Original Article

The Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) versus Transcranial Direct-Current Stimulation (tDCS) on Migraine Headaches: A Randomized Clinical Trial

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Abstract

Background: Non-pharmacologic prophylactic methods for chronic migraine have been developed, including the promising non-invasive techniques of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS). This study aimed to compare the efficacy of rTMS and tDCS on pain intensity, the impact of headaches on daily life, anxiety, and depression in migraine headaches patients.

Materials and Methods: This randomized clinical trial was conducted on 72 patients with migraine headaches, randomly allocated to the rTMS and tDCS groups. Participants received 3 and 12 sessions of stimulation over the left dorsolateral prefrontal cortex (DLPFC), respectively. Follow-up measurements, including pain intensity, anxiety, depression, and impact on daily life, were performed one month after the last sessions. Analyses were done by IBM SPSS statistics version 26 software.

Results: Of 72 patients enrolled in the study, 19 were male (8 in the rTMS group and 11 in the tDCS group). There was no significant difference in baseline characteristics between groups. During the follow-up visit, both groups showed a decrease in anxiety levels (P values = 0.005 and 0.015), while only the rTMS group displayed a significant improvement in depression (P value = 0.01). However, no statistically significant difference was found among the groups regarding changes in pain intensity, anxiety, and the impact of headaches on daily life (P values >0.05).

Conclusion: Our findings suggest that both rTMS and tDCS may be effective in reducing pain intensity and improving the impact of headaches on daily life and anxiety in patients with chronic migraine. However, significant improvement in depression was only observed in the rTMS group patients.

Keywords: Anxiety, depression, migraine headaches, repetitive transcranial magnetic stimulation, transcranial direct-current stimulation

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Introduction

Migraine headache is a leading cause of disability, second only to low back pain in terms of years lived with disability.[1] It affects approximately 12% of the population annually, with higher prevalence among women (17%) than men. Migraine is a common condition that affects individuals across various continents, including North America, South America, Central

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America, Europe, Asia, and Africa, as reported in previous studies.[2-4] The etiology of migraine is multifactorial and complex, as it involves a combination of genetic and environmental factors that are not yet fully understood.[5]

The management of migraine includes both acute and prophylactic treatments. While several pharmacologic preventative methods exist, including beta-blockers, antidepressants, anticonvulsants, calcium channel blockers, and calcitonin gene-related peptide antagonists, some patients continue to experience migraine despite taking these drugs.[6,7] Thus, several invasive and non-invasive techniques have been developed for migraine prophylaxis.[8]

While several techniques have been proposed for treating migraine, there is currently no established consensus on their use. Among the promising techniques are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS). Up to now, numerous studies showed the positive effects of these two methods on improving the related outcomes of patients with migraine headaches. However, establishing a decision-making diagram regarding non-invasive prophylactic techniques for migraine headaches requires evidence of the superiority of one method over the other. The present study aimed to compare the efficacy of tDCS and rTMS on pain intensity, and the effect of headaches on daily life, anxiety, and depression of patients with migraine headaches.

Materials and Methods

This randomized clinical trial (IRCT code: IRCT20190404043159N4) was conducted from February 2022 to September 2022 in Kashani Hospital, Isfahan, Iran. The study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences, and ethical consent was granted by the committee (IR.MUI.MED.REC.1400.511).

Patients who satisfied the following eligibility criteria were enrolled in the study: diagnosis of migraine headache based on the International Classification of Headache Disorders: Fourth edition,[9] aged between 18 and 60 years old, experiencing migraine attacks in the last year, and having indications of preventive treatment for chronic migraine according to the American Headache Society Consensus Statement.[10] Refusing to participate or continue in research at any stage of the study, diagnosis of any comorbidities interfering with therapy, suicidal thought or attempts, pregnancy, lactating, substance use, hSistory of seizure or neurologic disorders except migraine headache, presence of a pacemaker or any metallic implants, use of antidepressant drugs in previous two months, diagnosis of psychotic disorders, bipolar disease, and major depressive disorder according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) and history of previous brain stimulation were exclusion criteria.

Written informed consent was obtained from all patients after describing the aim and beneficial and harmful aspects of the study.

