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Effectiveness of tDCS on motor functions of the affected side in hemiplegic individuals: an overview

Deepak Nair[1*], Vaithiamanithi Perumal[2], Narkeesh Arumugam[3]
[1] Associate Professor, Physiotherapy, SAIMS Medical College & Post Graduate Institute, Indore MP, India
[2] Prof & Head, Occupational Therapy, SAIMS Medical College & Post Graduate Institute, Indore MP, India
[3] Prof & Head, Physiotherapy, Punjabi University, Patiala, Punjab, India

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ABSTRACT

Objective: To review the researches on the effectiveness of non-invasive brain stimulation in the form of transcranial direct current stimulation on rehabilitation of individuals suffering from stroke. **Design:** A computerized search of CINAHL, EMBASE, COCHRANE central register of controlled trials, PEDro, PUBMED, SCIENTECH, and OT SEEKER from January 1996 to December 2013 was conducted. **Participants:** The study considered patients suffering from stroke of age 18 years and above of both genders and of all duration. **Intervention:** tDCS in association with physiotherapy or occupational therapy was included. Different modes of application such as unihemispheric and bihemispheric stimulations of tDCS were also included. **Outcome Measure:** Functional scales that measured motor functions, motor control, hand functions, Gait or Activities of daily living were included. **Results:** Seven studies met the inclusion criteriawere included and reviewed for their methodological quality. The average score of these studies was 8.57 ± 1.72 with a minimum score of and a maximum score of 10. **Conclusion:** The review of all the seven studies on the effectiveness of the application of tDCS post stroke shows better recovery in the upper limb motor recovery and no significant difference in the lower limb motor recovery.

KEYWORDS: NIBS, tDCS, Stroke, Physiotherapy, Occupational Therapy, Rehabilitation

INTRODUCTION

Description of the condition

Stroke is the second leading cause of death worldwide and major cause for disability[1]. Every year, 15 million people worldwide suffer from stroke, among them nearly six million die and another five million are left permanently disabled[2]. It has become a major cause for premature death and disability in low- income and middle income countries like India. This is largely driven by demographic changes and enhanced by the increasing prevalence of the key modifiable risk factors. The estimated adjusted prevalence rate of stroke ranges from 84-262/100,000 in rural and 334-424/100,000 in urban areas[3].

Strategies that are supposed to improve functions post stroke still remains a desirable goal[4]. Loss of upper limb motor function poses significant challenges to ADL performance thereby affecting the quality of life. If left untreated, functional limitations can persist or worsen over time, leading to increased dependence and caregiver burden. Longitudinal studies of recovery revealed that approximately only 50 % of stroke survivors regain a functional arm[5].

***Corresponding author.**
Deepak Nair,
Associate Professor,
Physiotherapy, SAIMS Medical College &
Post Graduate Institute, Indore MP, India

Possible mechanism that may interfere with better functional use of the affected upper extremity may be due to learned non- use phenomenon or maladaptive plasticity that may occur post stroke. A relative imbalance between the primary motor cortex excitability (M1) has been reported with underexcitability in the stroke affected lesioned hemisphere and overexcitability in the contralesional hemisphere. This further worsens the motor outcomes for patients. Interhemispheric inhibition is considered as a beneficial cortico- cortical interaction, but it may be maladaptive for people suffering a neurological insult. Rebalancing of such cortical imbalance has been considered to be an important factor for rehabilitation and has been associated with improvement of upper limb function.

Such rebalancing could be promoted with Non Invasive Brain Stimulation. Transcranial Direct Current Stimulation is such a form of Non Invasive Brain Stimulation Technique that influences this cortical imbalance based on the electrode polarity[6] . Williams et. al (2010) have highlighted its effectiveness in improving motor function in people with stroke using interhemispheric modulation by transcranial direct current stimulation (tDCS)[7].

