



THERAPEUTIC IMPLICATIONS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON COGNITIVE MANIFESTATIONS IN STROKE SURVIVORS- A SYSTEMATIC REVIEW.

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ABSTRACT

Background: Identification of involved networks in a patient-specific context along with the deeper understanding of interconnected neuronal network may yield better outcomes when applied with conventional rehabilitation. Principles of the neural plasticity and motor and cognitive learning through cortical reorganization lead the extensive use of (tDCS) in management of Stroke. **Aim-** To ascertain the synergistic effect of (tDCS) on cognitive manifestations in stroke.

Methodology

Data Identification: identification of the english language literature search using Pubmed, Pedro, Medline, google scholar, Researchgate, Cocharne, and bibliographic review of textbooks & articles.

Data Extraction: Articles were extracted based on the explicit methodological criteria. Databases were searched for the search terms: tDCS, Stroke, cognitive impairments, memory.

Results- The review gathered the literature regarding use of "modern" tDCS protocols in treatment of Cognitive impairments in stroke. The most of studies found strong evidence in alleviation of symptoms with improvement in cognitive performance of patients in Stroke lasting up to several weeks, when applied appropriately. **Conclusion-** tDCS is effective at modulating neural activity, However Refinement is required to expand the effectiveness of tDCS with their exact physiological mechanisms behind.

KEYWORDS

Transcranial Direct Current Stimulation tDCS, Stroke, Cognitive Impairments

BACKGROUND

Globally, at every 10th second, a life is taken by stroke and on every ½ second an incident of stroke occurs. As a consequence of stroke, sometimes the cognitive impairments dominate the motor impairments that cause for life long disability among stroke survivors. Cognitive impairments reflect deficits in the executive functions, attention deficits, delayed mental processing, and language dysfunction in the form of aphasia⁽²⁾. Cognitive defects pose great challenges in physical, psychological, emotional and social domains of the affected individual thereby creating a negative impact on quality of life in stroke survivors.⁽¹⁾

Over the past few decades, the advancement in the field of neuroimaging has spurred the increased interest of neuroscientists regarding cortical reorganization and brain plasticity following stroke. They have drifted their focus towards the compensatory mechanisms following brain damage specifically on the two broad mechanisms; surviving regions of the hemisphere that incurred the injury versus homologous regions of the intact contra-lesional hemisphere^{(1),(2)}. The present review was conducted to specify the therapeutic effects of tDCS extensive efforts were devoted to retrieve the literature regarding effect of tDCS on various cognitive domains in the stroke survivors

Description Of Intervention (tDCS)

Out of pool of noninvasive brain stimulation techniques, transcranial direct current stimulation tDCS has re-emerged as one of the best techniques, that modulates the cortical activity by establishing the cortical balance between two hemispheres. tDCS is given in the form of weak intensity current via saline soaked surface sponge electrodes. Stimulation can be given in three forms; Anodal Stimulation i.e. (a-tDCS); anode placed over lesioned area and cathode over contralateral supraorbital region, Cathodal Stimulation i.e. (c-tDCS); cathode placed over targeted area and anode over supraorbital region and bi-hemispheric stimulation (dual-tDCS) that involves simultaneous application of anodal and cathodal stimulation to both the hemispheres. Anodal stimulation causes cortical excitation where as cathodal stimulation has inhibitory effect on the cortical activity⁽³⁾..

OBJECTIVES

1. To retrieve the current literature on therapeutic effect of transcranial direct current stimulation on cognitive manifestations in patients with stroke.
2. To ascertain the synergistic effects of (tDCS) along with the conventional cognitive rehabilitation programs on various cognitive manifestations in stroke.

METHODS

Types of studies

Randomized controlled clinical trials, cross over study trials, quasi experimental trials and parallel group study designs were eligible for the entry in the present review.

