Efficacy of Transcranial Direct Current Stimulation on Tension-Type Headache and Migraine: A Systematic Review

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Abstract

Introduction: Headache is one of the most common conditions troubling nearly 68% of the world's population. Tension-type headache (TTH) & migraine are the most common forms of classical headaches, which is nowadays mostly neglected, associated with frequent, severe pain and significant functional impairment. Transcranial direct current stimulation (tDCS), is a non-invasive, painless brain stimulation treatment that uses direct electrical currents to stimulate specific parts of the brain. Various studies demonstrated tDCS as a valued device to treat neuropsychiatric conditions such as chronic headache & associated anxiodepressive condition. **Objective:** The aim of this the current review was to evaluate the effectiveness of tDCS in the management of TTH and Migraine. Results generated from various studies for the effectiveness of tDCS in TTH & Migraine. **Methods:** We programmed our search strategy, to identify studies pertaining to use of tDCS and pain management in TTH & migraine, within the Database of the Cochrane Library of Systematic Reviews, & various author manuscripts in PMC, MEDLINE, EMBASE, NLM, PsycINFO, Other indexed citations from inception to December 2021 and potentially relevant studies. **Outcomes:** The outcomes of interest include: Effective pain management, in terms of headache intensity, frequency, its episodes, associated depression, anxiety, in target population prioritised by the individual reviews. The evidences were mapped and synthesised with appropriate health problem, patient subgroups, intervention type, context and outcome.**Conclusions:** We found a significant reduction of pain intensity in patients receiving tDCS treatment, also the pain intensity and duration were significantly improved from baseline after tDCS treatment and during a follow-up period. There was a significant reduction of pain intensity by both anodal and cathodal stimulation conditions, with noteworthy decrease in episodic headaches equally by both 1mA and 2mA current intensities. The aforementioned works support the utility of tDCS in the pain management of TTH and migraine offering a hope for patients with this debilitating disease. However, the review shows promising results in the pain management by tDCS, but the included studies must be analysed critically since most of them were pilot studies, with some having adapted an open-label design.

Keywords: Headache, Neuromodulation, Pain, transcranial direct current stimulation (tDCS)

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Introduction

Headache is one of the most common pain-related medical conditions of the modern era and it affects approximately 68% of the world's population.[1] Tension-type headache (TTH) and migraine are the two most common types of primary headache. The term tension-type was coined by the first Classification Committee of the International Headache Society, and it has been maintained in the second edition of the International Classification of Headache Disorders.[1] TTH is characterized by a bilateral, pressing, or tightening in pain quality, from mild-to-moderate intensity. Short episodes of variable duration are frequent in episodic TTH, occurring 1 in 14 days per month or continuously for more than 15 days/month in the chronic form of TTH.[2] Chronic form of TTH is a major health problem with enormous socioeconomic effects.[2] Alternatively, migraine, which is a more disabling condition compared to TTH in terms of headache intensity, also affects millions of

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people.[1,2] Migraine is defined as a primary headache disorder with repeated episodic flare-ups lasting 4–72 h, characteristic migraine headache has moderate-to-severe head pain intensity, unilateral location, and throbbing/pulsating pain quality, associated with photophobia, nausea, and/or vomiting.[3]

Globally, migraine and TTH together account for 6.5% of all years lost due to disability (YLDs), (7.7% among females and 5.1% among males), respectively.[2] It is also known that primary headache is less frequently reported than real prevalence as many of the patients do not take medical help and use over-the-counter pain-relieving medicine.[2] The global prevalence of migraine was estimated at 14.7% (around 1 in 7 people) in one study.[4] Based on the 357 publications reviewed, the authors estimate that (52.0%) of the global population have experienced a headache disorder within a given year, migraine (14.0%) and Tension Type Headache (26.0%).[5]