Description of the intervention

Nitsche and Paulus (2000) have analysed the changes in cerebral excitability after modulation of neuronal excitability by weak direct currents applied transcranially[8]. It was understood that application of weak direct currents through the scalp is capable of modulating motor cortex excitability. Also it was concluded that excitability changes of upto 40% was achieved that lasted for several minutes after stimulation. The effects were probably induced by modification of membrane polarization. It is now understood that patients with chronic stroke exhibit an abnormally high interhemispheric inhibition from the intact to affected motor cortices with movements of the paretic hand. This finding reveals that upregulation of activity in the affected hemisphere could influence motor functions. Non Invasive Brain Stimulation could elicit improvements in motor tasks that are involved in activities of daily living[9].

The corpus callosum plays a crucial role in the interhemispheric interactions that maintain independent processing and integrate information from both the hemispheres. Recent studies have revealed that modulation of interhemispheric interactions relates to neural plasticity, which refers to the brains ability to develop new neuronal interconnections, acquire new functions and compensate for impairments[10]. Several TMS studies have shown that the unaffected hemisphere inhibits the affected hemisphere through abnormal interhemispheric inhibition and restricts motor function after stroke. This interhemispheric competitive interaction is highlighted as a mechanism for maladaptive plasticity and should be considered as a treatment target post stroke[11].

Effective interventions for upper limb after stroke are limited. Transcranial direct current stimulation (tDCS) is a non-invasive procedure used to polarize underlying brain regions through the applications of weak direct currents through electrodes placed on the scalp. The current induces intracerebral current flow, which either increases or decreases the neuronal excitability in the specific areas of brain being stimulated based on the type of stimulation that is being used[12].

Aim of the review

There are several published studies that evaluate the effectiveness of rehabilitation therapy for recovery following stroke. Application of transcranial magnetic stimulation on recovery of motor functions post stroke has been also studied by various researchers. The aim of this review is to review current available literature on the effectiveness of transcranial direct current stimulation in addition to rehabilitation therapy in regaining motor control post stroke.

Types of studies

This review includes experimental studies that have measured the influence of transcranial direct current stimulation on motor recovery of the affected side among hemiplegic individuals. Full text articles published until December 2013 in English language were considered for this study.

Types of participants

Studies which included adult patients (over 18 years of age) with stroke of either side, all age group, all gender, of all duration were considered. Stroke was defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin"[13]. If not specifically stated, signs and symptoms of paresis or paralysis persisting longer than 24 hours was included.

Type of intervention

Application of transcranial direct current stimulation alone or in combination with Physiotherapy or Occupational Therapy was included. The definition of tDCS was considered as longer- lasting application of direct current to the brain to stimulate the affected hemisphere or to inhibit the healthy hemisphere[14].

Outcome measures

The outcomes that were assessed for the present review included motor recovery as well as changes in activities of daily living. The outcome measures that were considered for the study included Frenchay Activities Index (FAI), Barthel Index, Rivermead ADL Assessment, Modified Rankin Scale, Functional independence Measure. Also secondary outcomes that were identified included muscle strength and muscle tone. Interval scale outcome measure was preferred over ordinal or nominal scale outcome. Further outcome measures that were considered for the study in association with the primary outcomes were Action Research Arm Test (ARAT) Fugl- Meyer Score, Nine Hole peg test, Jebsen Taylor Hand Function test, 6 min walk test ,Wisconsin Gait Scale, Rivermead Mobility Index and MRC Grading.

Literature search

A comprehensive literature search was carried out to identify the pertinent research on application of transcranial direct current stimulation on post stroke motor function recovery. Following databases were searched CINAHL, EMBASE, COCHRANE central register of controlled trials, PEDro, PUBMED, SCIENTECH, and OT SEEKER. Subject heading and keywords were initially derived from the research question and included Transcranial Direct Current Stimulation, Stroke, Motor recovery, Hand Functions. Subsequently, keywords were then identified from initial articles including cortical inhibition, transcallosal inhibition, bihemispheric stimulation.

The review consisted of following steps. **1)** A systematic literature search to identify articles that included instruments like Transcranial Direct Current Stimulation or Noninvasive brain stimulation in patients with stroke. **2)** Articles were selected based on predetermined inclusion criteria.**3)** Extraction of all measurement instruments reported in the article. **4)** Further evaluation of the quality of evidence and classifying them.

