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Effect of Transcranial Direct Current Stimulation (Tdcs) on the Consumption of Medication for Migraine Control: A Systematic Review

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Migraine; Direct current electrical stimulation; Medication

1. Abstract

1.1. Background: Migraine is a disorder that has a pulsating, unilateral character, which worsens with physical exertion and hinders the quality of life of people who suffer from it. Even though there are several comorbidities related to the disease, pain control is the main objective and neuromodulation can be used in patients who have some drug intolerance or capacity for non-pharmacological management.

1.2. Objective: To identify the effect of tDCS on the consumption of medications to control migraines. Methods: This is a systematic review conducted and reported following the PRISMA guidelines, with 07 randomized clinical trials, including 288 predominantly female participants who met the inclusion criteria corresponding to the objective of this review. To analyze the risk of bias, the new version of RoB 2 was used, which confirms low risk among RCTs.

1.3. Results: In general, tDCS was effective in reducing the use of medications to control migraines, although this study points out variations in the size of the effect of tDCS interventions in different classes of medications, in addition to the technique being effective in reducing the number of attacks of migraine.

1.4. Conclusion: Our findings support a positive effect of tDCS in reducing the consumption of medications taken to control migraines, and the heterogeneity of applicability does not seem to negatively influence its effect, however, they do not allow the proposition of a specific tDCS protocol with the aim of controlling migraine attacks with or without aura.

2. Introduction

The neurovascular disease called migraine, more commonly known as migraine, is characterized by repeated attacks of pain, which generally involves half of the head, and may be associated with symptoms of nausea, vomiting, photosensitivity and discomfort when faced with loud sounds, and may persist for up to 72h. Its frequency can be quite variable, while some people are affected by isolated episodes throughout their lives, others suffer from recurrent episodes (STEFANE, et al 2012; BUSE et al., 2019) [31]. Transcranial direct current stimulation (tDCS) is composed of anodic current that increases cortical excitability, favoring membrane depolarization, and cathodic current that decreases cortical excitability, favoring membrane hyperpolarization. Due to this characteristic, it is a neuromodulatory technique that acts on the neuronal membrane potential, either exciting or inhibiting it, modulating its firing rate; The technique consists of applying a low-intensity electrical current to specific regions duly measured under the scalp using two electrodes that act on the balance of ions inside and outside the neural membrane, stimulating changes in the resting threshold (COSTA et al, 2020) [9]. Migraine can be related to

hormonal fluctuations, stress, food deprivation, sleep deregulation, or even due to external factors such as climate change, exposure to odors, alcohol use, among others. This neurovascular disease is one of the main causes of disability being among the most prevalent diseases worldwide, in addition, it can be divided into clinical subtypes with different manifestations: migraine with and without aura, vestibular, ocular and/or abdominal migraine and, depending on the frequency of attacks, it can be considered chronic or episodic (ZOBDEH et al, 2021) [34].

There are many impacts caused by migraines. The deleterious impacts of migraine on the quality of life, as well as on the economic conditions of its sufferers, employers and society, are well described in the literature, as it affects a large number of people who are economically active (LIPTON et al, 2001; DÁMICO et al, 2015; BUSE , LIPTON and HALLSTROM, 2018) [20, 10, 6]. However, the complaint of pain is still one that receives great attention given its high intensity and power to interfere with so many other biopsychosocial characteristics of the individual. Therefore, the most common form of migraine treatment is medication, but this treatment can bring with it a series of systemic consequences such as the liver, kidneys, heart and blood vessels (ASHINA et al, 2021) [2]. In this sense, neuromodulation can be used in patients who have some drug intolerance or prefer non-pharmacological pain management (ORNELLO, et al 2021) [24]. The analgesic effect of tDCS is cumulative, requiring multiple sessions to achieve clinically significant results, stimulation lasting at least 5 minutes is generally required to produce biological effects, and changes in neural activity occur not only during tDCS, but also several hours after the end of stimulation (XIONG et al 2022) [33]. Therefore, this study aims to identify the effect of tDCS on the consumption of medication for migraine control. The secondary objectives are to: 1) Evaluate which application protocol model has the largest effect size on reducing medication consumption for migraine control; 2) Verify which pharmacological groups show the best response to treatment with tDCS; 3) Analyze the relationship between changes in medication consumption and migraine frequency (i.e., number of migraine attacks).