The exact pathophysiology of migraine is not completely elucidated yet, prevailing theories include the existence of central and peripheral nervous system changes.[6] Likewise, the exact mechanisms of TTH are still not understood. The pain-detecting systems in both of these conditions with headache are implicated in peripheral, myofacial, and central disruption pathways, but their respective weights differ in terms of headache and patients. Recent studies suggested that central sensitization is a common mechanism of chronification of headache, in which increased sensitivity of cortical and spinal neurons to sensory stimuli and malfunction of descending pain pathways are key features of chronic primary headache disorders (e.g., chronic migraine, chronic TTH, and chronic daily headache).[7]

Current treatment options for chronic or high-frequency primary headache include both pharmacological and nonpharmacological options.[8] The high relapse rate after stopping drug and drug-related adverse reactions among the patients on pharmacological treatment compels the finding better ways of nonpharmacological treatment.[9] A recent systematic review and meta-analysis suggested that transcranial direct current stimulation (tDCS) could be a promising nonpharmaceutical alternative for both TTH and migraine patients.[9]

Over the last decade, tDCS has been explored as a preventive therapy in pain management. tDCS consists of delivering a weak current through two sponge electrodes fixed on the scalp and connected to a battery-driven stimulator.[10] It has been established that this intervention exerts its effects through the modulation of the resting membrane potential of neural fibers. The modulation of the resting potential depends on the polarity of the stimulation (anodal and cathodal) leading to depolarization and hyperpolarization, respectively.[10]

However, there is a paucity of comprehensive analyses on repetitive tDCS treatment results and whether tDCS has long-term effects on such headaches. Therefore, there is an unmet clinical need for using novel non-pharmacological interventions for both debilitating primary headache disorders. As a result, the current review was conducted to evaluate the effectiveness of tDCS in the management of TTH and migraine. To see the impact of tDCS on primary headache, various outcome parameters such as headache-related disability, the impact of headaches on quality of life, headache frequency, duration, pain intensity, and use of abortive medications were planned to be included. In addition, this review will establish the scope of tDCS in clinical practice for headache management and will also be helpful in future clinical trials.

Materials and Methods

Literature search

The literature search was conducted in more than five databases, including PMC, MEDLINE, Embase, NLM, and PsycInfo from the date of the first available article up to December 2021. We identified studies related to tDCS, TTH, and migraine using keywords "tDCS" or "Transcranial Direct Current Stimulation" for tDCS and "Headache," "Tension Type Headache," "Pain," "Migraine," "Chronic TTH," "Episodic Headache," "Cortical Stimulation," "Frequent TTH," and "Headache related Disability" for TTH. We applied the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to further screen and filter studies.

Two reviewers independently screened all the retrieved studies to determine and authenticate to meet the eligibility criteria. To resolve the differences, reviewers negotiated together and consulted a third reviewer. Then, the full text of all potentially relevant studies was analyzed to verify compliance with the eligibility criteria, and the results were adequately reported.

Eligibility criteria

We followed the PICOS[11] (Participants, Intervention, Comparators, Outcomes, Study types) framework to organize the inclusion criteria. Participants (P): Adults 18–85 years old with TTH and migraine including; Interventions (I): tDCS; Comparators ©: Patients do not receive stimulation treatment; Outcomes (O): Outcomes related to headache intensity, duration of each headache episode and frequency, number of headache attacks, and use of pain medication; and Study type (S): Controlled trials.

We excluded studies that used other types of electrical stimulation instead of tDCS for control comparison; that had subjects with headache disorders other than TTH and migraine; were published in the form of nonspecific reviews, conference abstract/posters, consensus guidelines, narrative reviews; and/or provided insufficient data for analyses (such as raw data and open gray material with no evidence).

Methods for reaching consensus

Risk of bias assessment

Two researchers autonomously assessed the risk of bias in each study. The third researcher resolved the discrepancies and the differences by 100% consensus. The following criteria were considered to assess the risk of bias in our analysis:

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random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias.

Data extraction and data items

Researchers extracted data from different articles and the following items were included: study type and design, the process of randomization, and blinding technique, participants in each group, stimulation protocols (combination of montage stimulation electrode and reference electrode, electrode size, current intensity, and duration), outcome measurements, and results. Outcomes included head pain intensity (scaled from 0 to 10 monthly) and duration of each headache episode. We also reviewed studies on the frequency and use of pain medications (analgesics).