Subject specific search was performed based on the following key words

Participant population- "Stroke" OR "Hemiparesis" OR "Hemiplegia" AND

Treatment intervention- "Transcranial Direct Current Stimulation" OR "Non Invasive Brain Stimulation" NOT "Transcranial Magnetic Stimulation" AND

Outcome measures – "Motor Functions" OR "Motor Function" OR "Motor Control" OR "Motor Skill" OR "Motor Skills" OR "Hand Functions" OR "Gait" OR "Activities of Daily Living" OR "Strength")
Assessment of the methodological quality

Two authors (DN &VP) independently reviewed the methodological quality of the retrieved articles independently. Any disagreement among the authors was resolved by consensus. Still, if no consensus was reached the third author (NA) made the final decision. The methodological quality of all studies that were retrieved was assessed by PEDro rating scale and then included for the study. The PEDro scale was used due to its superiority in assessment of experimental studies in stroke rehabilitation. It offers a more comprehensive measure of methodological quality in stroke literature.

The reviewer scored each items of the included studies with 'Yes' or 'No' based on the information received.

Data Extraction

Data was extracted using standardized data extraction form. The data extraction form was adapted from Cochrane database for systematic review. One reviewer independently extracted and recorded the data available in the full text articles that were retrieved. This was followed by the other reviewer who extracted the data in similar data extraction form. Both these were compared for any discrepancy or mismatch. Common data was accepted. Any discrepancy in data extraction was resolved by consensus.

RESULTS

PRISMA statement procedure[15] was used to ensure transparent and complete reporting of the review. The initial search strategy in various database with the key words revealed 147 articles (Figure 1). 43 articles were removed due to duplicity. Further, based on abstract and title relevancy, the reviewers were left with 62 articles.21 full text articles were retrieved which was taken into consideration for data

