

EFFECT OF ANODAL TRANSCRANIAL DIRECT CURRENT STIMULATION ON NAMING IN APHASIC PATIENTS WITH ACUTE ISCHEMIC STROKE

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INTRODUCTION

Stroke is one of the most devastating diseases, incurring significant morbidity and mortality. Incidence and prevalence of stroke have increased with time, with younger individuals also being affected. As of 2019, the global incidence of stroke was estimated to be 12.2 million(1), and prevalence was estimated to be 101 million(1). DALYs (disability adjusted life years) lost due to stroke were estimated to be 143 million(1), and deaths due to stroke were estimated at 6.55 million(1) . Stroke was found to be the second-leading cause of death globally and the third-leading cause of death and disability combined.(1)

Impairment in communication, in the form of aphasia or dysarthria and motor dysfunction in the form of hemiparesis or hemiplegia, are the two most significant morbidities suffered by survivors of stroke. Global estimates of occurrence of aphasia due to stroke is in the range of 20-40%. (2,3) Indian studies estimate aphasia due to stroke occurs in 21-38% of patients. (4) It has been stated “one never recovers from aphasia; one recovers with aphasia.” (5) An inability to communicate effectively can often hamper one’s quality of life in the form of mental health issues, unemployment with financial burdens, and social isolation.

Studies have focused on rehabilitation from aphasia, using various forms of behavioural aphasia therapy such as Constraint induced Language Treatment, Melodic Intonation therapy and Speech Entrainment.(4) Non-invasive Brain Stimulation (NIBS) methods such as Transcranial Magnetic Stimulation (TMS) have also been used for rehabilitation from aphasia.(4) Transcranial Direct Current Stimulation, another form of NIBS, is a newcomer to the field to aphasia rehabilitation, with limited number of studies overall. (5)

Transcranial direct current stimulation (tDCS) is a painless, non-invasive, cortical stimulation technique, which is carried out with a battery-driven device, and involves application of electrodes to the scalp, with a weak current flowing between the electrodes, through the brain.(6)

The effects of tDCS on brain function are hypothesized to be neuromodulatory.(6,7) tDCS is believed to be capable of inducing synaptic plasticity through mechanisms of long-term potentiation (LTP) and long-term depression (LTD). At the synaptic level, these changes are believed to be carried out by NMDA receptors of glutaminergic neurons. Therefore, tDCS may

have therapeutic potential for treating dysfunctions of the brain, occurring due to stroke or any other neuropsychiatric pathology, by facilitating recovery-related plastic changes.

The effect of tDCS on aphasia recovery in patients with ischemic stroke has only recently been explored. However, the results have not been consistent and there is still scarcity of data regarding effects of tDCS in stroke.

With this background, we hypothesize that application of tDCS to prespecified areas in the brain would lead to better outcomes in language function, as compared to sham application, in patients with acute ischemic stroke and aphasia.

REVIEW OF LITERATURE

Transcranial direct current stimulation involves the placement of electrodes over the scalp, with the emission of a weak electrical current that flows between the two electrodes. (6,7) The electrodes are themselves named the anode and the cathode. Either one of them can be used for the experiment being conducted, based on the experiment design, in which case the main electrode is known as the target electrode, while the other electrode is known as the reference electrode.

The electrodes can be placed in different montages; some montages place the reference electrode extracephalically, for example on the upper arm, while some montages place the electrodes “bihemispherically” to emit dual stimulation to two parallel cortices (e.g., the parietal cortices— Benwell et al., 2015). (Lindenberg et al., 2010). Various parameters that need to be decided prior to attaching the electrodes are the type of electrodes themselves, the size of the electrodes, the conducting material used, the stimulation duration, current intensity, and ramp up/ramp down times which need to be programmed. (6)

Current flows between the electrodes during stimulation. The current passes through the brain, completing the circuit. Anodal stimulation is believed to depolarise the underlying cortical neurons, thereby making them more sensitive to action potentials and is hence known as “stimulatory”. Cathodal stimulation has the opposite effect, hyperpolarising the underlying cortical neurons, making them less likely to fire, and is thus known as “inhibitory”. (6,7)

Effects of tDCS application can be measured in several ways. The most common method used is via behavioural measures, wherein the researchers aim to measure a given behaviour/activity that would otherwise not be observed under sham conditions.

What makes tDCS a lucrative option for stroke rehabilitation programmes is the fact that it is a non-invasive method. The equipment is reusable, relatively inexpensive, portable, easy to apply, and can allow for reversible modulation of activity in specific brain regions. This has provided an invaluable tool for establishing brain-behavior relationships across a variety of cognitive, motor, social, and affective domains. (8)

So far, tDCS has been used to reduce symptoms of depression (9), it has been shown to reduce hallucinations in schizophrenia(10) and has also been used in autism spectrum disorder (11).

