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Effect of Transcranial Direct Current Stimulation on Subjects with Lesions of Central Nervous System: A Narrative Review

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ABSTRACT

Background: Among different types of non-invasive brain stimulation techniques, transcranial direct current stimulation (tDCS) has been widely used to improve various outcome measures in subjects with neurological conditions. It is a neuro- modulatory technique that delivers low intensity, direct current to cortical areas facilitating or inhibiting spontaneous neuronal activity. Several studies have highlighted the therapeutic potential of tDCS in patients with neurological diseases, including dementia, epilepsy, post-stroke dysfunctions, movement disorders, and other pathological conditions.
Introduction: The tDCS stimulating device is a 13 cm×21 cm portable box, with two rubber electrodes applied with conductive gel or water-soaked pads. Typically, the protocol for tDCS utilizes 1-2 mA of continuous current for a duration of 10–20 minutes, with one electrode placed in the region of the motor cortex and the other on the contralateral supraorbital region. The current narrative review was planned to assess efficacy of tDCS while examining the role of specific regions of brain and the understanding of the underlying mechanism for treatment effects of brain stimulation in different neurological conditions involving lesions of Central Nervous System (CNS).
Method: Literature was explored on search engines (google scholar, scihub and pubmed) and databases for articles published from 2018 upto February 1, 2022. The key search phrase, transcranial direct current stimulation, tDCS and neurological conditions was used to identify potentially relevant articles. The following inclusion criteria were applied for article selection: (1) studies that used tDCS to treat neurological conditions (2) studies that rated at a score of 7 or higher according to the PEDro scale.
Results: Many potentially relevant articles were identified. After reading the titles and abstracts and assessing eligibility based on the full-text articles, 47 publications were included in our review. Majority studies showed that the outcome (ADL functions, motor control, pain, memory, speech, epileptic episodes, signs of consciousness, etc.) for each condition reviewed were significantly improved.
Conclusion: In conclusion, the addition of tDCS to conventional as well as latest method of treating disorders of central nervous system, led to significant improvement in various variables compared with general physical therapy only.

Keywords: Brain stimulation, neurological conditions, transcranial direct current stimulation

INTRODUCTION

Non-invasive brain stimulation (NIBS) is a safe and efficient method used to modulate human brain function. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are two of the most efficient NIBS modalities for the modulation of brain function.[1] Transcranial Magnetic Stimulation (TMS) is another technique of non-invasive brain stimulation which provide information on the conductivity of corticospinal neurons and the excitatory and inhibitory systems in the primary motor cortex.[2] For the past decade, tDCS studies reported that anodal tDCS stimulation usually increases cortical excitability while on the other hand, cathodal tDCS stimulation decreases cortical excitability in animal model as well as in humans.[3] It is an inexpensive, portable, easily attainable protocol and is better tolerated by patients.[3,4] tDCS can be applied continuously and safely for up to 30 min, close to the typical duration of a session of rehabilitative treatment, and can be administered in synchrony with motor training protocols.[5]

Transcranial direct current stimulation (tDCS) delivers a low (usually 1-2 mA) electrical current through the brain using two electrodes placed on the scalp, an anode and a cathode. It is assumed that anodal tDCS strengthens synaptic connections through a mechanism similar to long-term potentiation, whereas cathodal tDCS seems to have contrasting effect.[6] Thus it modulates the membrane potential dependently by type of electrode's application- anode is able to facilitate the depolarization of neurons, while conversely, cathode hyperpolarizes the resting membrane potential, reducing the neuronal firing.[7] Furthermore, a combination of anodal and cathodal tDCS may be applied as dual tDCS.[4]

The stimulation effects are achieved by the motion of electrons due to electrical charges. The two poles include- the anode (positive) and cathode (negative) electrodes. The flow of electric current is from the positive pole to the negative pole, penetrating the skull and reaching the cortex, with different reactions on biological tissues. Although most of the current is disoluted among the overlying tissues, a sufficient amount reaches the structures of the cortex and leads to changes in membrane potential of the surrounding cells. In rehabilitation processes, the aim of tDCS is to enhance local synaptic efficiency, thereby altering the maladaptive plasticity pattern that emerges following a cortex lesion.[8] the tDCS can lead to increased local synaptic efficacy by acting on the dysfunctional cortex region and changing the pattern of maladaptive plasticity that arises after a cortex lesion.[8,9] Stimulation is used to modulate the cortex activity by opening a pathway to increase and prolong functional gains achieved in physical therapy.[10]