3. Method

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) guidelines (PAGE et al., 2021). The searches were performed in august 2023, by two independent reviewers, in five databases: Web of Science, Scopus, Embase, Virtual Health Library (VHL), and PubMed. The only filter used during consultation in the databases was document type (i.e., Article or Journal Article). The list of search terms and concepts to identify relevant literature was formulated by consulting the Medical Subject Headings (MeSH/PubMed) scientific vocabulary database. The following string were used in all searched databases: ("Transcranial Direct Current Stimulation" OR "transcranial current stimulation" OR "Cathodal Stimulation Transcranial Direct Current Stimulation" OR "Cathodal Stimulation" OR "Anodal Stimulation Transcranial Direct Current Stimulation" OR "Anodal Stimulation" OR TDCS) AND (migraine).

The papers located in databases were imported in Rayyan website, where the screening steps were conducted. Rayyan is a tool that helps researchers to elaborate systematic reviews with low risk of selection bias, as it allows each reviewer to conduct blind assessment. After the screening process, it is possible to verify the agreement and divergence of opinions between reviewers regarding the decisions to include or exclude each paper (OUZZANI et al., 2016) [26]. Furthermore, as we aimed at providing a comprehensive review of publications on the use of tDCS in the treatment of migraine, we did not set any restrictions regarding publication date or language of the studies. During the screening process, the reviewers make decisions based on the following eligibility criteria.

3.1. Eligibility Criteria (PICOS)

Participants (P)

Studies that meet all the following sample criteria were included:

1. Adults between the ages of 18 and 65;

2. Established diagnosis of any migraine type (e.g., with or without aura).

3. Uses abortive or prophylactic migraine medication

A study is ineligible if its sample meets the following criteria:

1. Has a heterogeneous sample in the same intervention group (i.e., adults and adolescents or adults and elderly 65+) with mean age under 18 or over 65.

Interventions and comparators (I and C)

A study was eligible if its intervention and comparators meet all the following criteria:

1. At least one group received some form of tDCS (i.e., Anodal or Cathodal);

2. Comparison of tDCS group with any type of control group (e.g., sham, waitlist).

A study was ineligible if it used or compared tDCS with:

1. Any other type of brain stimulation (e.g., repetitive transcranial magnetic stimulation, deep brain stimulation), without a control group;

2. Uses combined treatment in the same intervention group (e.g. tDCS + deep brain stimulation or repetitive transcranial magnetic stimulation).

Outcomes (O)

A study was eligible if its outcomes meet the following criteria:

1. Changes in medication use (i.e., abortive/rescue medication) scores measured by medication dose or tablets taken;

2. Changes in migraine frequency measured by number of mi-

graine attacks;

3. Studies with some type of statistical evidence of efficacy (e.g., Cohen d or Hedges' g) or sufficient data to perform effect size calculation (e.g., means and standard deviations of each group at pre- and post-test) of the changes in medication use and migraine frequency outcomes.

A study was ineligible if:

1. The medication use was measured only considering the number of days with and without use;

2. It evaluated the acute effect of the tDCS (i.e., a single session/ application).

Study Design (S)

A study was eligible if its design meets the following criteria:

1. Randomized clinical trials (RCT) with a control condition (e.g., sham, waitlist), regardless of the level of blinding (i.e., both single- and double-blind studies are eligible).

3.2. Data Extraction

After the screening process, the data extraction of the included papers was performed by two independent reviewers. The following data were extracted: 1) Study identification (i.e., author's name, country, and study publication year), 2) Interventions and comparators (e.g. anodal or cathodal tDCS, sham); 3) outcomes (i.e., effect size of medication use and migraine attacks frequency); 4) Intensity and attack area of tDCS; 5) Number and length of intervention sessions; 6) Sample characteristics (e.g. number of participants per group, mean age, sex); 7) Type of migraine; 8) Name and dose of medication or pharmacological group name; 9) How long the medication has been used [3,5,7,8,12, 14, 16, 18, 21, 22, 29, 30].

3.3. Data Analysis and Risk of Bias

All statistical evidence of effectiveness was standardized to Cohen's d. The effect sizes are interpreted according with Cohen (1988): negligible (< 0.2), small (0.2 to 0.4), medium (0.5 to 0.7) and large (≥ 0.8). The risk of bias of the included papers was assessed using the Cochrane Risk of Bias tool for randomized trials (RoB 2 - HIGGINS et al., 2023) [15].

4. Results

Initially, 398 papers were found in all databases. After duplicates were removed the total number of records screened was 128. There was disagreement among the raters regarding the inclusion/ exclusion decisions for seven of the 128 studies (IRR = 0.94) and the opinion of a third senior researcher was consulted, these inconsistencies were resolved by group discussion. There was total agreement between all raters regarding the final inclusion of seven papers. (Figure 1) show the steps of data selection according with the PRISMA flowchart (PAGE et al., 2021). The seven included RCTs were organized in ascending order considering the publication year. Each study received an ordinal number (i.e., between 1 and 7) used as a reference throughout this review. An integrative narrative synthesis was employed to summarize and discuss the extracted data. (Table 1) shows the main characteristics of the seven included studies interventions. It is noteworthy that all included RCTs analyzed two outcomes in different time points. Hence, some studies could be counted twice throughout the quantitative and qualitative synthesis of the results (e.g., the same study may have reported a large effect size at T1 and a small one at T2).