Results

Selection and characteristics of the studies

According to the search criteria, our preliminary search yielded 310 results in which 199 nonduplicated studies were identified. After removing nonspecific and incomplete articles and conference and meeting abstracts, 115 articles were left for rigorous screening of eligibility. Finally, 15 eligible studies were included in the systematic analysis.[12-26] The detailed procedure adopted for the study selection and exclusion is shown in Figure 1. Data from 402 patients receiving tDCS were used to evaluate the effects of tDCS on headache intensity, frequency and its episodes, and use of pain or abortive medications. Totally, 10 studies address the role of tDCS in migraine headache and the term "Migraine" was used in five studies, "chronic migraine" in four studies, and "episodic migraine" in one study. In the rest of the selected studies, different terms were used like primary headache in one, chronic headache in one, pain disorder in one, chronic cluster headache in one, and medication-overuse headache (MOH) in one study. The number of sessions was not specified in four studies; the rest of the selected papers had different frequencies and duration of sessions. Wide variation was noted in the selection of polarity and follow-up period in tDCS protocol. Summary of tDCS protocol used in selected studies is shown in Table 1. Figures 2 and 3 show the electrode placement with instrument and cathodal (black) and anodal electrodes (red) used in headache protocol.

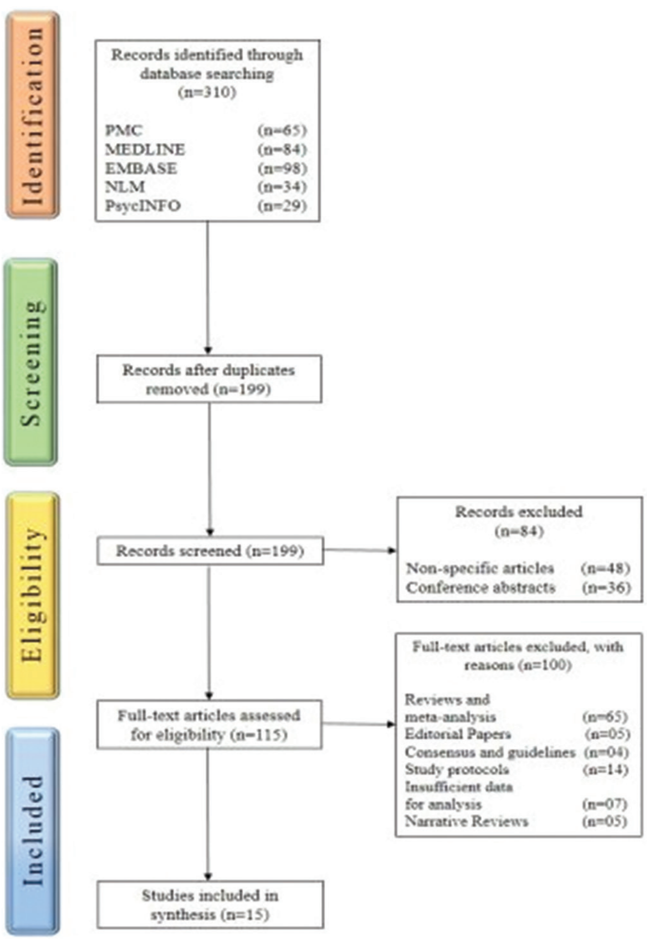

Figure 1: PRISMA flow diagram for study selection

Discussion

Transcranial direct current stimulation protocol: Polarity and sites of stimulation

In the current review, studies showed a great variation in terms of stimulation duration (10 vs. 15 vs. 20 min), electrode polarity (cathodal vs. anodal), current intensity (1 mA vs. 2 mA), cortical target (occipital vs. dorsolateral prefrontal cortex [DLPFC] vs. M1 vs. S1), stimulation side (left vs. right), and reference electrode (various cephalic vs. extracephalic positions). The number of stimulation sessions also differed across studies (3–22 sessions).[10] The baseline duration among studies ranged from 1 week to 8 weeks, treatment length varied from 4 weeks to 6 weeks, and follow-up duration ranged from 4 to 16 weeks.[15]