During the initial stage, we gathered demographic information, which included age, marital status, level of education, sex, family history of migraine headaches in first-degree relatives, number of analgesics used in the preceding month, duration of the latest migraine attack, and the duration since the initial diagnosis of migraine headaches. Next, we randomly assigned every two eligible participants to a block and sorted them based on their national identification number. The first participant received a random number by selecting one of ten sealed pockets containing a number between 0 and 9. If the number was 0 to 4, the participants were allocated to the rTMS group; otherwise, the participant was allocated to the tDCS group. The second participant in each block was allocated to the other group. The interventions were performed in the brain stimulation unit of Kashani Hospital under the supervision of a faculty member of the psychiatry department and a psychiatry resident.

Repetitive transcranial magnetic stimulation (rTMS)

We utilized Magstim Supra Rapid (Whiteland, Walsh, UK) to administer rTMS to the patients, using an air-cooled figure-eight coil with a diameter of 7 cm. The stimulator was positioned at the left dorsolateral prefrontal cortex (DLPFC) and 70% of the motor threshold was used for stimulation. To determine the motor threshold, five or more motor-evoked potentials of 50 mV were elicited out of ten consecutive stimuli at the right abductor digiti minimi's hotspot. Each rTMS session lasted 412 seconds and consisted of 600 pulses. The impulses were delivered in ten trains, with each train comprising 60 pulses at 10 Hz and an intertrain interval of 45 seconds. We administered three sessions of rTMS. This stimulation protocol was based on Misra's study.[11]

Transcranial direct-current stimulation (tDCS)

We administered transcranial DCS using a neurostimulator developed by ActivaTek Inc. (Utah, United States), with 5 × 5 cm electrodes and sponges moistened with 0.9% saline, as recommended by Andrade *et al*.[12] The anodal electrode was placed at the left DLPFC, corresponding to position F3 in the international 10–20 EEG electrode placement system, while the cathodal electrode was placed at the right DLPFC, corresponding to position F4. A current with an intensity of 2 mA and a density equivalent to 0.08 A/m2 was applied for 20 minutes. We conducted tDCS for three sessions per week for a month, resulting in a total of 12 sessions.

Outcome measurement

Baseline scores of depression, anxiety, and headache impacts on life were assessed by Hospital Anxiety and Depression Scale (HADS) and headache impact test-6 (HIT-6), respectively. Additionally, we assessed the baseline headache pain intensity using the Visual Analog Scale (VAS). With ending the interventions, scores of depression, anxiety, headache impacts on life, and headache pain intensity were assessed again.

Visual analog scale (VAS)

We utilized a self-administered Visual Analog Scale (VAS) to evaluate the pain severity, which consisted of a 100-mm line.

The scale ranged from 0, indicating no pain, to 10, representing the most severe pain imaginable. Each participant marked their pain severity over the previous 48 hours on the VAS. The reliability and validity of the VAS for clinical studies were confirmed in a study by Williamson *& Hoggart*.[13] *(2005)*.

Hospital anxiety and depression scale (HADS)

We employed the HADS, which is a self-administered 14-item questionnaire, to assess the symptoms of depression and anxiety in patients aged 16 years and older. HADS includes 7 items for anxiety and 7 items for depression, each with a four-point scale, giving maximum scores of 21 for each subscale. Scores ranging from 0-7 indicate a normal case, scores from 8-10 indicate borderline cases, and scores above 11 indicate a significant case of psychological morbidity. The Iranian version of HADS was validated in a study by Montazeri *et al*. in 2003.[14]

Headache impact test-6 (HIT-6)

To measure the impact of headaches on the daily life of the respondent, we used the HIT-6, which is a six-item questionnaire. HIT-6 comprises six five-point scale items (pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress), with each item having five possible responses: "never," "rarely," "sometimes," "very often," or "always." The total score ranges from 36 to 78, with a higher score indicating a more significant impact of headaches on the respondent's life. The HIT-6 was validated in the Iranian population in a study by Zandifar *et al*.[15]

Statistical analysis was performed by using IBM SPSS statistics 26. Qualitative and quantitative data were presented as frequency (percentage) and mean ± standard deviation. The Kolmogorov-Smirnov test was used to assess the normality distribution of data. Parametric and non-parametric variables were analyzed with an independent student *t*-test and Mann-Whitney U test. We used the independent and paired student T-tests method for normally distributed data. Also, the Chi-square test was used for comparison between categorical variables. *P* values of less than 0.05 were considered significant. Log-link generalized linear model with gamma distribution was employed to calculate odd ratios (OR) of potential factors for outcomes, i.e., pain intensity, the impact of headache on daily life, anxiety, and depression. Confidence intervals at the 95% level (95% CI) were reported for the ORs.