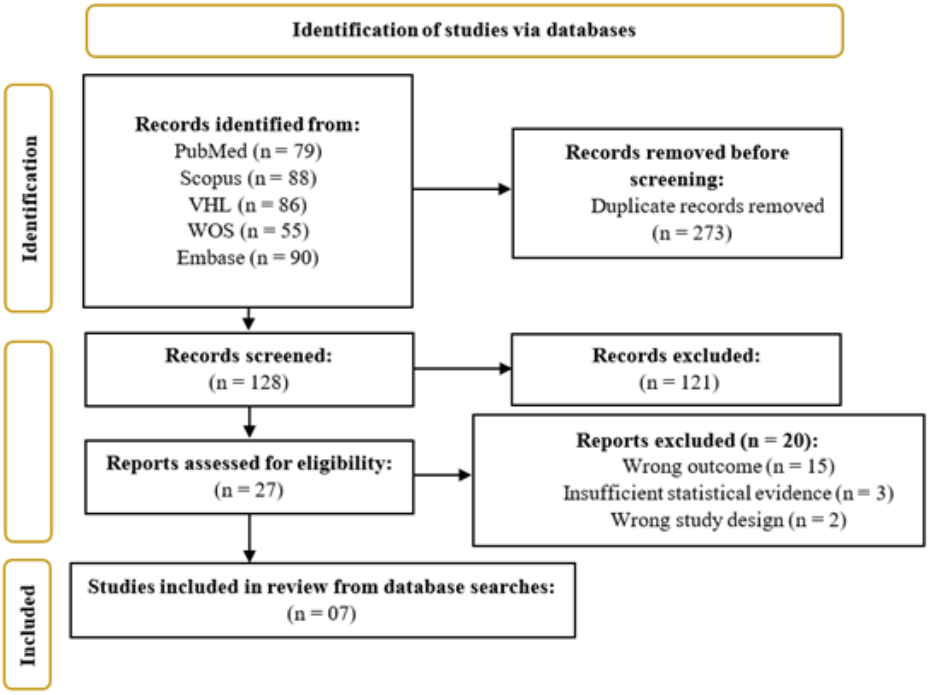

Figure 1: PRISMA flowchart of papers selection process

Table 1: Characteristics of studies and interventions

Reference and Country	Intervention (comparison)	N° sessions	Intensity	Attack Area	Effect size in migraine[1]:	
					Medication use	Attacks Freq
1. Auvichayapat et al. (2012) - Thailand	Anodal tDCS (Sham)	20 (daily, 20 min)	1mA	Left primary motor cortex and contralateral supraorbital	4 weeks: -0.74	4 weeks: -1.12
					8 weeks: -052	8 weeks: -1.01
					12 weeks: -0.63	12 weeks: -0.15
2. Rocha et al. (2015) – Brazil	Cathodal tDCS (Sham)	12 (3 per week, 20 min)	2mA	Primary visual cortex and vertex	3 weeks: -0.47	3 weeks: -0.66
3. Grazzi et al. (2020) – Italy	Anodal tDCS (Sham)	5 (daily, 20 min)	2mA	Right primary motor cortex and contralateral supraorbital	6 months: -0.12	6 months: -0.07
					12 months: -0.23	12 months: 0.26
	Cathodal tDCS (Sham)				6 months: -0.16	6 months: -0.09
					12 months: -0.22	12 months: 0.18
4. Mansour et al. (2020) - Lebanon	Anodal tDCS (Sham)	6 (daily, 20 min)	2mA	Prefrontal cortex	1 week: -0.43	1 week: -1.0
					2 weeks: -0.29	2 weeks: -0.46
	Cathodal tDCS (Sham)			Occipital cortex	1 week: -0.36	1 week: -0.92
					2 weeks: -0.42	2 weeks: -0.49
5. Icco et al. (2021) - Italy	Anodal tDCS (Sham)	5 (daily, 20 min)	2mA	Left primary motor cortex and contralateral supraorbital	1 month: -0.20	1 month: -1.31
					6 months: -0.58	6 months: -0.83
6. Hodaj et al. (2022) - France	Anodal tDCS (Sham)	5 (daily, 20 min) + 4 (1 per week, 20 min) + 2 (bimonthly, 20 min)	2mA	Left primary motor cortex	Triptans	
					1 month: -0.42	
					2 months: -0.35	
					3 months: -0.52	
					4 months: -1.07	1 month: -0.49
					5 months: -0.53	2 months: -0.71
					Weak opioid	3 months: -0.36
					1 month: -0.32	4 months: -0.94
					2 months: -0.50	5 months: -0.83
					3 months: 0.38	
					4 months: 0.09	
					5 months: -0.52	
					Non-opioid*	
7. Aksu et al. (2023) - Turkey	Anodal tDCS (Sham)	3 (daily, 20 min in the same week of every month for 5 months)	2mA	Left primary motor cortex and contralateral supraorbital	1 month: -0.53	1 month: -0.70
					3 months: -0.66	3 months: -0.74
					6 months: -0.82	6 months: -0.95