Selection Criteria

English language literature that investigated the effects of transcranial direct current stimulation as an independent intervention or as a co-intervention in stroke survivors were eligible for the present review. Selection criteria was widened to retrieve the literature regarding the effect of tDCS on global cognitive deficits vs any kind of placebo or control intervention as sham -tDCS, no intervention or conventional rehabilitation, on the participants irrespective of the gender, age, initial level of impairment, duration of stroke, side affected, and the mechanism involved. Studies on the cognitive consequences due to psychiatric disorders or neurological conditions other than stroke were excluded.

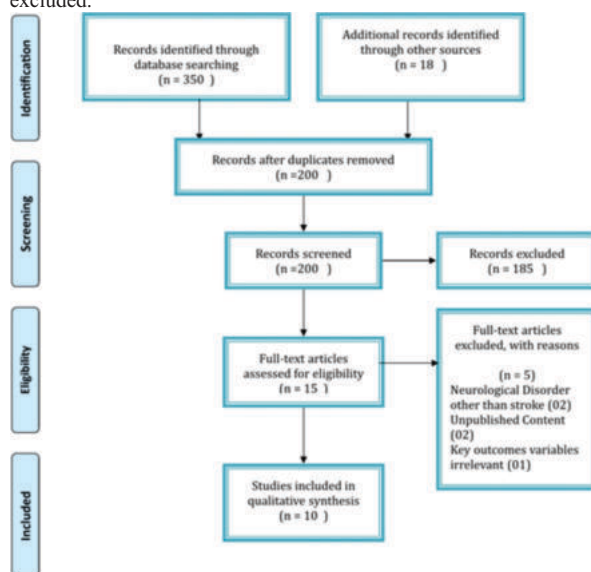


Figure1: PRISMA Flow Diagram

Search Strategy

Medical subject headings and the key words like transcranial direct

current stimulation tDCS, post stroke cognitive impairment, aphasia, memory impairment and executive function impairment were used for the literature search. Primarily two search engines i.e. Research gate and Google scholar, three databases i.e. Cochrane, Pubmed , and Scopus were searched from the year 2007 to 2017. Search was focused on the *general information* (title of the study, language of the trial and the year of publication), *participant information*: (gender, age and diagnosis), *trial information*: (study design, randomization, random allocation and level of blinding), *intervention information*: (type of intervention, parameters of tDCS, domains of cognitive impairment), *information of outcomes* : (measures for cognitive domains, psychiatric domains).

Search Procedure:

Entire retrieval was done by the two independent reviewers. Disagreements at the final stage were resolved by consensus. As per the specified criteria, available literature was screened. Studies not meeting the selection criteria were excluded as described in PRISMA Flow Diagram. (Figure-1)

Quality Assessment and Data Extraction (Assessment of Risk of Bias)

Quality assessment of the available literature was done using Physiotherapy Evidence Database (PEDRO). PEDRO is a standardized evaluation framework and a web-based database of evidence randomized controlled trials, systematic reviews and evidence-based clinical practice guidelines relevant to physiotherapy. Assessment and evaluation were done using methodological domains like: selection bias, study design, confounding factors, blinding, data allocation, concealment, dropouts and analysis. Database provides global rating on (0-10) criteria, with the interpretation as (0-3=Poor), (4-5=Fair), (6-8=Good), (9-10=Excellent).

Types Of Outcome Measures

Current review was conducted to retrieve the literature regarding the effect of tDCS on global cognitive impairments following stroke. The primary outcomes included in the study were measures of global cognitive deficits e.g., memory impairment, aphasia, anomia etc. To facilitate the qualitative pooling, outcome measures were prioritized as: korean-boston naming test, verbal fluency test, computerized neuropsychological test (CNT), korean mini mental state examination (K-MMSE), picture naming (accuracy and response time), re auditory verbal learning test (RAVLT), computerized neuropsychological function tests (SCNT, MAXMEDICA, Seoul, Korea), go/no-go test, communicative effectiveness index (CETI), partner communication questionnaire (PCQ). Secondary Outcomes included in the studies were: Korean Version-Modified Barthel Index (K-MBI), wong baker faces pain rating scale.