The sample size calculation was based on a significance level of 0.05 (allowing for multiple comparisons) and a power of 80%. The standard deviation of the HADS score was measured as 1/6 of the range of the HADS score. This sample size was sufficient to detect a difference of ≥3 points in the HADS score between groups. Therefore, each group's calculated sample size was 36.

Results

Recruitment took place between March 2022 and June 2022, when accrual reached n = 77. The final measurement was performed on September 2022. Of the 77 eligible patients, 5 declined to participate (recruitment rate = 93.5%). The study accrual is described in detail in Figure 1.

Analyses were performed on 72 patients and no adverse events were reported for either intervention. Of them, 19 were male (8 in the rTMS group and 11 in the tDCS group). The mean age of participants was 40.8 ± 12.1 and 38 ± 10.4 years for the rTMS and tDCS groups, respectively. Participants in rTMS and tDCS groups reported using 32.9 ± 12.2 and 30.6 ± 10.2 analgesics pills in the month before study enrollment. The mean duration of the last migraine headache attack was 138.3 ± 72.1 and 140.8 ± 66.4 minutes in rTMS and tDCS groups. Other baseline characteristics of the groups are described in Table 1.

The final measurements revealed that there was no statistically significant difference in the pain score between the two groups at either baseline or follow-up (*P* value = 0.211). However, the intragroup analysis revealed a significant decrease in the pain score for both groups, from 8.8 ± 1.19 to 7.2 ± 1.18 (*P* value <0.001) for rTMS and from 8.9 ± 1.1 to 7.6 ± 0.9 for tDCS (*P* value <0.001). Regarding the HIT-6 score, no significant difference was observed between groups at baseline and follow-up (*P* value = 0.599). However, significant reductions were observed in both groups, from 47.6 ± 5.2 to 43.4 ± 4.4 (*P* value <0.001) for rTMS and from 47.6 ± 4.6 to 43 ± 4.4 for tDCS (*P* value <0.001). Analysis of the HADS score revealed that both groups experienced less anxiety at the follow-up visit (*P* values = 0.005 and 0.015) [Table 2]. Nevertheless, the depression subscale of HADS exhibited a significant reduction in the rTMS (10 ± 4.5 to 9.4 ± 4.2, *P* value = 0.01) and a non-significant reduction in the tDCS groups (10.8 ± 3.2 to 10.5 ± 3.3, *P* value = 0.057).

The findings of the generalized linear regression analysis are presented in Table 3. The analyses revealed that having a negative family history of migraine [OR: -0.111, 95% CI: -0.202- -0.018], receiving rTMS [OR: -0.70, 95% CI: -0.136 - -0.004] and having a higher baseline depression

Table 1: Baseline characteristics of patients in rTMS and tDCS groups

Characteristic	Groups	
	rTMS (n=36)[b]	tDCS (n=36)[b]
Age (year), Mean±SD[a]	40.8±12.1	38±10.4
Analgesic pill, Mean±SD[a]	32.9±12.2	30.6±10.2
Duration Attack, minute, Mean±SD[a]	138.3±72.1	140.8±66.4
Sex, male, *n* (%)[b]	8 (22.2%)	11 (30.6%)
Marital, married, *n* (%)[b]	26 (72.2%)	23 (63.9%)
Education, *n* (%)[b]		
High school and less	4 (11.1%)	6 (16.7%)
Diploma degree	12 (33.3%)	9 (25%)
Bachelor's degree	14 (38.9%)	10 (27.8%)
Master and higher	6 (16.7%)	11 (30.6%)
Positive family History (*n*%)[b]	29 (80.6%)	31 (86.1%)
Time of diagnosis, <3 months, *n* (%)[b]	0	4 (11.1%)

[a]Values are presented as mean (SD). [b]Values are presented as number (%)