Note. [1] = All statistical evidence of effectiveness is standardized as Cohen's d for intervention vs sham posttest and follow-ups when available. A negative change indicates a reduction in the scores of medication consumption and/or migraine attack frequency; * = Negligible effect size in all months. Min = Minutes; NR = Not reported.

4.1. Publication and Intervention Related Information

Most of the included studies were conducted in Italy (n = 2; 28.6%), the other studies were each conducted in a different country (i.e., Brazil, Thailand, Lebanon, France, and Turkey). Five studies (71.4%) have been published between 2020 and 2023 indicating a growing interest in tDCS based interventions. Four of the included studies (57.2%) used anodal tDCS, followed by two (28.6%) that used both anodal and cathodal tDCS. The cathodal tDCS alone was tested only in one RCT (Table 1). The treatment duration ranged from 5 days to 5 months, in most studies (n = 4; 57.2%) the sessions occurred daily; the other three studies also used daily sessions, but applied weekly, biweekly and/or monthly reinforcement sessions. In all studies, each session lasted 20 minutes and in all but one (study 1) the tDCS intensity was 2mA. The main brain region chosen for attack by the RCTs was the primary motor cortex (n = 5; 71.4%). The administration of tDCS to the visual, occipital, and prefrontal cortex has only been tested by one RCT (Table 1).

4.1.1. Effect of tDCS on the Medication Consumption

tDCS was effective in reducing the use of medication to control migraine in all but one RCT (study 3). All but one RCT (study 3) uses more than one posttest assessment point, ranging from one week to six months. Although few studies have used cathodal tDCS, there seems to be no difference in effect sizes between anodal and cathodal tDCS. Among the studies that found a reduction in medication consumption after using tDCS, two identified large effect sizes, four medium and five small in different posttest assessment points. The largest effect size found was d = -1.07 (study 6) at four-month posttest for triptans medications. Regarding small effect sizes of study 3, although Cohen d effect sizes of .20 may be considered marginal and/or small, the authors of study 3 understood that the intervention with both anodal and cathodal tDCS showed no significant difference compared to the sham group.

In study 5 the effect size at one month posttest was also marginal and may also be interpreted as negligible by some researchers. However, at six-month posttest the intervention effect rises for medium. This may suggest that it takes some time for patients to start reducing their medication use after the tDCS intervention. This finding can also be observed in the studies 4, 6 and 7, which also show an increase in effect size after the first posttest assessment. However, in studies 6 and 7 this may be explained by the application of booster sessions. Another possible explanation may be related to the pharmacological group used, because as shown in study 6, the effect size of the intervention increased month by month until the fourth month for triptans but not for opioids and non-opioids. Unfortunately, only study 6 investigated differences between medication groups. Therefore, it is recommended that future clinical trials assess possible variations in the effect size of tDCS interventions in different medication classes. Especially considering the existence of evidence suggesting that tDCS may not work to reduce non-opioid consumption (study 6). Furthermore, some individual characteristics should be considered when interpreting the effect size related to medication use of study 1. Although the effect of the intervention seems to be sustained after 12 weeks, it is noteworthy that there was an increase in medication consumption in both groups at this time point, but this was greater in the SHAM group, which contributes to the maintenance of the effect of the intervention. Therefore, it is probable that medication consumption scores would return to their baseline levels after 16 weeks.

4.1.2. Effect of tDCS on the Migraine Attack Frequency

tDCS was also effective in reducing the number of migraine attacks in all but one RCT (study 3) without a significant difference in effect sizes between anodal and cathodal tDCS. Among the studies that found a reduction in migraine attack frequency after using tDCS, five identified large effect sizes, three medium and three small in different posttest assessment points. The largest effect size found was d = -1.31 (study 5) at one month posttest.