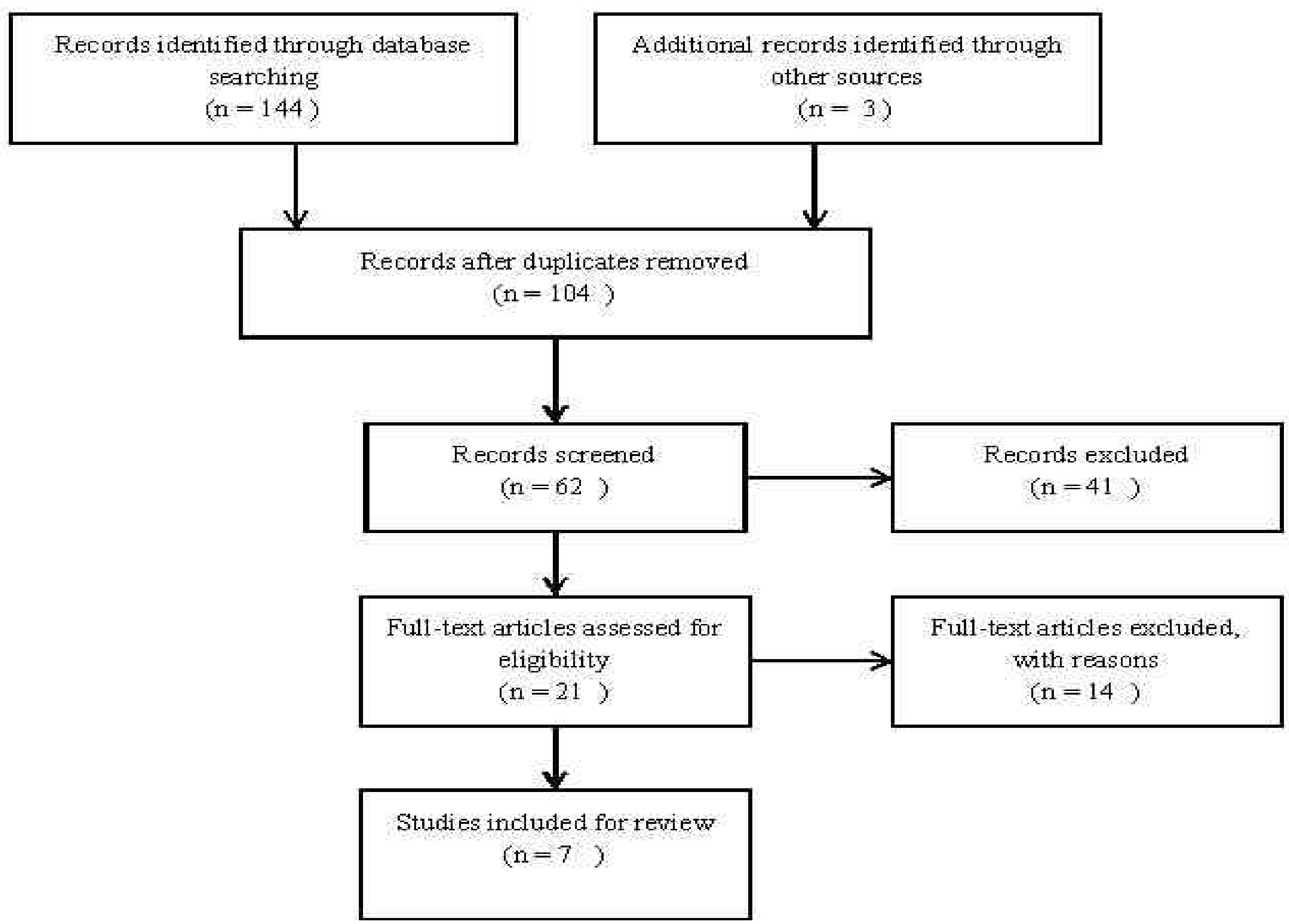

Figure 1: Prisma figure for Data Extraction strategy

extraction. Among the 21 full text articles, 14 articles were rejected due to specific reasons. Finally, 7 articles had been included for data extraction. 14 studies (Appendix 2) were excluded as either a single subject design was used, or outcome measures were beyond the scope of this review. Data were extracted from these 7 eligible studies in a systematicformat (Appendix 1).

Appendix 1: Data Extraction Summary

Study	**Hesse (2007)[17]**
Methods	Design: Single group. Pre – post test Baseline: Pre Treatment Treatment: 6 weeks- 30 – twenty minutes sessions of robot assisted arm training (robotic) and 7 minutes of tDCS
Participants	6-8 weeks of stroke, FM <18 Sample Size: 10 Age Range: 32-76 yrs Mean Age: 63.3 Onset: 6-8 weeks
Intervention	20 min of robot assisted arm training (AT), additionallythe patients received tDCS in the first seven minutes of the AT simultaneously
Outcome measures	Fugl-Meyer Motor Assessment Score(Primary), MRC grading of Upper limb muscle strength (Secondary)
Results	The FM (0–66) improved significantly over time (p = 0.018)MRC grading score improved (p= 0.027.)
Loss of follow up	Nil
Quality Score	5

Study	**Hesse (2011)[18]**
Methods	Design: Parallel ; 3 groups Baseline: Pre Treatment Treatment: 20minutes per day for 6 weeks Randomization: Double blind; Randomization trial eligible patients were allotted in 3 groups by an individual person by drawing a lot out of an envelope containing 96 lots
Participants	Sample Size: 96 Age Range: Group 1: 39-79 ; Group2: 46-79 Group3:39-79 Mean Age: Group1: 63.9 ±10.5 ; Group2: 65.4± 8.6 ; Group3: 65.6 ± 10.3 Onset: 3-8 weeks
Intervention	In group A patients (anodal group), the anodal electrode was placed over the presumed hand area of the lesioned hemisphere (C3 position according to the 10-20 system) and the cathodalelectrode was placed above the contralateral orbit (C4 position). In group B patients (cathodal group), the cathodal electrode was placed over the presumed hand area of the nonlesioned hemisphere (C3 position) and the anodal electrode was placed above the contralateral orbit (C4 position). In group C patients (sham group), the positions of the electrodes either followed that of group A or group B patients; the order changed consecutively from patient to patient. The panel of the stimulator was invisible for the patients; in group A and B the intensity was set to 2 mA and in group C to 0 mA.
Outcome measures	Upper limb motor control Fugl-Meyer motor score Upper limb motor control Responder Box and Block MRC sum score Modified Ashworth Barthel Index
Results	All patients significantly improved in UL functions but no between the group difference was seen.
Loss of follow up	Group 1: 4 Group 2: 3 Group 3: 4
Quality Score	10