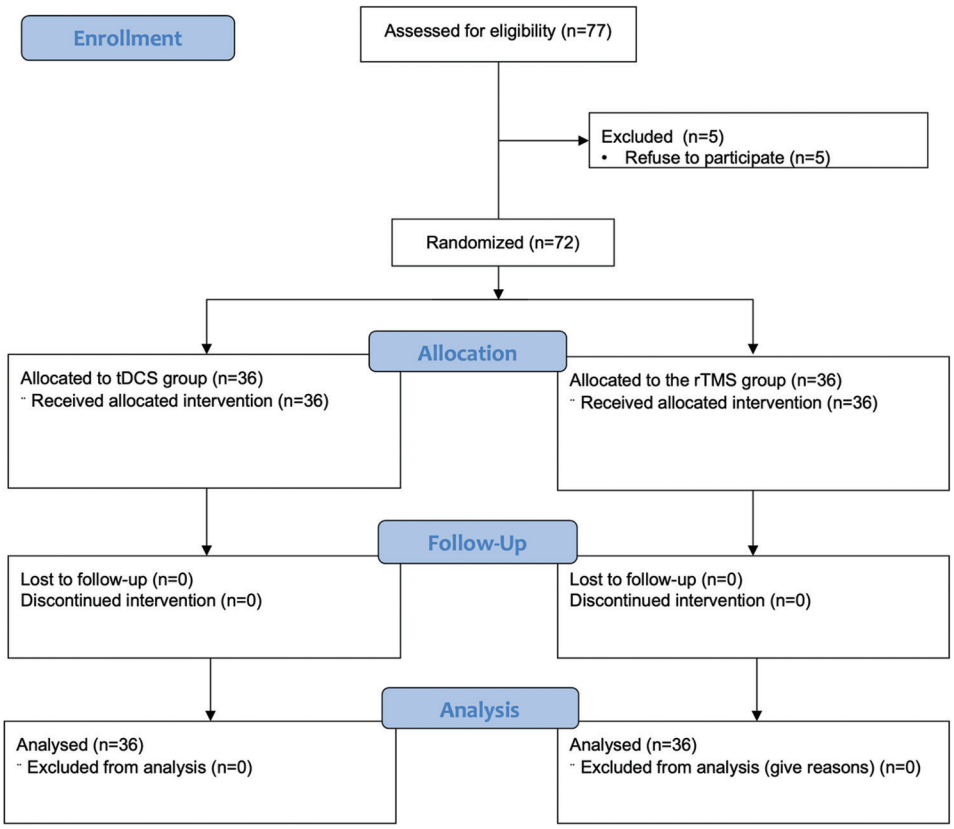

Figure 1: Consort flow chart of patients

Table 2: Comparison of the outcomes in both groups at baseline and follow-up

Outcome	Groups		*P**
	rTMS (*n*=36)	tDCS (*n*=36)	
Pain, score (mean±SD)			
Baseline	8.8±1.19	8.9±1.1	
Follow-up	7.2±1.18	7.6±0.9	0.211
P†	<0.001	<0.001	
HIT-6, score (mean±SD)			
Baseline	47.6±5.2	47.6±4.6	
Follow-up	43.4±4.4	43±4.4	0.599
P†	<0.001	<0.001	
Anxiety, score (mean±SD)			
Baseline	9.9±4.2	9.7±4.2	
Follow-up	9±3.6	8.9±3.6	0.676
P†	0.005	0.015	
Depression, score (mean±SD)			
Baseline	10±4.5	10.8±3.2	
Follow-up	9.4±4.2	10.5±3.3	0.024
P†	0.01	0.057	

*Independent samples *t*-test. †Paired sample *t*-test

score [OR: 0.101, 95% CI: 0.092-0.109] were factors associated with the depression score at follow-up. Also, being male [OR: -0.053, 95% CI: -0.093 - -0.013], older [OR: -0.002, 95% CI: -0.004 - -0.001], and having a higher HIT-6 score [OR: 0.014, 95% CI: 0.011-0.017] were associated with the HIT-6 score at follow-up, indicating the impact of headaches on daily life.

Discussion

The present study compared the efficacy of rTMS and tDCS on pain, the impact of headaches on daily life, depression, and anxiety in patients with migraine headaches. Our findings suggest that both rTMS and tDCS have a similar and significant effect on pain, the impact of headaches on daily life, and anxiety in these patients. However, rTMS, unlike tDCS, significantly reduced the depression score. The study also identified negative family history of depression and use of rTMS as predictive factors for response to treatments in terms of depression, and age and male sex as predictive factors for response to treatments in terms of the impact of headaches on daily life.