In study 5, contrary to the medication use outcome, the largest effect size was observed at the one-month post-test, with a reduction in effect size (i.e., an increase in migraine attacks) through time. Despite this reduction, the intervention effect size remained large after 6 months (d = - 0.83). A pattern of reduction in the effect size of the intervention on the frequency of migraine attacks can be observed in most of the RCTs analyzed (studies 1, 4, 5 and 6). Two of the RCTs (studies 1 and 6) indicate that the duration of the tDCS intervention effect tends to last an average of 3 months. Especially considering that in studies 6 and 7 the effect sizes after three months were sustained due to the use of booster sessions. Furthermore, none of the included studies evaluated if there is any relationship between the pharmacological group used by the patients and the effect size of tDCS in reducing the number of migraine episodes.

4.2. Participants Related Information

(Table 2) shows the main characteristics of the participants of the seven RCTs analyzed in this review.

The sample size of the included studies ranged from 15 to 135 participants. The sum of samples from all studies was 285. The distribution by sex was unbalanced, with a significantly higher proportion of women in all RCTs. Furthermore, the estimated overall mean age of the participants for all included studies was 41.78 (SD = 9.14). This finding may indicate that middle-aged women are more affected by migraine than men.

Chronic migraines with or without aura were the most prevalent type of migraine (n = 4; 57.2%), followed by chronic with medication overuse (n = 3; 42.9%). Analgesics, triptans and non-steroidal anti-inflammatory drug – NSAIDs were the most used medication groups between the included RCTs (n = 4; 57.2%), followed by prophylactic medication (n = 3; 42.9%). All but one (study 3)

of RCTs used medications from more than one pharmacological group. Studies 3 and 5 applied medication withdrawal protocols during the tDCS intervention. However, study 5 prescribed the use of prophylactic medication after the intervention for some participants. It is inferred that the prescriptions were made for the control group and/or to maintain the dose of prophylactic medication used before the intervention, but this information is not entirely clear in the paper. Despite that, all the included studies controlled the participants' medication use before, during and after the intervention.

Table 2: Characteristics of the participants

N°	Sample size	Mean Age (SD)	Sex ratio (F/M)	Migraine Type	Group of medication used (dose)	Time of use
1	Anodal tDCS: 20	28.6 (6.83)	14/6	Chronic with or without aura	Acetaminophen (paracetamol) (1mg every 6 hours); Ibuprofen (400mg every 4 hours); Ergotamine (1mg with 100mg of caffeine six tablets per day or 10 per week); Sumatriptan (50 to 200mg per day)	Control doses through diary 1 month before, during and after intervention
	SHAM: 18	35.06 (13.54)	12-May			
2	Cathodal tDCS: 10	22 (4)	09-Jan	Chronic with or without aura	Paracetamol (NR); Dipirona (NR); Cefaliv (NR); Dorflex (NR); Neosaldina (NR)	Control doses through diary 1 month before, during, and after treatment
	SHAM: 5	28 (14)	5/0			
3	Anodal tDCS: 45	47.8 (10.8)	41/4	Chronic with medication overuse	None during treatment. Analgesics pre and post intervention (NR).	Control doses through diary before and after intervention. 5-day acute drug withdrawal protocol during treatment
	Cathodal tDCS: 44	47.7 (13.1)	36/8			
	SHAM: 46	45.5 (9.2)	37/9			
4	18*	40.3 (NR)	17-Jan	Chronic with or without aura and medication overuse	NSAIDs (NR); Paracetamol (NR); Paracetamol codeine (NR)	Stable dose in the last three months. Control doses through diary during and after treatment
5	Anodal tDCS: 10	50.1 (9.6)	08-Feb	Chronic with medication overuse	None during treatment. Some participants receive prophylaxis prescribed drugs at treatment end: monotherapy with ß-blockers, calcium channel blockers, or angiotensin II receptor antagonists. Before and after intervention the medication overused were NSAIDs (NR) and Triptans (NR)	Control doses through diary before and after intervention. 7-day in-hospital detoxification protocol
	SHAM: 10	46.4 (9.7)	08-Feb			
6	Anodal tDCS: 18	54.5 (10.6)	10-Aug	Chronic	Triptan (NR); Non-opioid (NR); Paracetamol (NR); NSAIDs (NR); Weak opioid analgesic (NR); Prophylactic medications: antidepressants, antiepileptics and antihypertensives (NR)	Stable dose 1 month before treatment. Control doses through diary during and after intervention
	SHAM: 18	46.1 (14.1)	16-Feb			
7	Anodal tDCS: 11	36 (12.29)	All female	Chronic with allodynia and/ or with aura	Triptan (NR); NSAIDs (NR); Prophylactic medications: antidepressants, ß-blockers, and calcium channel blockers (NR)	Stable doses in last three months
	SHAM: 12	43.08 (10.3)				

Note. * = All participants receive both Anodal and Cathodal tDCS in different moments after washout period, for this reason there was no separation of age and gender by groups; F = Female; M = Male; NR = Not reported; NSAIDs = non-steroidal anti-inflammatory drugs; tDCS = transcranial direct current stimulation.