DATA SYNTHESIS (RESULTS)

Description of Study Parameters

Out of 10 trials, 5 trials were identified as randomized control trials and other 5 were cross over trials. Retrieved literature included evidences on global cognitive deficit (2 trials), post stroke aphasia (5 trials), attention and memory deficit (3 trials).

All the trials vary significantly with respect to the stimulation protocols in terms of single session / multiple sessions, single-tDCS/bilateral tDCS and stimulation parameters like duration, intensity, and electrode size etc. Bilateral dorsolateral prefrontal cortex (DLPFC) was modulated with tDCS in 2 trials. Whereas, other targeted sites of stimulation were broca's area, wernicke's area, occipital cortex, fronto-temporal cortex, inferior frontal gyrus and primary motor cortex (M1), designated based on 10-20 EEG international classification system. In the present review tDCS has been used as an independent intervention as well as a co intervention in many studies. Authors have variably used korean CACR program which consist of 10 training programs related to attention and another 10 training programs related to memory.

PARTICIPANT CHARACTERISTICS

The mean age of the participants varied from 58.25±15.06 (M. *et al.*, 2016) to 65.3±14.3 (Park *et al.*, 2013) in RCTs and from 47.9±7.15 (Jo *et al.*, 2009) to 71.5±7.40 (Kazuta *et al.*, 2017) in the cross over trials included in the review. Participant characteristics have been described in the (Table -1) and (Table-2).

Table (1) Demographic Characteristics Of Participants (RCT)

Author	Age M(SD)	Gender Ratio M (%) / F (%)	Post Stroke Duration	Side Affected
(Fujita, Yoneda and Harada, 2010)	65.50(11.44)	5(50)/5(50)	64.60(68.42)	0/10/0
(Kazuta <i>et al.</i> , 2017)	71.5(7.40)	7(58)/5(42)	6.7(4.1)	2/4/4
(Jo <i>et al.</i> , 2009)	47.9(8.7)	7(70)/3(30)	2.4(1)	0/10/0
(Kang <i>et al.</i> , 2009)	69.9(3)	6(60)/4(40)	544.1(388.6)	3/7
(H. <i>et al.</i> , 2013)	52.6(13.4)	9(82)/2(18)	51.9(55.3)	11/0/0

Table (1) Demographic Characteristics of Participants (RCT)

Table (2): Demographic Characteristics Of Participants (Crossover Trials)

Author	Age (Mean(SD))		Male (%) / Female (%)		Post Stroke Duration		Side Affected L/R/M	
	EG	CG	EG	CG	EG	CG	EG	CG
(M. <i>et al.</i> , 2016)	59.15 (12.50)	60.76 (11.54)	07/06	11/03	> 12 months	-	-	
(Monti <i>et al.</i> , 2008)	58.25 (15.06)	62.5 (9.8)	2(50)/ 2(50)	2(50)/ 2(50)	5 (2.1)	4(2.8)	4/0	4/0/0
(Marangolo <i>et al.</i> , 2013)	-	40-75 YRS	8(67)/ 4(33)	10(50) / 10(50)	3.75 (2.05)	-	12/0	20/0
(Wu, Tang and Ma, 2008)	EGI (60.9 (12.9) EGII 58.9 (15)	68.5 (14.6)	6(40)/ 9(60) 7(47)/ 8(53)	7(47)/ 8(53)	EGI(42 .2(31.9) EGII(3 8(27)	39.5 (29.6)	6/6/3 6/5/4	8/4/3
(Park <i>et al.</i> , 2013)	65.3 (14.3)	66 (10.8)	2(33)/ 4(67)	4(67)/ 2(33)	29 (18.7)	25 (17.5)	5/6	