Previous studies in healthy subjects have reported no major adverse effects of tDCS, while only mild adverse effects are reported in healthy subjects and patients. Commonly observed adverse effects are transient itching, tingling and burning sensations at the place of the electrodes, headache and general discomfort.[4]

Many therapeutic studies of tDCS in patients with neurological diseases involving central nervous system have been carried out, which includes-dementia, epilepsy, post-stroke dysfunctions, Parkinson's disease, movement disorders, and other pathological conditions. The current narrative review planned to appraise the underlying mechanism for treatment effects of brain stimulation in different neurological conditions involving lesions of central nervous system. This study also **aims** to assess efficacy of tDCS while examining the role of specific regions of brain and the best electrode placements and other parameters for the same neurological diseases.

MATERIALS & METHODS

Literature search and study design

Our study concentrated on all the tDCS studies of all neurological conditions affecting brain affection. We began searching from November 2021 upto February 2022. Publication dates ranged from 2018 to March 1,2022. Literatures were explored on different search engines - Google Scholar, Scihub and Pubmed. Three keywords were used- (1) transcranial direct current stimulation, (2) tDCS and (3) neurological conditions. The search was performed combining all the chosen keywords across the above databases.

Selection criteria

Inclusion criteria for our narrative review were- (1) studies that used tDCS to treat neurological conditions (2) studies in English language (3) studies that rated at a score of 7 or higher according to the PEDro scale (4) Case reports

Data synthesis and analysis

Figure 1 displays the total articles of different neurological conditions included in this study.

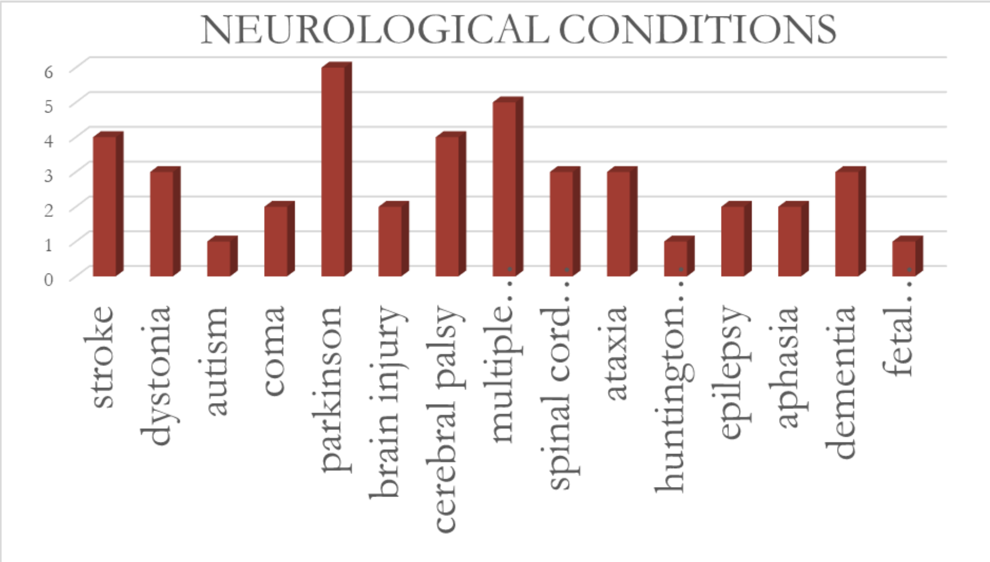

Figure 1: Included neurological conditions

RESULT

Study selection

73 such articles were obtained from the search strategy and. following the inclusion criteria 24 studies were excluded. One study was further excluded as effect of tDCS was questionable on writer's cramp and focal hand dystonia as a central nervous system pathology. Thus, total 47 studies qualified our criteria.

Study characteristics

Out of the total 47 studies, 37 studies were RCTs and experimental studies, 7 consisted of meta-analysis and systematic reviews and 2 study included case reports.

tDCS parameters used in different systematic reviews and meta-analysis are listed in Table 1, while those parameters used in RCTs are listed in table 2 to 5.