4.3. Risk of Bias in Included RCTs

The RoB 2 was used to assess five types of biases in RCTs (i.e., bias arising from randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result). It is noteworthy that the new version of RoB 2 suggests that risk of bias analysis should be performed specifically for the outcomes assessed in the systematic review (Higgins et al., 2023). Therefore, a summary of the possible biases that may have affected the medication use and/or migraine frequency outcomes were presented in (Table 3).

Overall, all but one (study 2) of the analyzed RCTs showed low risk of bias. There were some concerns or a high risk of bias in at least one of the analyzed topics in almost half (n = 3; 42.9%) of the studies. Study 2 was rated as high risk of bias in the bias that may arise from randomization process due to differences in baseline scores between the tDCS and SHAM groups in both outcomes evaluated in this review (i.e., medication use and migraine frequency). The scores were higher in the SHAM group, which possibly inflates the effect size of the intervention since comparisons were made between the groups. When comparing the baseline with post-test scores of the SHAM group, we identified significant effect sizes for medication use (d = -0.30) and migraine attack frequency (d = -0.47), which are similar of those found in the comparisons between post SHAM and post tDCS (i.e., d = -0.47 and d = -0.66, respectively). These findings suggest that there was no significant difference in the reduction of the outcomes between the tDCS and SHAM conditions, which is not usual in the literature. Furthermore, study 2 also had a dropout rate of almost 50% and it was not reported how and if this effect was controlled during data analysis. This fact may have contributed to the differences in scores observed at baseline as much or more than randomization bias. For these reasons, study 2 was also rated as high risk of bias due to missing outcome data.

Study 5 was rated as some concerns in the bias due to deviations from intended interventions due to a "optional prescription of preventive medication based on the physician judgment" after the intervention, which is not the usual practice in the literature. Furthermore, it is not clear to which participants were prescribed prophylactic medication and whether they were properly randomized between the SHAM and tDCS groups. Despite that, this effect does not impact the immediate results after the intervention, nor is it known for sure whether it would impact the results of the 6-month follow-up. Furthermore, study 5 presented a low risk of bias in all other analyzed biases. For these reasons, overall, this RCT was rated as low risk of bias.

Study 7 was rated as some concerns in the bias arising from the randomization process due to a small difference in the baseline scores between the tDCS and SHAM groups in the medication use outcome. The scores were slightly higher in the SHAM group (i.e., 18 vs 13), and when comparing the baseline (T0) with post-test scores (T1) of the SHAM group, we identified a small effect size for medication use (d = -0.30), which is lower than the effect found in the comparison between SHAM and tDCS conditions (d = -0.53). Despite that, this effect in the SHAM group does not persist in comparisons with the scores at T2 and T3, which shows that the use of medication in the SHAM group decreased slightly 1 month after the intervention but remained stable between 3 and 6 months after the intervention. Therefore, despite this risk of bias in T1, the effect of tDCS condition was superior. Thus, considering that study 7 presented a low risk of bias in all other analyzed biases, in overall, this RCT was rated as low risk of bias.

Table 3: Risk of bias assessment

Study	Randomization process	Deviations from interventions	Missing outcome data	Outcome measurement	Selection of the reported results	Overall study risk of bias
1	-	-	-	-	-	-
2	+	-	+	-	-	+
3	-	-	-	-	-	-
4	-	-	-	-	-	-
5	-	?	-	-	-	-
6	-	-	-	-	-	-
7	?	-	-	-	-	-

Note: +High risk of bias; –Low risk of bias; ? Some concerns.