SD-Standard Deviation

EG-Experimental Group, CG-Control Group, L-left Side, R-Right Side, M-Multiple Lesion affecting Both Sides

QUALITY ASSESSMENT (ANALYSIS OF RISK OF BIAS IN INCLUDED STUDIES)

Qualitative analysis of the trials was done based on PEDro Rating. The qualitative analysis revealed that 9 studies obtained scores between 6 to 8, depicting good quality of the evidences included in the review, whereas 1 trial obtained score of 4 to 5 indicating fair quality of the evidence. Overall, the weakest scores were obtained for concealed allocation. High number of weak ratings were also assigned for blinding of assessor. However, the strongest scoring dimensions were; random allocation and selection criteria. The numerical summary of components ratings has been described in the (Figure-2)

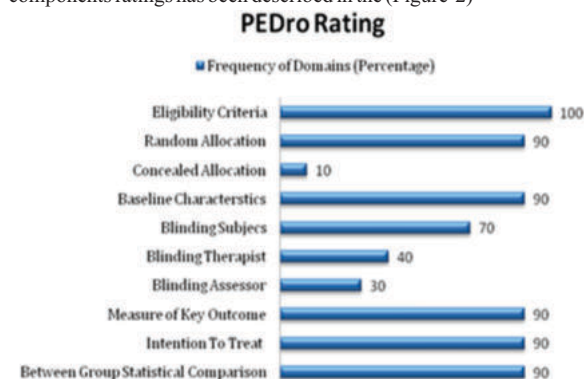


Figure-2-Quality Assessment of Studies (PEDro Analysis)

Study Findings (Effects of Intervention) (Table-3)**Effect of tDCS on Post Stroke Cognitive Impairment**

Wu, Tang and Ma conducted a study on 45 stroke survivors in the year 2008 in which beneficial effects of tDCS were reported on memory function. Anodal stimulation to left temporal Lobe (LFTAS) effectively improved auditory memory of the patients with statistical significant results with $p \leq 0.05$, as indicated by the improvement in backward digit span test, verbal learning test-delayed recall, visual span test and KMMSE. However, RFTAS (Right Side Fronto Temporal Anodal Stimulation) group revealed improved verbal learning test-delayed recall⁽⁴⁾. A Similar trial was conducted on 11 stroke patients with the aim to find out the synergistic effects of CACR, and tDCS on prefrontal cortex on cognitive function. They concluded that (tDCS) can concomitantly be used with cognitive rehabilitation for additional beneficial effects on cognitive impairments in stroke, based on the statistical significant findings for auditory CPT (Continuous Performance Test) ($p \leq 0.017$) and visual CPT ($p \leq 0.017$) for attention in the active stimulation group.⁽⁵⁾

Effect of tDCS on Aphasia

M. *et al.*, (2016) conducted a randomized, parallel group, sham-controlled, double-blind clinical trial. 26 patients with chronic aphasia received a highly intensive naming therapy over 2 weeks (8 days, 2 _ 1.5 h/day). Concurrently, anodal transcranial direct current stimulation was administered to the left primary motor cortex twice daily at the beginning of each training session. Transcranial direct current stimulation can improve both function and activity-related outcomes in chronic aphasia, with medium to large effect sizes, and that these effects are maintained over extended periods of time⁽⁶⁾. H. *et al.*, 2013, conducted a trial on 11 stroke survivors, with fluent and non fluent aphasia, to find out the effect of dual tDCS in post stroke aphasia. They reported statistically significant decrease in the mean response time for the picture naming task from (13.68 $\pm$ 1.81 seconds) to (9.96 $\pm$ 1.51 seconds) with dual tDCS application and statistically non significant decrease in the mean response time from 12.76 $\pm$ 1.61 seconds to