Figure 2: Electrode placement

Table 1: Details of studies included

Author	Year	Diagnosis	Number of patients	Cathodal site	Anodal site	Number of sessions	Treatment duration	Follow-up duration	Positive response to pain intensity	Positive response to headache Frequency	Positive response to duration of attack	Reduction in the use of abortive medication
Antal *et al*.[13]	2011	Migraine	26	Visual cortex	Vertex	3 times per week	6 weeks	8 weeks	Yes	Yes	Yes	No
Auvichayapat *et al*.[19]	2012	Migraine	37	Primary motor cortex	Not known	20	12 weeks	4, 8, 12 weeks	Yes	Yes	No	Yes
Dasilva *et al*[20]	2012	Chronic migraine	13	Frontal	Primary motor cortex	10	4 weeks	8,16 weeks	Yes	No	Yes	No
Pinchuk *et al*[26]	2013	Primary headache	86	2 cm above the mastoid	Frontal	5 to 9 with 4-7 days of interval	18 weeks	9 weeks	Yes	Yes	Yes	Yes
Viganò *et al*[14]	2013	Migraine	11	Chin	Visual cortex	16	8 weeks	NA	No	Yes	Yes	Yes
Rocha *et al*.[15]	2015	Migraine	15	Visual cortex	Vertex	12	4 weeks	4 weeks	No	Yes	Yes	Yes
Andrade *et al*[18]	2017	Chronic migraine	13	Frontal	Primary motor cortex and DLPFC	NA	NA	Unspecified	Yes	No	No	No
Alhassani *et al*.[21]	2017	Chronic headache	9	Frontal	Primary motor cortex	NA	4 weeks	4 weeks	Yes	Yes	No	Yes
Naegel *et al*[22]	2018	Pain disorders	13	Primary motor cortex	Frontal	NA	8 weeks	Unspecified	NA	NA	NA	NA
Magis *et al*.[25]	2018	Chronic cluster headache	31	Cervical spine C7	Frontal	8 weeks	8 weeks	2 weeks	Yes	No	Yes	Yes
Ahdab *et al*[16]	2019	Episodic migraine	42	Visual cortex	Frontal	3 daily sessions per week	2 weeks	4 weeks	Yes	Yes	No	Yes
Mansour *et al*.[12]	2020	Medication-overuse headache	18	Visual cortex	Frontal	10	NA	2 weeks	No	Yes	No	Yes
Dalla Volta *et al*.[24]	2020	Chronic migraine	45	Frontal	Not known	13 weeks	13 weeks	4 weeks	Yes	Yes	Yes	Yes
Rahimi *et al*[23]	2020	Migraine	45	Primary motor OR sensory cortex	Not known	No specified	10 weeks	52 weeks	Yes	Yes	Yes	No
Mastria *et al*[17]	2021	Chronic migraine	16	Visual cortex	DLPFC	3 times per week	4 weeks	4 weeks	No	Yes	No	Yes

DLPFC: Dorsolateral prefrontal cortex, NA: Not available

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Figure 3: tDCS instrument. tDCS: Transcranial direct current stimulation

Most of the studies have focused on the role of tDCS in migraine; very few studies could be elicited on TTH.[21,26] One study has investigated the efficacy of tDCS on MOH in primary headache.[12]

Various cortical areas were used for electrical stimulations in the selected studies for headache. Different sites used for stimulation were the visual cortex.[13-17] DLPFC,[17,18] the primary motor cortex,[18-21,23] the primary sensory cortex (S1),[23] and frontal.[12,20,24,25]

Most of the studies selected cathodal type of polarity for stimulation for headache like cathodal Occipital (Visual) Cortex stimulation was mentioned in 5 studies,[12,13,15-17] one study used anodal visual cortex stimulation[14] cathodal primary motor cortex (M1) in 2 studies,[22,23] and the cathodal primary sensory cortex (S1) in one study.[23] However, anodal stimulation was used for the left primary motor cortex in four studies (M1),[18-21] and frontal pole anodal stimulation in four studies.[12,17,25,26] One study described a personalized "cold patch" stimulation approach that was used to stimulate the cathodal frontal cortex, guided by thermography.[24] They termed the location the cold patch, which is a hypothermic area present due to a shunt between the internal and external arteries.[24]