5. Discussion

To date, the number of systematic reviews focusing on migraine treatment using tDCS is limited. Of the existing reviews, none aimed to evaluate the influence of using the technique on medication consumption. In the present study, we investigated the available evidence regarding the effect of transcranial direct current stimulation on the consumption of medications to control migraines and our results support the effectiveness of the use of tDCS in reducing not only the use of analgesic medications, but also in the number of migraine attacks. In general, there is a slight heterogeneity between study designs, intervention period and frequency of application, however the anatomical position of the electrodes,

the parameters used and the stimulation time converge in studies 3, 4, 5, 6 and 7, representing 71.4% of the findings, being application on the left primary motor cortex, using the anode electrode at a direct current of 2mA for 20 minutes, the most prevalent protocol (of the studies that had the primary motor cortex as something, only study 3 chose the right side). Baptista et al (2019) [4], in their consensus-based recommendations for the use of non-invasive brain stimulation in clinical practice, corroborate our findings by demonstrating that 19 studies out of a total of 24 used in their systematic review, opted to apply anodal attack, on the primary motor cortex, with the aim of reducing symptoms regardless of diagnostic heterogeneity, such as pain related to fibromyalgia, neuropathic pain, myofascial pain associated or not with temporomandibular joint disorder, pain related to HTLV-1 infection, hepatitis Chronic C, abdominal pain, vestibulodynia and episodic migraine.

Study 1 differs only in the application dose (1mA) and study 2 differs in both the anatomical position and the type of electrode (visual and cathodal cortex respectively); It is worth mentioning that part of the study 4 sample was subjected to cathodal tDCS over the visual cortex, however, the results were similar to the compared group that received anodal tDCS over the prefrontal cortex, demonstrating that both groups presented reduction in the total number of migraine days and severe migraine days in the week following the intervention. In convergence, when it comes to the use of neurostimulation for non-invasive analgesic purposes, Martorella et al (2022)[22] when testing the effect of anodal tDCS on the primary motor cortex, this time self-administered and remotely supervised at home, including 5 daily sessions of 20 minutes during 3 weeks, with an intensity of 2mA for 20 minutes, is capable of significantly reducing the intensity of pain resulting from knee osteoarthritis in the elderly. Burns, Chipchase and Schabrun (2016) justify the choice of the primary motor cortex for stimulation aiming for analgesia by the fact that there are three important mechanisms of the pain matrix: (a) bilateral: putamen, thalamus, insula, anterior cingulate and secondary somatosensory cortex; (b) left: primary somatosensory cortex and supplementary motor cortex, and (c) right: ventral premotor area. Through layer V or pyramidal neurons, the primary motor cortex establishes several caudal and rostral connections with somatosensory cortices and other brain structures, including the medial dorsal nucleus of the thalamus, hypothalamus, and periaqueductal gray, each of which plays a specific role in the processes of pain, such as modulation (STEPNIEWSKA, 2003) [32]. However, Lugo et al (2002) [21], from a psychophysical study, suggested a functional asymmetry towards the right hemisphere for pain perception based on higher pain ratings for stimuli applied to the left side, regardless of laterality (LUGO et al, 2002), however, evidence of pain-related lateralization is scarce and controversial (JI and NEUGEBAUER, 2009; RAHIMI et al, 2020) [28, 19].

In the latest guideline published regarding the use of tDCS, it is seen that the use of the technique for migraines, in the primary motor cortex is probably effective in reducing migraine pain (Level B) (FREGNI et al, 2021) [13]. Both anodal and cathodic neuromodulation can also be used as a promising way of preventing migraines, without causing adverse effects to patients, since its greatest advantage is its non-pharmacological nature, with promise for those with a previous history of comorbidities or low tolerance to pharmacological treatments (ORNELLO et al, 2021) [24]. Its analgesic effect can be observed in other comorbidities, as stated by Soler et al (2010) through a study that states the analgesic power of using tDCS (10 treatment sessions, 20 minutes each, for 2 weeks. virtual reality (visual illusion through a video game) in a patient with neuropathic pain resulting from spinal cord injury.

On the other hand, the consensus for the use of non-invasive brain stimulation described by Baptista et al (2019), states that it finds low to moderate benefit in montages addressing the primary motor cortex (M1), with a reduction of >20 or >30% in the intensity of stimulation. pain at the end of sessions and during follow-up; the last result is related to neuropathic pain and not migraine, however it gives us a general idea of the use of tDCS as a non-invasive analgesia technique; Such a conflict of results reinforces the importance of further investigation into the effectiveness of using the technique as analgesia and whether there is in fact an infallible attack site for pain control.

Drug therapy is the basis of acute migraine treatment (ASHINA et al, 2021) [2]. In this sense, Diener et al (2019) [11] point out that the success of rescue treatment, that is, the use of medication during migraine attacks, is possible by achieving two objectives: the first defined as the absence of pain within 2 hours after treatment and the second is defined as absence of the most bothersome symptom associated with migraine (i.e., nausea, vomiting, photophobia or phonophobia) within 2 hours after treatment, however, none of the studies evaluated the acute effects of tDCS during attacks of migraine. Ashina et al (2021) [2] state that the pharmacological options for the acute treatment of migraine involve simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and triptans, basically, just as the studies reviewed followed the change in consumption. Only study 01 used Ergotamine, an ergot alkaloids used infrequently (ASHINA et al, 2021) [2]. Another possibility for managing migraine attacks is through the use of preventive medications, the aim of which is to reduce the frequency, severity or duration of migraine attacks in affected patients in whom the use of acute medications is not sufficient as an independent treatment strategy (STEINER et al, 2019)[31] such as those used in studies 5, 6 and 7.