In aphasia rehabilitation, several studies have been undertaken that have utilised tDCS.

Monti et al, in a group comprising of 8 patients of chronic post stroke aphasia, with 4 patients of global aphasia and 4 patients of Broca's aphasia, showed that cathodal tDCS improved naming accuracy in picture naming task. (12)

Hesse et al, in a group comprising of 5 patients with subacute post stroke aphasia, of which 3 patients had global aphasia and 2 patients had Wernicke's aphasia, showed that anodal tDCS improved performance testing on Aachenner aphasia test. (13)

Baker et al, in a group of 10 patients of whom 6 had anomia and 4 had Broca's aphasia, showed that anodal tDCS improved accuracy on picture naming test, and that the benefits lasted for 1 week after treatment. (14)

Kang et al, in a group of 10 chronic aphasia patients, of which 3 had global aphasia, 4 had Broca's aphasia, 2 had anomia and 1 had transcortical aphasia, showed that cathodal tDCS increased accuracy on picture naming task 1 hour after the last session. (15)

Jung et al, in a group of 37 patients, showed that cathodal tDCS improved the aphasia quotient on the Western aphasia battery validated for Korean. (16)

What impedes its use in Stroke rehabilitation, especially its use in aphasia rehabilitation is the lack of comparable research available. Firstly, unlike several studies that examine effects of tDCS on healthy motor physiology, effects on healthy language networks haven't been as thoroughly explored. (17,18,19) Secondly, so far it has been used experimentally in small scale

studies to investigate possible advantages of using tDCS and its possible role in rehabilitation. Since the studies are investigative, there is great variability among the protocols, the sampling and the results; furthermore, only studies with positive results tend to get published, leaving lacunae about methods or protocols that didn't work .

Additionally, across almost all the studies utilising tDCS in aphasia, tDCS hasn't been used in isolation, but has always been used with other rehabilitative measures. As per American Heart Association, "inclusion of behavioral training in the majority of tDCS/aphasia studies may inhibit an understanding of what tDCS does autonomously to language functions." (5) Though one can argue that an aphasia experiment without language training would deprive aphasic subjects of concomitant proven therapy, it might also enable better understanding of tDCS, introducing better paradigms which can then be combined with previously proven methods of rehabilitation.

Finally, studies regarding the use of tDCS in patients with acute stroke with aphasia are also scarce. (20, 21)

In light of the above information, we decided to use anodal tDCS autonomously, in patients with acute ischemic stroke with aphasia.

LACUNAE IN EXISTING KNOWLEDGE

The use of transcranial direct current stimulation (tDCS) for the management of deficits developed in stroke is a relatively new type of management option. Many of the studies performed using tDCS have focused on improvements noted in hemiplegia as compared to aphasia, which is an equally disabling outcome of strokes. The results of these studies have not been conclusive and concordant with each other.

In aphasia management, majority of the studies have focussed on subacute to chronic strokes, and since the use of tDCS is relatively new, the studies have not focussed on a particular type of deficit, or a particular type of stroke. Very few studies have focussed on the impact of solely using tDCS. Very few studies have focussed on acute strokes. The results of the studies have nevertheless, been encouraging.

Improvements in aspects of language tested, after a single session of tDCS, is short lived. There is an unmet need to probe the utility of repetitive tDCS on aspects of language function in patients who are aphasic due to acute stroke. There is also a paucity of data in the Indian scenario regarding the same.

RESEARCH QUESTION

Does transcranial direct current stimulation (tDCS) to prespecified areas of the brain lead to improvement in naming function of aphasic patients with Acute Ischemic Stroke?

RESEARCH HYPOTHESIS

Application of tDCS to prespecified areas in the brain leads to improvement in naming function of aphasic patients with Acute Ischemic Stroke.

AIMS AND OBJECTIVES

AIM: To determine the effect of Anodal Transcranial Direct Current Stimulation on naming function of aphasic patients with Acute Ischemic Stroke.

OBJECTIVES:

Primary Objective: Difference of change in Accuracy between Anodal tDCS group and Sham tDCS group at 5 days on the ICMR Picture Naming Test.

Co-Primary Objective: Difference of change in Reaction Time between Anodal tDCS group and Sham tDCS group at 5 days on the ICMR Picture Naming Test.

Secondary Objectives:

- Difference of change in Correct Response between Anodal tDCS group and Sham tDCS group at 5 days on the ICMR Picture Naming Test.
- Difference of change in PNT Score between Anodal tDCS group and Sham tDCS group at 5 days on the ICMR Picture Naming Test.
- Difference of change in Accuracy between Anodal tDCS group and Sham tDCS group at 4 weeks on the ICMR Picture Naming Test.
- Difference of change in Reaction Time between Anodal tDCS group and Sham tDCS group at 4 weeks on the ICMR Picture Naming Test.
- Difference of change in Correct Response between Anodal tDCS group and Sham tDCS group at 4 weeks on the ICMR Picture Naming Test.
- Difference of change in PNT Score between Anodal tDCS group and Sham tDCS group at 4 weeks on the ICMR Picture Naming Test.