Study	**Geroin (2011)[19]**
Methods	Design: Pilot randomized clinical trial Baseline: Pre Treatment Treatment: 2 weeks ; 5 days a week Randomization: Simple ransom (software generated)
Participants	Prior to 12 months of ischemic stroke Sample Size: 30 Age Range: <75 Mean Age:63.6 Onset: <12 months of ischemic stroke
Intervention	Group 1: n=10 : robot-assisted gait training combined with transcranial direct current stimulation Group 2: n=10 : a robot-assisted gait training combined with sham transcranial direct current stimulation Group 3: n=10 : overground walking exercises
Outcome measures	six-minute walking test 10-m walking test The Functional Ambulation Categories The Rivermead Mobility Index The Motricity Index leg subscore
Results	No differences were found between groups 1 and 2 for all primary outcome measures at the after treatment and follow-up evaluations A statistically significant improvement was found in favour of group 1 and group 2 compared with group 3. All improvements were maintained at the follow-up evaluation.
Loss of follow up	Nil
Quality Score	8

Study	**Hummel (2005)[20]**
Methods	Design: double blind, Sham-controlled, crossover study experimental design Baseline: Pre Treatment Treatment: tDCS applied to the motor cortex of the affected hemisphere Randomization: Not mentioned
Participants	Sample Size: 6 Age Range: 38-84 Mean Age:62.2±7.56 Onset: 3.7±1.1 Year
Intervention	Session 1: Familiarization of JTT 10 times to reach a stable motor performance Session 2 : Two counter balanced sessions (tDCS and Sham) separated by 10.3 ± 2.06 days
Outcome measures	Jebsen–Taylor Hand Function Test
Results	Results document that non-invasive stimulation of motor regions of the affected hemisphere in patients with chronic stroke results in functional gains in motor function of the paretic hand.
Loss of follow up	NIL
Quality Score	10

Study	**Nair (2011)[21]**
Methods	Design: Double blind Sham controlled study Baseline: Pre treatment Treatment: 5 days Randomization: simple randomization
Participants	Stroke wither right or left Sample Size: 14 (6R – 8L) Age Range: 40-76 Mean Age: 55.8 Onset: group 1: 33±20 months – Group 2: 28±28 months
Intervention	Group 1: n=7 Real tDCS and Occupational Therapy; Each patient received 60 min of occupational therapy and simultaneously 30 minutes of tDCS (during

Study	Nair (2011)[21]
	The first 30 minutes of OT) each day for 5 days in a row. tDCS session was 1mA direct current withthecathodal electrode over the non-affected (contralesional) motor region (either C3 or C4 of the 10–20EEG system) and a reference electrode over the contralateral supraorbital region Group 2: n=7 Sham tDCS and Occupational Therapy
Outcome measures	Range-Of-Motion (ROM) Upper-Extremity Fugl-Meyer Assessment FMRI
Results	UEFM taken after the end of 5 day intervention and on day 12 ROM taken on day 5 and day 12 Both showed significant improvement in group1 than group2
Loss of follow up	Nil
Quality Score	9

Study	Lindenberg (2010)[22]
Methods	Design: 2 groups; prospective ; parallel; double blind Baseline: Prior to treatment Treatment: 5 sessions Randomization: Block randomization with 3 strata of impairment based on UE-FM score (13–28, 29–41, and 42–56 points)
Participants	Ischemic stroke in the territory of the middle cerebral artery at least 5 months prior to enrollment Sample Size: 20 Age Range: 34-77 years Mean Age: 55.8± 12.9 Onset: 5 months
Intervention	Group 1: n=10 tDCS – 30 min & simultaneous PT/OT =60 min Group 2: n=10 Sham tDcs& PT/OT = 60 min
Outcome measures	Upper Extremity Fugl-Meyer Wolf Motor Function Test Functional MRI
Results	Significantly greater improvements in motor function in the group 1 (20.7% in Fugl-Meyer and 19.1% in Wolf Motor function test) than compared to group 2 sham (3.2% in Fugl Meyer and 6.0% in Wolf Motor Function Test). The observed effects persisted beyond the intervention by at least 1 week and were accompanied by functional changes in motor cortex activation.
Loss of follow up	Nil
Quality Score	9