The frequent use of medications to control migraines was observed in a linear fashion in all studies. All research makes it clear how to survey the use of medications to control migraines, which is a daily self-report document, containing information such as the type/classification of medication used, the quantity/daily dosage,

in addition to the number and duration of migraine attacks, date of occurrence, pain intensity (using grading scales); The most relevant findings appear in (Table 2). However, no study can monitor the immediate or acute effect of the technique in migraine attacks. Ornelo et al (2021)[24] state that one of the advantages of tDCS is its non-pharmacological nature. This condition is very important as the main medications used to treat migraines are related to liver disease, kidney failure, gastrointestinal bleeding, heart failure, coronary disease, cerebrovascular disease, uncontrolled high blood pressure, peripheral vascular disease, among others (ASHINA et al, 2021)[1,2]. Although some studies do not provide clear information on adverse effects related to neuromodulation, all forms of active and simulated non-invasive brain stimulation appear to be frequently associated with minor or transient side effects (O'CONNEL et al, 2018); Symptoms of itching and local tingling sensation are frequently described, which ceases spontaneously immediately or within a few minutes after exposure to the technique (ORNELLO et al, 2021; MARTORELLA et al, 2022; HOU et al, 2020) [17, 23, 25].

In our findings, it is possible to observe the use of medications to control migraines (non-steroidal anti-inflammatory drugs in most studies - 85.8%), and the use of new analgesic therapies must be treated urgently. Misuse of controlled substances is associated with morbidity and mortality and annually millions of people misuse prescription analgesics and sedatives, stimulants and tranquilizers, and the most common reason for misuse is the treatment of physical pain (PREUSS et al 2023) [27]. Baptista et al (2021) [4] present a level B recommendation attributed to tDCS for migraines and also for secondary benefits, such as improved quality of life, decreased anxiety and increased pressure pain threshold. These results are in line with what was exposed by Eskandari et al (2019), who, when comparing the effectiveness of tDCS (anodal, cathodal and sham) on brain-derived neurotrophic factor (BDNF) and psychological symptoms in opioid-addicted patients, found that in participants who received active stimulation, there was a significant change in the increase in the level of BDNF ($P = 0.031$), the reduction in symptoms of anxiety ($P = 0.001$), stress ($P = 0.012$), level of depression ($P = 0.018$) and even reduced craving for excessive opioid consumption ($P = 0.001$).

In study 01 it was evident that the use of tDCS is effective, but the effect on the frequency of migraine attacks reduces over time and after 12 weeks there is no significant difference compared to Sham. This can also be observed in studies 4 and 5, which may indicate the need to repeat the tDCS intervention after certain times. Especially considering that this reduction was not observed in studies 6 and 7 that applied booster sessions. Medication use remains lower after 12 weeks, while Sham increases use even further. However, in study 3 there was a significant reduction in the frequency of headache episodes and medication use at 6 and 12 months after medication withdrawal from patients who used excessive medication. However, these effects were similar across conditions (i.e. anodal, cathodal and sham). Therefore, tDCS did not interfere with the short- and long-term course of chronic migraine with medication overuse after acute medication withdrawal. Furthermore, effect sizes are small or negligible. If we consider .20 some were small. If we consider .30, all were negligible. However, in the same sample profile of participants who used excessive medication, positive effects were found with the use of tDCS, as evidenced by study 4, where there was a significant reduction in the frequency of headache episodes and medication use after 1 and 2 weeks. Likewise, in study 05 it was possible to observe a significant reduction in the frequency of headache episodes and medication use after 1 and 6 months. These results suggest that the use of anodal tDCS in conjunction with detoxification of patients with excessive medication use is effective in treating headaches in individuals with excessive medication use.

6. Conclusion

Our findings demonstrate that 85.8% of the studies analyzed advocate a positive effect of tDCS with a reduction in the consumption of medications taken to control migraines, and the heterogeneity of application protocols does not seem to negatively influence its effect. Therefore, given the nonconformity of the protocols regarding the number of applications, their frequency (daily, weekly, fortnightly or monthly), the time interval between applications, our findings are inconsistent in defending a specific tDCS protocol that predicts response capable of reducing the consumption of medications used to control migraines with or without aura.

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