Table 1: Review papers and the outcomes improved with tDCS

	AUTHOR	YEAR	TYPE OF PAPER	TOTAL ARTICLES	OUTCOME	RESULTS
1	Seoyon Yang et al [11]	2021	Narrative review	34	Neuropathic pain	beneficial in treating patients with Neuropathic pain
2	Elsner B et al [12]	2019	Review summary	21	Aphasia	not recommended the routine use of tDCS for aphasia
3	Mohammad Ali Salehinejad et al[13]	2019	Meta-analysis	10	Inhibitory control and working memory	a promising method for improving neuropsychological and cognitive deficits in ADHD
4	Pablo cruz Gondaleze et al [14]	2017	Systematic Review	16	mild cognitive impairment	Significant improvement in memory, but not long term
5	Nyeonju Kang et al	2015	Systematic Review	17	motor learning	Novel long-term motor learning effects and motor practice

Table 2: tDCS parameters in Parkinson's disease

	Study and design	participants	Anodal/cathodal	Electrode placement	tDCS parameters	Sham parameters	No. of sessions	outcome	Effect of intervention
1	Mitsuya horiba et al RCT	N=18 Healthy= 10	anodal	primary motor cortex	1 mA 20 min	Same parameters turned off after 30 secs	4 sessions	memory	a new strategy for improving task-specific motor memory without real motor movements in PD.
2	Pattarapol Yotnuengni [15] RCT	N=30	both	Anode-lower limb motor cortex Cathode- supraorbital area on the forehead	2 mA 30 min 5 * 7 cm	Same parameters turned off after 1 min	6 sessions	gait	could be used alone or together as a combination treatment in Parkinson
3	Adriana Costa-Ribeiro1 16 RCT	56	both	Anode on left dorsolateral prefrontal cortex, and the cathode electrode will be positioned over the right contralateral supraorbital frontal cortex	1 mA 20 min 5 * 7 cm	Same parameters turned off after 30 secs	12	gait	Combining tDCS as a rehabilitation intervention is a way to enhance motor training
4	Blake J. Lawrence [17] RCT	42	both	left dorsolateral prefrontal cortex	1.5 mA 20 min 5 * 7 cm	Same parameters turned off after 30 secs	For 4 weeks	cognition	tDCS demonstrated significant improvements on cognitive and functional outcomes
5	Bijan Forogh 18 RCT	23	both	left dorsolateral prefrontal cortex	1 mA 20 min 5 * 7 cm	Same parameters turned off after 30 secs	20 session	sleepiness	tDCS is an effective and safe complementary treatment on fatigue reduction
6	Vida Alizad [19] RCT	18	both	Anode on premotor and primary motor cortices with the cathode over the cerebellum	1 mA, 20 min, 10 × 4 cm2	Same parameters turned off after 30 secs	2-4 weeks	gait	Trial is on going.

Table 3: tDCS parameters in cerebral palsy

	Study and design	participants	Anodal/ cathodal	Electrode placement	tDCS parameters	Sham parameters	No. of sessions	outcome	Effect of intervention
1	Nata´lia de Almeida et al RCT	N=12 Sham=12	anodal	primary motor cortex	1 mA 20 min 5 × 5 cm	Same parameters turned off after 30 secs	5/week for 2weeks	balance	Gait training + tDCS =improve static balance and functional performance in children with cerebral palsy
2	Luanda Andre´ Collange et al	N=24	Active anodal	primary motor cortex of the dominant hemisphere	1 mA 20 min 5 × 5 cm	Same parameters turned off after 30 secs	5/week for 2weeks	Gait	tDCS potentiated the effects of motor training
3	Renata Calhes Franco RCT	N=34	both	primary motor cortex of the ipsilesional hemisphere.	1-2 mA 20 min 5 × 5 cm	Same parameters turned off after 30 secs	three nonconsecutive	spasticity	Not given
4	Roberta Delasta Lazzar [20] RCT	N=20	both	primary motor cortex of the ipsilesional hemisphere	1 mA 20 min 5 × 5 cm	Same parameters turned off after 30 secs	10 sessions	Virtual reality	tDCS can potentiate the effects of virtual reality training on static and functional balance among children with CP.