Headache frequency and the number of abortive medicines were two other outcome variables used for testing the effectiveness of tDCS in headache. A headache diary is commonly used to assess headache frequency and frequency of abortive (rescue) medications used. The reduction in the usage of pain abortive medication consumption was shown in 10 studies.[12,14-17,19,21,24-26] The duration of headache was the fourth parameter to check the effectiveness of tDCS in headache management and eight studies found a significant reduction in the duration of headache after stimulation.[13-15,20,23-26]

Effects on pain intensity

Pain intensity was the endpoint parameter in 10 of 15 studies and the visual analog scale was the most common tool used for measurement of pain intensity. Notably, most of the studies showed a significant reduction in pain intensity by tDCS.[13,16,18-21,23-26]

Within the active tDCS participants, tDCS showed an effect in the reduction of pain intensity; this was evident from the finding of post tDCS, which was lower compared to the baseline and in the long-term follow-up period. A study by Mansour *et al*.[12] showed that DLPFC stimulation elucidated long-lasting effects on headache frequency, its intensity, and reduction in pain abortive medication consumption.

Another study by Rahimi *et al*. used cathodal stimulation in place of anodal tDCS over M1 and S1 areas, both of which take part in the pain matrix and the results confirm the reduction of frequency, duration, and intensity of pain in migraine patients.[23]

Duration and frequency of headache episodes

A total of 11 of 15 studies found a positive response of tDCS in the reduction of headache frequency.[12-17,19,21,23,24,26] In the only study that applied anodal stimulation, there was no reduction in migraine duration. Both treatments with 1 mA and 2 mA current intensities significantly reduced the migraine duration.[24]

Use of pain medications

Studies showed a significant reduction in the use of rescue pain medications when comparing patients with tDCS with patients without stimulation. The stimulatory group was associated with a significant reduction in the use of medications, including tramadol, ibuprofen, triptans, acetaminophen, valproate, flunarizine, SSRIs, and others compared to baseline.

Our review recommends that there is a long-term sustained benefit of daily repetitive tDCS for at least 4 weeks, in the management of TTH and migraine. Pinchuk *et al*. measured the levels of state anxiety and trait anxiety, which significantly decreased after tDCS treatment.[26] Furthermore, the assessment of pain control in such patients is a subjective self-evaluation, which may change because of hormonal influence and their own ethnic and cultural differences.

Stimulation parameters such as electrode montage setup, stimulation polarity, the duration of each session, number of sessions, and current intensity are selected to achieve the desired therapeutic effect of tDCS. In general, anodal stimulation is presumed to result in depolarization, whereas cathodal stimulation results in hyperpolarization. However, stimulation of either polarity may have both depolarizing and/or hyperpolarizing effects. Future studies with larger sample sizes and matched group assignments are needed for validation.

In our review, tDCS modality in TTH and migraine is emerging as a potential clinical intervention against such headaches. However, no standard montage configuration is available for studies with cathode positioning targeting the occipital region, the visual cortex, and S1, whereas studies using anode stimulation positioned above M1 with varying sides, prefrontal lobe, and the DLPFC, which were found to be effective in the respective cases. Our finding is consistent

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with polarity depending on the targeted region for therapeutic effect. Notably, it was also evident that the pain intensity was significantly reduced by both 1 mA and 2 mA current intensities, in the long-term follow-up period. Depending on the montage configurations, the electrical field generated via tDCS generally spreads to nearby cortical and subcortical structures. The duration of electrical changes is maintained only for an hour locally after one-time tDCS treatment, while sustained and repeated tDCS sessions can provoke cumulative and long-lasting neuroplasticity changes in the cerebral cortex. It may be beneficial to execute subgroup analyses to compare treatment responses in men and women separately.