MATERIAL AND METHODS

Place of Study: Department of Neurology, ABVIMS & Dr. RML hospital, New Delhi.

Study design: Randomized, double blinded, sham controlled study.

Sample size: The study of Eun Kyoung Kang, et al observed that post-stimulation response accuracy in tDCS was 31.9 ± 6.9 and in Sham stimulation was 29.9 ± 6.2 . Taking these values as reference, the minimum required sample size with 80% power of study and 5% level of significance is 169 patients in each study group. For finite sample size taking population as 20, total sample size calculated is 19. To reduce margin of error, total sample size taken is 20 (10 per group).

Formula used is:

For comparing mean of two groups

$$N \geq 2(\text{standard deviation})^2 \times (Z\alpha + Z\beta)^2 (\text{mean difference})^2$$

Where $Z\alpha$ is value of Z (normal variate) at two sided alpha error of 5% and $Z\beta$ is value of Z (normal variate) at power of 80% and mean difference is difference in mean values of two groups.

$$\text{Pooled standard deviation} = \sqrt{(S1^2 + S2^2)/2}$$

Where S1 is standard deviation of 1 group. and S2 is standard deviation of other group. Finite population correction factor:-

$$SS \geq n / (1 + [(n - 1)/\text{Pop}])$$

Where Pop is population

Calculations:

$$\text{Pooled standard deviation} =$$

$$= 6.56$$

$$N \geq 2(6.56)^2 \times (1.96 + .84)^2 (2)^2$$

$$\geq 168.66 = 169 (\text{approx.})$$

$$\sqrt{(6.92 + 6.22)/2}$$

So total sample size to be taken is $169 \times 2 = 338$

Finite population correction factor:-

$$SS \geq 338 / (1 + [(338 - 1)/20])$$

$$\geq 18.93 = 19 (\text{approx.})$$

Assuming 20% attrition, each group will consist of at least 12 patients.

Block Randomization

Block Randomization with Sealed Envelope System: - In this technique, patients will be randomized in a series of blocks of 4, using an online randomization generator. Patients will be allocated to either of the groups (group A - true or group B- sham) in a 1:1 ratio. The randomization list will be generated by the biostatistician and transferred to a sealed opaque envelope, and each envelope will be opened by the primary investigator (supervisor) when the corresponding number of eligible participants is enrolled. However, the technician who administers the anodal tDCS procedure will know about the identity of the groups. A blinded investigator will record outcomes. Neither the patient nor the investigator knows which label represents which group, making this a double-blind study.

Study population: Aphasic patients with acute ischemic stroke with left Middle Cerebral Artery territory infarcts.

INCLUSION CRITERIA

- Aphasic patients with left middle cerebral artery territory Acute Ischemic Stroke
- Patients between 18-65 years of age.
- Within 5 days of onset of stroke.

EXCLUSION CRITERIA

- Patients with malignant Middle Cerebral Artery territory infarcts and previous clinical history of cerebral hemisphere stroke.
- Patients with history of previous brain surgery or skull defect due to surgery e.g. craniectomy.
- Patients with epilepsy.
- Patients with history of significant head trauma in the last 1 month.
- Patients with documented history of major depression prior to stroke.
- Patients with alcohol/drug abuse in the past 6 months.
- Patients with prior significant cognitive impairment.
- Pacemaker in-situ, cochlear implant in-situ.
- Pregnancy.

PROCEDURAL DETAILS

- All consenting patients recruited for the study will be evaluated clinically in detail. The patients will undergo aphasia testing using the Western Aphasia Battery and will be classified accordingly into the subtypes of aphasia. The patients will then be randomized into either the true stimulation group or the sham stimulation group as mentioned.

Picture Naming Test

- The Indian Council of Medical Research (ICMR) validated the Picture Naming Test (PNT), part of the ICMR MUDRA Toolbox for use in patients with Dementia. The PNT was used to objectively quantify Naming ability during and after sessions of anodal Transcranial Direct Current Stimulation. The ICMR PNT has been validated in five languages, including English and Hindi.
- The ICMR PNT consists of 30 line drawings.
- The administration of the test is as follows:
 - The pictures are shown one by one.
 - The subject has to identify each item by telling the first name that comes to their mind upon seeing the stimulus. 10 seconds are given for an unprompted response.