11.90 $\pm$ 1.58 seconds with single tDCS⁽⁷⁾. Marangolo *et al.*, (2013) investigated the combined effect of (tDCS) and intense conversational therapy treatment for speech production in 12 patients with post stroke aphasia. Results of their studies indicated anodal stimulation over Broca's Area together with the intense conversational therapy improved informative speech in such patients along with the persistence of the effects post one month of the treatment⁽⁸⁾. In a study conducted by Monti *et al.*, (2008), significant improvement in the accuracy of picture naming was reported with cathodal-(tDCS) by 33.6 $\pm$ 13.8% with $p=0.033$, in comparison to anodal-tDCS and sham-tDCS while investigating the effect of (tDCS) on naming abilities in patients with post stroke aphasia⁽⁹⁾. Similar study was conducted by (Baker, Rorden and Fridriksson, 2010 for improving the naming accuracy in post stroke aphasia, and have reported significant findings following (a-tDCS) as compared to Sham (tDCS) with $p \leq 0.04$.⁽¹⁰⁾

Effect of tDCS on Attention and Working Memory

In a trial conducted by Jo *et al.*, (2009) cortical stimulation was given to dorsolateral prefrontal cortex to analyze the effect of tDCS on working memory in 10 post stroke survivors. Anodal (tDCS) enhanced working memory performance indexed by significant improvement in recognition accuracy with $p=0.03$. Thus, it can be used for therapeutic purposes in order to improve memory functions in patients with stroke⁽¹¹⁾. Similarly Kazuta *et al.*, (2017) investigated the effect of tDCS on audio-verbal memory in stroke patients. Authors revealed that anodal stimulation (A-(tDCS)) over left temporoparietal area in the cortex resulted in the increase in the number of correctly recalled words from first to fifth trial with $p \leq 0.01$ and number of correctly recalled words with in first five words over second to fifth trials⁽¹²⁾. Kang *et al.*, (2009) al investigated the effect of single session of (tDCS) with excitatory anodal stimulation to the left dorsolateral prefrontal cortex on attention deficit in patients with stroke. They concluded that tDCS applied to left DLPFC significantly improved attention with respect to the increase in the number of correct responses and decreased reaction times in active stimulation group in comparison to the sham stimulation group⁽¹³⁾.

(Table 3): Description Of Studies (Intervention Characteristics And Outcomes)

	Sample Characteristics / Sample Size of Trial	Intervention Parameters	Outcome Measures	Outcome
(M. <i>et al.</i> , 2016)	Post Stroke Aphasia	1mA, 20 Min/Session)x Battery driven stimulator, A-(tDCS) Anode- (C3-10-20 EEG system), Cathode-Right Supraorbital Region, Sham (tDCS)- High Intensity Naming Therapy (2 weeks (8 days, 2 _ 1.5 h/day).	Naming ability for trained items (primary outcome) & Untrained items (secondary outcome) Communicative Effectiveness Index (CETI, Partner Communication Questionnaire	Immediate Improvement in the Naming Ability (Both Groups) Improvement in the Functional Communication in (A-(tDCS))
(Fujita, Yoneda and Harada, 2010)	Chronic Stroke Induced Aphasia (N=40)	[1mA,20Min/Session) x 5Days via Saline Soaked Electrodes (5x5cm) A-(tDCS) (Anodal Stimulation) Anode- Left Frontal Cortex Reference Cathode- Right Shoulder + Sham-(tDCS) (Stimulation stopped after 30 sec till 30 Min) along with Computerized anomia treatment- Picture word Matching Task	Computerized Naming Test	Improvement in the Naming Accuracy
(Monti <i>et al.</i> , 2008)	NonFluent Post Stroke Aphasia (N=8)	[2mA,10 Min, Electrode-35cm ²] Experiment –I A-(tDCS)- Anodal Stimulation Group Anode- Left Fronto-Temporal Area Ref Cathode- Opposite Right Shoulder C-(tDCS) Cathodal Stimulation Group Active- Occipital Area Ref Electrode- Right Shoulder Sham (tDCS) – Electrode Placement Same as Above, (Stimulation stopped after 10 sec)	Picture Naming Task	Cathodal Stimulation improved Picture Naming Accuracy No significant Improvement with A-(tDCS) & Sham Stimulation.
(Kazuta <i>et al.</i> , 2017)	Post Stroke Audioverbal Memory Impairment (N= 12)	[Saline Soaked Electrodes 35cm, 1- 2mA, Gradually Increased to 15 Sec and Maintained for 9.5 Min. Then Decreased in 15 Sec] A-(tDCS) (Anodal Stimulation)	Rey Auditory Verbal Learning Test	Increase in Number of Recalled Words with A-(tDCS)

