CIMT) in children and adolescents with hemiparesis in a randomized double-blind control trial [9]. Collectively, there are many surveys and published guidelines to support the safety and feasibility of TDCS in adults. Whereas, very few studies have been performed to investigate the TDCS application in children with CP, the available evidences confirm the tolerability and the potential of using TDCS technique in these children. No seizure or other adverse side effects have been reported so far. The existing studies have mentioned some symptoms like transient tingling or mild itching [32,35-38]. Therefore, application of TDCS as a clinical procedure in pediatric CP is desirable for many clinicians and researchers. Nevertheless, it should be cautiously applied in children.

Repetitive Transcranial Magnetic Stimulation

Human transcranial magnetic stimulation (TMS) was invented in approximately last three decade [61]; abundant studies have been carried out using TMS for investigating neuroplasticity after brain injuries. However, few studies have focused on children. TMS is a simple painless, non-invasive technique that applies based on the principle of electromagnetic induction to produce electrical currents in the brain [62]. Passing of an electric current through a figure-eight conductive coil located over the scalp creates an electromagnetic field across neuronal membranes that causes the regional electrical changes and depolarizes cortical neurons according to Faraday's Law. Repetitive stimulation with TMS can modulate cortical excitability and generate permanent changes in brain function [63]. Cortical excitability was facilitated or inhibited via manipulation of the frequency and intensity of the repetitive TMS (r TMS) pulses [64,65]. A magnetic stimulator is used to deliver pulses of varying intensity, frequency and duration. That is based on the theory model suggesting the Low-frequency rTMS inhibits regional brain activity [66] and increases contralateral cortical excitability via modulation of interhemispheric inhibition [67]. In the beginning, TMS was applied to investigate recovery and prognosis after stroke [68,69] and neuropsychiatric diseases [70]. Whereas, several studies have raised the concern of application of repetitive rTMS as therapeutic intervention to remedy the some neurological and psychiatric diseases including stroke, refractory epilepsy, neuropathic pain, schizophrenia and major depression [71,72]. The utilization of rTMS especially in children is thought to be the perfect research method to study the maturational process of corticospinal tracts [73] as well as in the treatment of psychiatric disorders including attention deficit hyperactivity disorder (ADHD) and Autism spectrum disorder (ASD) [74]. High frequency rTMS (>5-10 Hz) stimulation of cortex in adults with stroke suggest capacity of rTMS in facilitation of motor function [75,76]. Furthermore, rTMS is well suited to randomized, sham-controlled clinical trials [77]. So far, serious adverse events in rTMS studies have not reported [78-80] It seems that application of this therapeutic approach in adults [81-84] and children with stroke are safe and tolerable [85]. Although substantial evidence is emerged about rTMS effect on improved motor function in chronic adult stroke [86-88], interventional studies related to rTMS in children expose to some barriers because of the methodological and safety consideration [79]. The most pediatric trials about the rTMS application in neurological diseases were mainly accomplished on pediatric stroke and spasticity. Application of rTMS in chronic stroke relies on the idea that a significant higher interhemispheric inhibitory drive from the cortical non-lesioned homologue area to the cortical lesioned area during the generation of a voluntary movement is occurred after stroke than healthy condition that correlates with poor motor performance [89]. Kirton et al. [85] took a design in which ten patients with chronic subcortical Arterial Ischemic Stroke (AIS) who had transcallosal sparing, aged more than 7 years, suffered hand motor impairment and had no seizures or dyskinesia were randomly separated to sham treatment (five patients) or inhibitory, low-frequency rTMS (five patients) over contralesional motor cortex (20 min, 1200 stimuli) once per day for 8 days. rTMS was well tolerated with no serious adverse events. Non-lesional inhibitory rTMS improved function of affected hand but did not result in any changes in function of unaffected hand. Clinical utilities in some paradigms of movement such as grip strength were maintained a week after treatment ending. Serious adverse events did not pose in this study [85]. Initial evidence to use of cortical stimulation in treatment spasticity was provided by Valle and colleagues. They focused on the effect of rTMS to improve spasticity in CP children. They designed a randomized, double-blinded sham-controlled clinical trial in which 17 patients with spastic quadriplegia were allocated to receive sham (six patients), 1 Hz rTMS (six patients) or 5 Hz rTMS (five patients). High frequency (5Hz) rTMS were safe and tolerable and modestly reduced spasticity and improved elbow movement. It is not clarified whether the improvements were transient or long lasting [90]. I seems that increase in cortical motor activity by excitatory rTMS would induce an overall increase in inhibitory projection of motor cortex on spinal cord through the corticospinal tract, thus reduce the spinal excitability and spinal H-reflex consequently improve spasticity [91,92]. One double-blind randomized clinical trial phase II has been running since 2012 so far [NCT02057276] in which benefits and safety of rTMS combined to occupational therapy on children and adults with chronic hemiparesis are investigated. Another rTMS study is now executing on pediatric CP [NCT02518867] to evaluate the clinical efficacy of low and high rTMS on motor disability of these population. The results of these two studies have not been reported yet. It is concluded that rTMS for pediatric motor disability has therapeutic potential and patients tolerate the treatment well. There is no evidence based on the appearance of seizure and permanent hearing loss following rTMS using in pediatric researches but it induces transient EEG changes and transient threshold shifts and tinnitus [93-95]. Other potential side effects include headache and local scalp pain. [96]. However, further well-designed studies for pediatric CP are demanded. It should be mentioned that patients having intracranial metallic implants, cardiac pacemakers and implanted medication pumps should not be undergone the rTMS. Also, rTMS using for those are taking antidepressants must be cautiously exerted because of these medications lower seizure threshold. However elements such as age, etiology of disorder and sex can be effective in result using brain stimulation modalities [73-77].

Conclusion

Brain stimulation techniques have opened new potential avenues in neurorehabilitation of pediatric CP and is not associated with an increased risk in children. Literature shows that modulation of the brain activity using stimulation techniques can be useful in pediatric populations, therefore increasing the scope for application of these therapeutic approaches in children. Current evidence supports the bold beneficial influence of DBS, TDCS and rTMS in dystonia, spasticity and pediatric stroke induced-hemiparesis respectively. Besides these positive findings, evidence for the use of stimulation techniques clinically in pediatric motor disability and paralysis should be viewed with caution because of extremely small sample size in most of studies and substantial heterogeneity in characteristics. It seems that these approaches cannot yet be applied as a clinical procedure in children

which indicates further confirmatory trials are worthwhile. Inexpensive cost and safety of rTMS and TDCS relative to DBS has been preferred them for users. One safety aspect that should be considered is the potential of rTMS and TDCS to trigger seizures in children with stroke. Since the lesioned motor cortex often displays abnormal electrical activity, monitoring the electrical activity with electroencephalography and electromyography is crucial during rTMS and TDCS. Another aspect that needs to be deliberated is clinical efficacy persistence. Whether clinical utilities represent a change in quality of life should be elucidated. In summary, brain stimulation in various frameworks offers new insights into a novel therapeutic approach for pediatric CP, but efficacy and safety need to be further addressed.

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