Study	Lindenberg (2012)[23]
Methods	Design: pre post experimental study with control group Baseline: Pre Treatment Treatment: Noninvasive brain stimulation (30 minutes) and simultaneous PT/OT (60 minutes) for 5 consecutive days. This first treatment period was followed by a second 5-day intervention that was separated from the first by 2 to 29 days (mean 9.9± 9.4 days). Randomization: Double blinded randomized

Study	Lindenberg (2012)[23]
Participants	Occurrence of first ischemic stroke at least 5 months prior to enrollment, no previous or subsequent cerebral ischemia, Medical Research Council (MRC) strength grade of =3/5 in extensor muscles of the affected upper extremity in the acute phase Sample Size: 10 Age Range: 34-71 Mean Age: 50.3 ± 15.2 Onset: less than 5 months
Intervention	Group 1: n=4 ; underwent 5-day trial of tDCS and simultaneous PT/OT, After finishing the trial again they underwent a second 5-day intervention Group 2: n=6 ; underwent two 5-day interventions of bihemispheric tDCS and PT/OT
Outcome measures	Upper-Extremity Fugl-Meyer assessment (UE-FM) Wolf Motor Function Test (WMFT)
Results	The first 5-day period yielded an increase in Upper-Extremity Fugl-Meyer (UE-FM) Scores by 5.9±2.4 points (16.6% ±10.6%). The second 5-day period resulted in further meaningful, although significantly lower, gains with an additional improvement of 2.3±1.4 points in UE-FM compared with the end of the first 5-day period (5.5% ±4.2%). The overall mean change after the 2 periods was 8.2± 2.2 points (22.9% ±11.4%). The results confirm the efficacy of bihemispheric tDCS in combination withperipheral sensorimotor stimulation.
Loss of follow up	Nil
Quality Score	9

Appendix 2: Excluded studies with the reason for exclusion

Reference	Reason for exclusion
Reis J (2009)[24]	outome measure was different
Sparing (2009)[25]	outome measure was different
Lindenberg R (2011)[26]	outome measure was different
Schambra HM (2011)[27]	outome measure was different
Tohyama T (2011)[28]	single subject design
Hodics TM (2012)[29]	out come measures of two different studies were compared
Kai KengAng (2012)[30]	outome measure was different
Kasashima (2012)[31]	outome measure was different
Lefebvre (2012)[32]	outome measure was different
Madhavan S (2012)[33]	outome measure was different
Zimerman M (2012)[34]	outome measure was different
Danzl MM (2013)[35]	outome measure was different
Lefebvre (2013)[36]	outome measure was different
Plow (2013)[37]	trail under process

Quality of the Studies

Pedro Rating scale was used for quantifying the methodological quality of the studies included in the study. Table 1 shows the detailed score of individual studies on Pedro scale. The average score of these studies (n=7) was 8.57 ± 1.72 with a minimum score of 5 and a maximum score of 10. The reviewer could not perform a meta-analysis due to an inadequate number of studies, lack of adequate data and use of different outcome measures.

DISCUSSIONS

The search strategy resulted in 7 full text articles fulfilling the criteria set by the reviewers. Performing double blinded studies in stroke rehabilitation are often not possible due to the nature of interventions, breaking down the levels of blinding and accounting for concealed allocation, intention to treat and attrition[16]. This could have been a probable reason for finding less number of quality studies which matched the reviewers' criteria. The methodological criteria was analyzed and it ranged from 5 to 10 (mean value 8.57 ± 1.72). Specifically the 'compliance' and 'intention to treat' were analyzed separately. Any disagreements were resolved by consensus. If disagreement still persisted, then the third reviewer (NA) was asked to assess for methodological quality and his conclusion was considered as final.