Table 4: tDCS parameters in stroke

	Study and design	participants	Anodal/ cathodal	Electrode placement	tDCS parameters	Sham parameters	No. of sessions	outcome	Effect of intervention
1	Tae gun kwon et al in 2016 RCT	N=20	Both simultaneously	active- contralateral motor cortex refrence ipsilateral supraorbital region	2mA 10mins 5*5cm	Not mentioned	10	Motor performance in stroke	improved
2	Julius Fridriksson [21] RCT	74	both	Anode- left scalp on cortical region, cathode-supraorbital	2 mA 20 min 5 * 5 cm	Same parameters turned off after 30 secs	5 sessions	aphasia	Anodal tDCS during speech therapy is feasible and potentially transformative for aphasia treatment

Table 5: tDCS parameters in other neurological disorders

	Study and design	participants	Anodal/ cathodal	Electrode placement	tDCS parameters	Sham parameters	No. of sessions	outcome	Effect of intervention	Notes
1	F Costano et al in 2015[22] Case report	N=1	both	Cathode- right dorsolateral prefrontal cortex; anode-left	1 mA 20 min 5 × 5 cm	no	28 daily	Catonia in autism	tDCS could be innovative future direction for the treatment of catatonia in ASD	
2	Prateek C. Gandiga et al RCT	Healthy -24 Stroke-23	Anode=22 Cathode=15	e motor cortex and on the contralateral forehead above the orbit	1 mA for 20 min 5 × 5 cm	Same parameters turned off after 30 secs	170	f attention, fatigue in stroke	supports the feasibility of using tDCS	
3	Aurore Thibaut et al RCT	N=30	anodal	left DLPF cortex	2 mA for 20 min 7 × 5 cm	Same parameters turned off after 30 secs	Once a week for 12 months	conciousness	improved	
4	A. Fusco et al Pilot study	N=9	both	Cathode-primary motor cortex of the affected hemisphere Anode- n unaffected hemisphere in an analogue position	1.5 mA 20 mins 5×7 cm	Same parameters turned off after 60 secs	Not mentioned	9hole peg test	highlight the potential efficacy of tDCS	
5	Aurore Thibaut et al RCT	N=19	anodal	left prefrontal cortex	2 mA 20 min 5 × 5 cm	Not mentioned	5 consecutive days	conciousness	improves the recovery of consciousness	Side effect- redness of the skin under the electrodes; signs of discomfort, as assessed by observation of the facial expression
6	Géraldine Martens et al [23] RCT	N=46	both	prefrontal and occipital areas	1 mA 20 min	Same parameters turned off after 30 secs	1 session each of sham and tDCS crossover	Coma	behavioral effect of multifocal frontoparietal tDCS varies across patients	
7	Jesper Mortensen et al [24] RCT	Sham=7 N=8	anodal	ipsilesional primary motor cortex	1.5mA 20 mins 5×7 cm	30-s fade in/fade out sequence	5 cosecutive	stroke	s well tolerated by patients and can easily be applied for home-based training	
8	Jamie Young [25] RCT	30	both	Anode- contralateral to the side of pain, cathode- supraorbital	1mA 10 minutes of stimulation, 25 minutes of nonstimulation, and then another 10 minutes of stimulation 5 * 7 cm	Same parameters turned off after 30 secs	5 days	pain	repeated stimulation with a-tDCS for five days can reduce pain intensity for a prolonged period in patients with Multiple sclerosis.	
9	Leigh E Charvet [26] RCT	42	both	left dorsolateral prefrontal cortex	1.5 and 2mA 20mins 5 × 5 cm	Same parameters turned off after 30 secs	20	fatigue	tDCS is a potential treatment for MS-related fatigue.	