According to the major burden of migraine headaches, non-pharmacologic management options become worthwhile, particularly for treatment-resistant individuals or who experience major adverse drug reactions. Various non-invasive neurostimulation techniques have been developed and studied; transcranial magnetic stimulation (TMS), tDCS, transcranial alternating current stimulation (tACS), functional electrical stimulation (FES), transcutaneous electrical nerve stimulation,[16] pulsed radiofrequency, peripheral nerve stimulation (vagus, trigeminal, supraorbital, occipital nerves)

Table 3: The generalized linear model of factors associated with outcomes

Outcomes	Factors	Crude odds ratio (95% CI)	*P*[a]
Pain intensity	Age	-0.001 (-0.004–0.002)	0.363
	Number of analgesics used	0.000 (-0.002–0.003)	0.839
	Male Sex	-0.056 (-0.123–0.011)	0.114
	Negative family history	0.021 (-0.052–0.096)	0.579
	rTMS	-0.035 (-0.089–0.019)	0.211
	tDCS	0	
	Baseline pain intensity	0.067 (0.043-0.091)	<0.001
Anxiety	Age	0.001 (-0.003–0.006)	0.552
	Number of analgesics used	0.000 (-0.003–0.004)	0.836
	Male Sex	0.009 (-0.088–0.107)	0.852
	Negative family history	-0.060 (-0.166–0.048)	0.364
	rTMS	-0.016 (-0.095–0.048)	0.364
	tDCS	0	
	Baseline anxiety score	0.081 (0.071-0.091)	<0.001
Depression	Age	-0.001 (-0.005–0.002)	0.443
	Number of analgesics used	-0.001 (-0.004–0.002)	0.602
	Male sex	-0.004 (-0.087–0.079)	0.914
	Negative family history	-0.111 (-0.202–-0.018)	0.034
	rTMS	-0.070 (-0.136–-0.004)	0.024
	tDCS	0	
	Baseline depression score	0.101 (0.091-0.109)	<0.001
Impact of headaches on daily life	Age	-0.002 (-0.004–-0.001)	0.005
	Number of analgesics used	0.001 (-0.001–0.002)	0.361
	Male sex	-0.053 (-0.093–-0.013)	0.008
	Negative family history	0.015 (-0.029–0.059)	0.556
	rTMS	0.008 (-0.023–0.040)	0.599
	tDCS	0	
	Baseline HIT-6 score	0.014 (0.011-0.017)	<0.001

[a]Generalized linear Model (GLM)

and transcranial near-infrared stimulation (NIRS). Currently, there is no consensus on the most effective non-invasive management of migraine headaches and the priority of using these techniques needs to be clarified.

rTMS and tDCS are two promising non-invasive techniques. TMS is a technique that was first introduced by Barker *& Jalinous & Freeston*. (1985) drawing inspiration from Faraday's law of electromagnetic induction.[17] The FDA has approved the single-pulse TMS for the acute and prophylactic treatment of migraine based on the results of randomized clinical studies.[18] TMS induces stimulation by means of a brief but powerful magnetic field, which can incite or suppress a small region of the brain, with intensities that can reach up to 2 Tesla.[19,20] Repetitive TMS refers to a sequence of TMS pulses that are delivered at frequencies ranging from 1 to 50 Hz; low-frequency (1 Hz) rTMS is associated with cortical inhibition, while high-frequency stimulation (5-20 Hz) is associated with cortical excitation.[8] In contrast, tDCS utilizes electrodes to transmit a low voltage, direct current to the scalp, resulting in the polarization of the resting membrane potential and inducing neuronal firing.[21]

Several studies have investigated the efficacy of rTMS or tDCS alone, but there is no evidence comparing these two techniques. According to Brighina *et al*., there was a marked impact of rTMS over the left DLPFC compared to a placebo on headache attacks, headache index, and the number of abortive medications that persisted for at least a month following the conclusion of the treatment.[22] A different study reported noteworthy enhancements in migraine frequency, VAS, migraine severity, and functional disability in comparison to the sham group.[23] In contrast to the study of Brighina, a study on 18 patients showed that rTMS over the left DLPFC was not superior to the sham rTMS. They found a significantly greater reduction in the sham group (58.1 ± 3.1%) compared to the decrease in the active rTMS group (15.0 ± 18.9%), suggesting a strong placebo effect of sham rTMS.[24] They also reported a decrease in depression scores of participants in both groups, which was greater in the rTMS group. Our findings support the current evidence on the effectiveness of rTMS for pain, the impact of headaches on daily life and depression.