		Anode- Left Temporo Parietal Area Cathode- Right Supraorbital Region (Wash Out Period-7 Days) Sham Stimulation (Stimulation stopped after 15 sec)		
(Jo et al., 2009)	Post Stroke Cognitive Deficit (Working Memory) (N= 10)	Saline Soaked Electrodes, 25cm ² , 2mA, 30 Min A-(tDCS) (Anodal Stimulation) Anode- Left DLPFC Cathode-Right Supraorbital Area Wash Out Period-48 hours Sham Stimulation Electrode Placement Same (Stimulation stopped after 10 sec)	Two Back Verbal Working Memory Task	Enhanced Working Memory Performance with Left Anodal Stimulation with Significant Improvement in Accuracy.
(Wu, Tang and Ma, 2008)	Post Stroke Cognitive Dysfunction (N=45)	[Saline soaked Electrodes, 25cm ² , 2mA, 30Min/Session, 5times/week x 3Weeks] Experimental Group-I (L-FTAS) Anodal Stimulation of Left Temporal Lobe Anode- at T3 Experimental Group-II (R-FTAS) Anodal Stimulation of Right Temporal Lobe Anode- at T4 Experimental Group-III Sham Stimulation Electrode same placement as of LFTAS Group (No Stimulation)	CNT (Computerized Neuropsychological Test) K-MMSE (Korean Mini Mental State Examination) K-MBI (Korean Version of Modified Barthel Index)	Improvement in Verbal Learning Test in CNT with Left Anodal Stimulation Group
(Marangolo et al., 2013)	Post Stroke Aphasia (Chronic) (N= 12)	[Surface Soaked Sponge electrodes, 35cm ² , 1Ma, 20 Min /Session, 10 Sessions, 5days/Week.] Experimental Group A-(tDCS) (Anodic Stimulation) + Intensive Conversational Therapy Anode- F5-Broca's Area Anode - C5-wernicke's Area Reference Electrode- Contralateral Fronto polar Cortex Control Group Sham Stimulation Electrode Placement same (Stimulation stopped after 30 sec)	Treatment Videoclips Generalization Videoclips	Improvement in Informative Speech with Anodal stimulation to Broca's Area.
(Kang et al., 2009)	Post Stroke Attention Decline (N= 20)	Group-I Stroke Patients GroupII-Health Controls Anodal Stimulation A(tDCS)- Left DLPFC 2mA, 20 minutes Washout Period (2 Days) Sham Stimulation 2mA, 10 Min (Slowly Intensity Tapered to 0)	Go/No-Go Test	Significant Improvement in Response Accuracy 10 min Post Stimulation. , lasted upto 3 Hrs Post stimulation
(H. et al., 2013)	Post Stroke Aphasia (N=11)	[Saline Soaked Electrode with Surface area 25 cm ² , 2mA, 30 Min/Session] Single Anodal Stimulation A-(tDCS) Anode- Left Inferior Frontal Gyrus Cathode- Left Buccinator Wash Out Period > 24 Hrs Dual (tDCS) Anodal Stimulation (Similar as above) Cathodal Stimulation Cathode- Right Inferior Frontal Gyrus Anode- Right Buccinator Muscle + Speech Therapy (Naming & Reading Short Paragraphs) (tDCS)During last 15 Min	Korean Boston Naming Test Verbal Fluency Test	Significant Improvement in Response Time for Korean Boston Naming Test
(Park et al., 2013)	Post Stroke Cognitive Impairment (N= 11)	[Sponge Electrodes, 25cm ² Surface area, 2mA x 30 Min, 5 Times/week]	Seoul Computerized Neuropsychological Test (SCNT)	Significant improvement in Post/Pre Ratio of Auditory Continuous