Studies have proven that in long-term tDCS follow-up consumption of pain medication is significantly decreased. Future trials need to be programmed with numerous patients to maintain compliance with regular follow-ups for repeated tDCS sessions for pain management.

Various tDCS studies are executed with a varied diversity of montages, the applicability of broad aspects of performance. Despite, no standard montage configuration, some researchers have suggested that the efficacy of tDCS depends on individualized montage design guided by thermography, which can be customized to every single patient.

Future clinical trials using tDCS for such headache management may include administering tDCS while simultaneously measuring the neuronal activity using electroencephalographic (EEG) or functional magnetic resonance imaging to better understand the underlying mechanism of action, also high-definition tDCS, which can provide a more focal stimulation in selected brain regions, which will be effective in facilitating better pain management.

Strengths and limitations of this study

The study strength is that it is the only up-to-date overview of studies examining such trials for the effectiveness of tDCS in migraine and population with TTH. Furthermore, our methodology acknowledges and empowers us to identify the available evidence and map where the evidence base is tough or fragile.

The main weakness is that we have only included studies that clearly state, "the use of tDCS in TTH and migraine management. This study excludes broader reviews on use of novel tDCS technique with 'psychological interventions." Another weakness is that we are reliant on the information provided in various studies. From the study databases we have synthesized the studies, there is a possibility we might have omitted other trials if they are excluded in database.

The various comprehensive methods used in this review are the key strengths of the research presented. However, this review indicates an extreme lack of potential research in this area, with no comparative studies.

Conclusions and Perspectives

The above-mentioned work supports the utility of tDCS in the management of TTH and migraine, offering a glimmer of hope for patients with this debilitating disease. However, the review shows promising results in the pain management by tDCS, but the included studies must be analyzed critically since most of them were pilot studies, with some having adopted an open-label design. Moreover, various studies exhibited a great variation in terms of stimulation durations (10 vs. 15 vs. 20 min), electrode polarity (cathodal vs. anodal), current intensity (1 mA vs. 2 mA), cortical target (occipital vs. visual cortex vs. prefrontal cortex vs. DLPFC vs. M1 vs. S1), stimulation side (left vs. right), and reference electrode (various cephalic vs. extracephalic positions). Furthermore, different studies had a varied number of stimulation sessions (3–20 sessions) with varying stimulation frequencies, which is an important factor to be considered in future study designs.

In different studies, the strategies used to locate the cortical sites differed vastly and the locations were determined according to the international EEG system. There were broad differences in patient profiles across studies, with some of them excluding the pain medication intake, while some subjects with previous medication intake were considered for the study.

Furthermore, the research outcomes were also varied across different studies (e.g., number, duration and episodes of attacks, the impact of headache on quality of life, the intensity of pain, analgesic consumption, etc.). Therefore, extensive research is much needed, to define these unanswered facts, define the appropriate cortical site to stimulate, the efficient design to adapt, and outline the adequate stimulation duration and rhythm to be given to such subjects.

tDCS studies corresponding to neurophysiological autonomic nervous system measures and evoked potentials along with neuroimaging modalities such as functional brain MRI will surely allow us to understand the neural stimulation of various clinical responses considering TTH and migraine, considering the changes in regional activation pattern, cortical excitability, autonomic nervous system activity, and resting-state functional connectivity. In addition, performing neuropsychological evaluations would allow us to identify potential psychological and cognitive factors associated with some studies (i.e., presence of anxiety/depression, personality traits, specific coping strategies, and various cognitive manifestations) and might serve as predictors of tDCS response. In India, the future is near to open the way for home-based tDCS. The safety has been proven in various treatment regimens across different neuropsychiatric diseases and this technique is currently under exploration around the globe, in numerous research settings. Moreover, this technique could also be coupled with various psychotherapy (e.g., cognitive–behavioral therapy, interventions including mindfulness, and educational components) and various nonpharmacological interventions, such as trans-spinal direct current stimulation,

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with the utility to manage anxiety and depression, which is frequently accompanied in such patients.

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Conflicts of interest

There are no conflicts of interest.

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