Table no.5 continued………										
10	Samar ayeche [27] RCT	16	anodal	left dorsolateral prefrontal cortex and supraorbital region	2 mA 20 min 5 * 7 cm	Same parameters turned off after 30 secs	3 weeks	Pain	tDCS act in a selective manner and would ameliorate specific symptoms, particularly neuropathic pain	
11	Giuseppina Pilloni [28] RCT	18	both	left dorsolateral prefrontal cortex	2.5 mA 20 min 5 * 5 cm	Same parameters turned off after 60 secs	4 week	Gait and fatigue	tDCS paired with aerobic exercise lead to cumulative and persisting improvements in walking and endurance in patients with MS.	
12	Marzieh Mortezanejad [29] RCT	36	anodal	primary motor and dorsolateral prefrontal cortices	1.5 mA 20 min 5 * 7 cm	Same parameters fade in and fade out	4 week	fatigue	-tDCS can be used for rehabilitation of patients with multiple sclerosis to control their fatigue and to improve their quality of life	
13	Paul J. Wrigley [30] RCT	10	both	prefrontal cortex and supraorbital region	2 mA 20 min 5 * 7 cm	Same parameters turned off after 30 secs	5 days for 4 weeks	pain	tDCS is an effective analgesic only in individuals with relatively recent injuries and pain	this trial tDCS did not provide any pain relief in subjects with neuropathic SCI pain
14	Niran Ngernyam [31] RCT	20	anodal	left primary motor area	2 mA 20 min 5 * 7 cm	Same parameters turned off after 30 secs	Single seesion	pain	active treatment condition but not sham treatment resulted in significant decreases in pain intensity	
15	Nai-Chen Yeh [32] RCT	12	anodal	Primary motor cortex and supraorbital area	2 mA 20 min 5 * 7 cm	Same parameters turned off after 5 secs	12	pain	anodal tDCS combined with moderate upper body exercise were feasible for individuals with neuropathic pain after spinal cord injury	
16	Alberto Benussi [33] RCT	20	both	Anode- cerebellum Cathode- spinal lumbar enlargement	2 mA 20 min 5 * 7 cm	Same parameters turned off after 5 secs	5 days for 2 week	ataxia	tDCS reduces symptoms in patients with ataxia and restores motor cortex inhibition exerted by cerebellar structures	
17	Roderick P [34] RCT	20	both	Anode- cerebellar hemisphere,cathode-rigjt deltoid muscle	2 mA 20 min 5 * 7 cm	Same parameters turned off after 30 secs	10	ataxia	tDCS treatment has proven feasible in cerebellar ataxia	
18	Jaume Rosset-Llobet [35] RCT	30	both	cathode over left and anode over right parietal region	2 mA 20 min 5 * 7 cm	Same parameters turned off after 30 secs	10	dystonia	tDCS can increase therapy effectiveness in rehabilitation patients with right-hand task-specific focal dystonia	
19	Sara merceglia [36] Case study	2	both	Anode- scalp, cathode- right deltoid muscle	Not mentioned	Same parameters turned off after 10 secs	5 consecutive days	dystonia	safe and low-cost effective adjuvant in the therapy of involuntary flexion or extension of hand and limbs	
20	Clare M. Eddy [37] Cross over trial	20	anodal	left dorsolateral prefrontal cortex	1.5 mA 15 min 5 * 7 cm	Same parameters turned off after 60 secs	2 sessions	memory	Well tolerated and enhance working memery in huntington's disease.	
21	Assenza G, et al 38 RCT	10	cathodal	Temporal lobe	1 mA 20 min 5 * 7 cm	Same parameters turned off after 10 secs	Single session	epilepsy	ctDCS reduced seizure frequency in drug resistant temporal lobe epilepsy patients without any safety concern	

Table no.5 continued………

22	Maryam Zoghi [39] Pilot RCT	20	cathode	primary motor cortex ipsilateral to the affected temporal lobe	1 mA 20 min 5 * 7 cm	Same parameters turned off after 10 secs	4 weeks	epilepsy	t tDCS may be a safe and efficacious nonpharmacologic intervention for patients with drug-resistant temporal lobe epilepsy	
23	Clara Sanches [40] RCT	60	both	Anode-Primary motor cortex and cathode – contralateral supraorbital area	1.59 mA 20 min 5 * 5 cm	Same parameters turned off after 30 secs	10 sessions	dementia	Novel therapeutic approach in language deficit where no other treatment is available.	
24	Alberto Benuss [41] RCT	70	both	Anode- eft prefrontal cortex, cathode- right deltoid	2 mA 20 min 5 * 7 cm	Same parameters turned off after 5 secs	2 weeks	Dementia	potentially promising therapeutic approach, even in the presymptomatic stages of dementia disease	
25	Elias Boroda [42] RCT	44	both	left dorsolateral prefrontal cortex and supraorbital region	2 mA 13+13 mins 5 * 5 cm	Same parameters turned off after 30 secs	5 sessions	memory	Working memory did not improve in fetal alcohol spectrum disorder	

Outcome measures

Majority studies showed that improved outcome for each condition reviewed-which consisted of motor control, pain, memory, speech, epileptic episodes, signs of consciousness and ADL functions. (Table 6).