- If the subject is unable to name the image shown or makes an error during naming, cues are provided.
 - First, a category/semantic cue is provided, and the patient is given 10 seconds to name the picture.
 - If the subject fails to respond or responds incorrectly, a phonemic cue is provided, and the subject is again given 10 seconds to respond.
 - If the subject is still unable to respond or makes an error, the test moves on to the next picture.
 - Hence, the maximum time for naming an image is 30 seconds.
 - Care is taken that the entire test be conducted in the same language.
- Additionally, scoring is done based on the prespecified names provided. A few objects shown in the pictures may have more than one name, but the response accepted is the response prespecified in the validated PNT.

The scoring for the ICMR PNT is as follows:

- Correct response in the testing language spontaneously (without cues) (NL)= +3
- Correct response in testing language with a semantic cue (NL) = +2
- Correct response in testing language with a phonemic cue (NL) = +1
- If the responses are given in another language, and not the testing language, the scores are marked as follows:
 - Correct response in the testing language spontaneously (without cues) = OL3
 - Correct response in testing language with semantic cue = OL2
 - Correct response in testing language with phonemic cue = OL1
- Total correct responses are calculated as NL + OL.
- If the subject makes an error in naming, it is marked as ER. If the subject is unable to name, the scoring is done as 0.

For the purpose of our study:

- The instructions provided for administering the PNT, as laid down by the ICMR, will be followed for scoring correct responses. Since all patients tested will have Hindi as their native language, there will be no OL responses.

- Additionally, response times were noted for each picture named. If the patients could not name the pictures even after providing both semantic and phonemic cues, a response time of 30 seconds was noted. A calibrated stopwatch was used for marking the response times.

The ICMR PNT will be performed on:

- Day 0 (i.e. the day anodal tDCS/sham tDCS sessions were initiated, before the first session of anodal tDCS).
- Day 1 (i.e. 1 day after the first session of anodal tDCS/sham tDCS, before the second session).
- Day 5 (i.e. after 5 sessions of anodal tDCS/sham tDCS).
- 1 week +/- 2 days after the last session of anodal tDCS/sham tDCS, to look for the persistence of benefit, if any.
- 4 weeks +/- 2 days after the last session of anodal tDCS/sham tDCS, to look for the persistence of benefit, if any.

The various parameters assessed in the study using the ICMR-PNT are defined as follows:

- Accuracy is defined as the number of words spoken without the help of a semantic or phonemic cue on the ICMR Picture Naming Test
- Correct Response is defined as the total number of words spoken, with or without the help of either a semantic or a phonemic cue on the ICMR Picture Naming Test.
- PNT scores will be calculated for all the correct responses provided. The guidelines provided for the use of ICMR–PNT will be used. A response obtained without any semantic or phonemic cue is scored as 3. A response obtained with a semantic cue is scored as 2. A response obtained using both semantic and phonemic cues is scored as 1. No response obtained is scored as 0.
- A stopwatch will be used to record the reaction times of the patient during the process of naming items on the PNT. Timings, as suggested by the ICMR-PNT guidelines, will be used. 10 seconds will be provided for the patient to name the picture without any semantic or phonemic cues. At the end of 10 seconds, the stopwatch will be paused, a semantic cue provided, and the patient then continued to be timed. At the end of the next 10 seconds, the

stopwatch will be paused again, a phonemic cue provided, and the patient then continued to be timed. A total of 30 seconds will be provided per picture for naming. Patients will be timed as per their responses with or without cues. Reaction time will be noted as 30 seconds if the patient fails to name the picture after both semantic and phonemic cues.

tDCS Parameters:

- Stimulation site: left Brodmann area 45 (Broca's area) localized based on the 10-20 system of electroencephalography. On the tDCS equipment, the montage created using the leads Fp2 and F3 corresponds to maximal stimulation of Brodmann area 45.
- Reference electrode: Right supraorbital area (Fp2).
- Electrode size: Gel electrodes.
- Intensity of stimulation provided: 2mA.
- Duration of stimulation provided: 20 minutes, with ramp up & ramp down of 10 seconds each. Patients undergoing sham stimulation will receive stimulation for the first and last 10 seconds of 20 minutes period.
- Number of sessions: 5 sessions in 1 week.
- Task performed for assessment: ICMR Picture Naming test. (detailed above)

The tDCS procedure will be conducted as follows:

- The patients preferably seated in a chair. If the patients have evidence of dense hemiplegia with difficulty sitting in a chair or wheelchair, the sessions will be conducted with the patients in the semi-recumbent position to prevent dislodgement of the tDCS equipment during the sessions.
- Once the tDCS cap is placed on the head, care will be taken to part the hair from underneath the proposed area of electrode placement, to prevent the development of excess impedance.
- Gel electrodes will then be placed over the scalp.
- The tDCS machine will then be connected to the patient, and either true or sham stimulation will be provided.
- During the stimulation sessions themselves, care will be taken to note any side effects such as an uncomfortable sensation due to the stimulation themselves.
- A total of 5 sessions will be provided over 7 days. Care will be taken not to have a gap of more than 1 day between sessions.

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