Furthermore, the efficacy of tDCS on migraine headaches has been investigated in several studies. A study by Przeklasa-Muszyńska *et al*. showed a significant reduction in the use of analgesics (72% reduction) and triptans (59% reduction). Additionally, pain was significantly more reduced in the group receiving tDCS (36-40%) compared to groups receiving pharmacotherapy (10-12.5%).[25] Similarly, a study

on 13 patients revealed that tDCS over the left DLPFC significantly improved headache impact, pain intensity, and quality of life compared to patients who received M1 tDCS or sham tDCS.[26] However, the evidence regarding the efficacy of tDCS on depression scores is weak. One study reported no efficacy of anodal frontal tDCS on depression.[27] Variations in individual responses to tDCS dosage may contribute to its different effectiveness. For instance, administering a 2 mA current for 20 minutes over 12 sessions may not be sufficient to observe improvements in depression in certain individuals, as the relationship between dosage and response is not always straightforward.[28] Furthermore, the lack of a sham group in our study may impede the ability to conclude the efficacy of tDCS in treating depression. Our study is consistent with these studies' findings, which showed the effectiveness of tDCS in reducing pain intensity and the impact of headaches on daily life. Furthermore, our study's significant difference between rTMS and tDCS and the positive effect of rTMS on depression are supported by previous evidence. A point to consider regarding this matter is that the placebo effect appears to be stronger in the rTMS group compared to the tDCS group. This may be due to patients feeling more positively about a more complex modality of treatment, which they perceive as more effective.

Research studies have demonstrated that tDCS involving the activation of DLPFC and M1 can ameliorate migraine pain intensity, while tDCS that inhibits VC has been shown to lower the number of migraine days per month. Inhibiting M1, S1, and VC with tDCS has also been shown to reduce pain intensity in migraine patients. However, inhibiting M1 alone did not result in a reduction in the number of migraine days per month during the post-treatment period of more than three months, as per the findings of the study.[29] Furthermore, studies have demonstrated that high-frequency rTMS can restore normal or near-normal levels of DLPFC activation, which could potentially reset or reduce the fronto-limbic dysfunction associated with chronic headaches.[30] In addition, research studies indicate that rTMS induces its antidepressant effects by modulating levels of different neurochemicals, electrophysiology, and cerebral blood flow and activity in a frequency-dependent manner. Specifically, rTMS has been found to increase activity in the prefrontal cortex and decrease activity in the amygdala, enhancing the release of neurotransmitters such as GABA and serotonin and promoting neuroplasticity.[16,31] Similarly, tDCS has been found to modulate cortical excitability and plasticity in specific brain regions, leading to changes in neural activity and neurotransmitter release that may alleviate symptoms of depression.[32] Specifically, tDCS can increase activity in the prefrontal cortex, enhance the production, and release of neurotrophic factors such as BDNF,[33] modulate activity in the DMN,[34] and modify the cortical spreading depression.[35]

Our study had some limitations. First, the relatively short follow-up limited our ability to investigate the persistence of the observed effects, especially in rTMS due to its sham effect, as well as long-term effects. Second, the outcomes of our study were limited to four variables, and future studies could consider additional outcomes such as the number of days with a headache, the duration of headaches, the severity of headaches, and the number of analgesics and triptans used. Also, due to the nature of the study, blinding the patients was not possible, which could have introduced bias into the study.

Conclusion

This study is the first to compare the efficacy of rTMS and tDCS on pain intensity, the impact of headaches on daily life, anxiety, and depression in patients with migraine headaches. Our findings demonstrated a significant reduction in pain intensity and improvements in the impact of headaches on daily life and anxiety in both groups, with no significant difference between groups. Nonetheless, the rTMS group was the only one to exhibit a substantial improvement in depression according to the results.

Ethics approval and consent to participate

This randomized clinical trial has been registered in www.irct.ir with the code of IRCT: IRCT20190404043159N4. The study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences, and ethical consent was granted by the committee (IR.MUI.MED.REC.1400.511). Written informed consent was obtained from all patients after describing the aim and beneficial and harmful aspects of the study.

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Isfahan University of Medical Sciences sponsored the current study.

Conflicts of interest

There are no conflicts of interest.

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