Table 6 improved outcome measures with tDCS

No.	Condition	Outcome measure
1	Stroke	Fugl-Meyer Assessment (upper limb motor function; higher score indicates motor improvement; seven comparisons), Jebsen-Taylor Hand Function Test (measure of unilateral hand function; decreased time to complete each task denotes improved motor function; three comparisons), National Institute of Health Stroke Scale (overall stroke impairment; lower score reveals better recovery post-stroke; three comparisons), modified Ashworth scale (assessment for the affected wrist and elbow; lower score indicates no muscle tone; one comparison), Nine Hole Peg Test (hand function test; reduced time to put pegs into the holes shows motor improvement; one comparison) and (range of motion joint tests (upper limb functions; range of motion in wrist extension, elbow extension and shoulder abduction; one comparison), Attention, fatigue, and discomfort self rated using visual analog scales
2	Autism	kanner's score
3	Disorders of consciousness and brain injury	Glasgow Outcome Scale– Extended, Coma Recovery Scale-Revised (CRS-R), ADL performance with Jebsen–Taylor test (JTT)
4	Parkinson's disease	- mirror visual feedback (MVF), gait speed and gait parameters functional mobility measured by Timed Up and Go Test, Fatigue Severity Index (FSI)
5	cerebral palsy	Pediatric Balance Scale and Pediatric Evaluation of Disability Inventory, gait variables (spatiotemporal and kinematics variables), modified ashworth Scale, Timed Up and Go Test
6	multiple sclerosis	visual analog scale (VAS), Neuropathic Pain Scale (NPS), Depression Anxiety Stress Score (DASS), Short Form McGill Pain Questionnaire (SFMPQ), and Multiple Sclerosis Quality of Life 54 (MSQOL54). e Patient-Reported Outcomes Measurement Information System (PROMIS)—Fatigue Short Form
7	spinal cord injury	visual analogue scale for chronic neuropathic pain
8	cerebrospinal ataxia	Scale for the Assessment and Rating of Ataxia, International Cooperative Ataxia Rating Scale, 9-Hole Peg Test, 8-m walking time
9	Huntington's disease	digit reordering, computerised n-back tests and a Stroop task to test working memory
10	epilepsy	number and duration of episodes
11	aphasia	naming verbs and common objects
12	dementia	Mini-Mental State Examination (MMSE), phonemic verbal fluency, trail making test (TMT-A and TMT-B), Stroop test, digit symbol substitution test, the modified Ekman emotion recognition test, and the Cambridge Behavior Inventory (CBI)
13	fetal alcohol distress syndrome	Delis-Kaplan Executive Function System (DKEFS): trail making test (TMT) and verbal fluency test (VFT)
14	attention-deficit hyperactivity disorder	to assess inhibitory control- Go/No-Go, Stop Signal Task (SST), Flanker, Stroop, Continuous Performance Test (CPT), and Neuropsychological Development Assessment (NEPSY II).

DISCUSSION

Majority of the experiments were done with anodal electrode as an active electrode and cathodal as passive or reference electrode. Nearly all articles stated that anode is chiefly placed on the left dorsolateral prefrontal cortex and cathode electrode on supraorbital area of forehead. The parameters of sham or control group were usually similar to the intervention group but the intensity was ramped off after first 30-60 seconds.

The period of follow-up after intervention ranged from immediate to 12 months post stimulation with majority of immediate and 1 month post stimulation follow-up, however the frequency of longer term follow-up (after more than 3 months) was found in 6 articles only.[6,20,23,24,35,36] Thus, the long term effects of tDCSis to be further explored to be conclusive.

Weak current (1-2mA) works best to improve almost all outcome measures.

Additional safety issues

There are unique issues concerning the safety, applicability, and ethics of tDCS application in pediatric population which is mainly due to limited available data from children compared to the adult population.[43] Another concern is about current intensity due to children's thinner skull and the smaller distance between scalp and brain, implicating that 0.5 mA applied in children results in similar physiological effects as 1 mA in adults.[44] Out of total 47 articles reviewed in this paper, 7 articles were on children but all of them have used 1mA current intensity[22,40,41] and show improved outcome measures with none or very less adverse effects.

Future direction

Although robust evidence of the efficacy of tDCS could not be provided in this review, the current literature suggests a trend toward efficacy, and further studies are warranted to obtain conclusive results. Since tDCS is painless and easy to apply, further studies with larger patient populations, examining the role of specific regions of brain are needed in the future to validate the efficacy of tDCS. Moreover, longitudinal monitoring and effect of tDCS should be searched for.

CONCLUSION

This review suggests that tDCS may be a promising treatment for patients with various types of central nervous system disorders. The results of the included studies suggest that tDCS may be beneficial in conventional as well as latest method of treating disorders of Central Nervous System. tDCS will lead to significant improvement in various variables and improve outcomes compared with general physical therapy only.

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