		Experimental Group Anodal Stimulation A-(tDCS)- Bilateral Prefrontal Cortex + Korean Computer assisted cognitive rehabilitation Program Control Group Sham Stimulation (Stimulation stopped after 30 Secs)+ + Korean Computer assisted cognitive rehabilitation Program	Korean Mini Mental State Examination (K-MMSE)	Performance test and Visual Continous Performance Test on SNCT Items.
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DISCUSSION

Clinical Efficacy Of (tDCS)

Most notably data from various studies suggest that tDCS has substantial potential to ameliorate various cognitive impairments. Brain injury causes interhemispheric imbalance. Data of included RCTs and cross over trials revealed that neuromodulatory effects can be induced in the cortex by single or multiple sessions of stimulation to pre frontal cortex augmenting the therapeutic utility of tDCS.. tDCS over DLPFC in cognitive deficits receives somatosensory and visual input information from parietal heteromodal association cortex regarding peripheral vision, motion, spatial orientation and tactile sensations from trunk and extremities and projects to subcortical monoaminergic and cholinergic sources. Hence, DLPFC have influential effects on global behavior of an individual as in attention and arousal (Kazuta *et al.*, 2017). Also, tDCS have been observed to affect the cortical excitability by activating N methyl D aspartic acid (NMDA) receptors and suppressing the cortical activity via gamma aminobutyric acid (GABA)⁽³⁾

(tDCS) and Concomitant Cognitive Training

Structural and functional alterations due to stroke, pose a big challenge in neurocognitive rehabilitation. Neuroscience community has shifted their perineal interest from lesion approach to the behavioral phenomena associated with the neural illness, promoting adjuvant strategies that supplement the cognitive rehabilitation in the clinical settings. In some trials tDCS has been administered as an add-on therapy to the cognitive training programs. Findings of the studies have been justified with the fact that weak intensity stimulation cannot induce neural firing however it is believed to modulate the increased rate of spontaneous neuronal firing specific to the polarity of the electrodes thus justifying the synergistic effects with the better functional outcome at the end⁽⁴⁾.

Intervention Parameters (tDCS)

Extensive amount of variability was observed with respect to intervention parameters of tDCS such as size of the electrodes, intensity of stimulation, duration of stimulation, positioning of electrodes, number and frequency of stimulation. Infact, substantial heterogeneity was found among the studies in which tDCS was intended to treat similar cognitive domains. Most of the studies have been limited by the small sample size a thus difficulty in generalizability of results

Safety Concerns

Ease of tolerability and minimal adverse effects were reported by the majority of participants included in the trials of the present review. minimal side effects in the form of mild transient effects like itching, tingling lead to the conclusion that tDCS is a safe technique. Administration of tDCS interventions that comply with recommended safety regulations (I=<2mA, duration-20-60min/session, frequencies ≤twice /day) has been reported by the authors with minimum risk in wide range of participants⁽¹⁴⁾. Mild to moderate effects like localized itching, tingling and headache has been reported by authors that lead them to the conclusion that tDCS is a safe procedure.^{(15),(16)}

CONCLUSION

Qualitative analysis of the trials in the present review suggests that tDCS has potential beneficial effects in augmentation of cognitive functions like memory impairment, attention deficits, speech enhancement etc in post stroke survivors. However large experimental trials are explicitly required for development of standardized guidelines with respect to the Intervention parameters while keeping safety concerns and ethical issues into kind consideration.

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