Administration of transcranial direct current stimulation

Transcranial Direct current stimulation was administered in the following ways 1) Anodal stimulation to the lesioned hemisphere alone[17,18,19,20], or 2) Cathodal stimulation to the unaffected hemisphere alone[18,21] or 3) Bihemispheric stimulation with anode over the affected hemisphere and cathode over the unaffected hemisphere[22], 4) Bihemispheric transcranial Direct Current stimulation associated with peripheral stimulation to the affected upper limb[23] .

Number of sessions

A minimum of 5 sessions of Non-invasive Brain stimulation in the form of Transcranial Direct Current Stimulation was administered. The treatment administered ranged from 5 to 30 minutes. Rehabilitation in the form of Physical Therapy or Occupational therapy was administered for all participants. Therapy was administered either simultaneously or following transcranial direct current stimulation.

Role of associated intervention

Studies that included simultaneous administration of Physical/ Occupational therapy have revealed better outcome in the form of motor scores among patients with subacute stroke. Authors did not receive any randomised controlled trial that compared simultaneous physical/ occupational therapy and tDCS with tDCS alone. On the contrast studies revealed better functional outcome in those patients who had undergone simultaneous Physical/ Occupational Therapy and tDCS when compared with Physical/ Occupational therapy only.

Outcome measures

Among the selected studies, one study done by Geroin (2011) was done on done on lower limb functions and the remaining 6 were on upper extremity functions[19]. The outcome measures that had been used for screening upper extremity functions were Upper Extremity Fugl Meyer score1[17,18,21,22,23],Jebsons Taylor Hand Function Test[20], Wolf Motor Function Test[22,23], Upper extremity Muscle strength[17,18,23]. Study done by Geroin (2011)on the effectiveness of tDCS on gait used Rivermead Mobility Index, six- minute walk test, ten minute walk test and motricity index leg subscores[19].

tDCS and upper limb functions

6 out of 7 studies that were retrieved included simultaneous motor training of the paretic upper limb of stroke survivors. The type of training included peripheral sensorimotor training or robot assisted arm training.The observations based on outcome measures revealed significant influence of tDCS paired with motor rehabilitation in improving upper extremity control. Lindenberg et al., (2010) have shown that the combination of bihemispheric tDCS and peripheral sensorimotor activities tends to improve motor functions that outlasted the intervention period.

tDCSand Lower limb Functions

A single RCT was retrieved for the effectiveness of tDCS in lower limb function post stroke. This study was done by Geroin, et al., (2011) among chronic stroke patients who received tDCS and Robot Assisted Gait Training was compared with robot assisted gait training alone. The study did not reveal any significant inter group difference between tDCS and robot assisted gait training with robot assisted gait training alone among the chronic stroke survivors.

Duration of the condition

None of the studies were reported for acute stroke population. All studies that were included for the review comprised of patient population who were either subacute or chronic stroke patients.

CONCLUSION

This systematic review explored the efficacy of tDCS intervention among individuals suffering from stroke. Two types of intervention was categorised based on the findings of different studies included for the study. Unihemispheric stimulation and bihemispheric stimulation by using weak direct current were recognised. The duration of application of current ranged from 5 minutes to 30 minutes. It was understood that Physical/ Occupational Therapy in conjunction to tDCS yielded better results. The intergroup comparison of administration of tDCS for upper limb recovery had shown significantly better results while that for lower extremity rehabilitation did not show a statistically significant difference between both groups.The analyses revealed that tDCS could be an important adjunct in upper limb rehabilitation post stroke. The relatively insufficient RCTs and insignificant difference between application of tDCSalongwith rehabilitation or Rehabilitation therapy in the form of robotic assisted therapy alone poses some doubts in the efficacy of tDCS as a valuable adjunct to lower extremity rehabilitation post stroke. The studies that were received for this review included rehabilitation in conjunction with tDCS. The reviewers did not receive any study that compared the efficacy of application tDCS alone among individuals suffering from stroke.

Recommendations for future research

From the review the author would recommend that further RCT evaluating the long term gains of tDCS on stroke recovery have to be conducted. The physiological background of the effectiveness of non-invasive brain stimulation on lower extremity recovery has to be understood and any modifications if desirable must be done to get better functional recovery of the lower extremity.

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