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The Efficacy of Repetitive Transcranial Magnetic Stimulation in Treating Patients with Chronic Daily Headache

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ABSTRACT

Background: Chronic daily headache (CDH) is a headache that lasts at least 15 days, 3 months, and 4 hours a day without treatment. Transcranial Magnetic Stimulation (TMS) uses short magnetic pulses over the head to temporarily alter brain cortical excitability. Prefrontal cortex rTMS has shown analgesic benefits.

Objective: The purpose of the current study was to assess the effectiveness of repetitive transcranial magnetic stimulation in the management of chronic daily headache patients.

Patients and methods: A clinical trial was conducted in the period from July 2022 to December 2022 A total of 40 patients participated in the study. All patients were monitored at the Neurology Department of Al-Azhar University Hospital, New Damitta. A total of 25 patients made up the experimental group, which received genuine (5 Hz) rTMS, while 15 patients made up the control group received phoney (5 Hz) rTMS.

Results: There were no statistically significant differences between the intervention and control groups in terms of age, sex, BMI, headache frequency, or duration. Prior to treatment, the intervention and control groups had comparable incidence and indices of headache. Following therapy, compared to the control group, the intervention group's headache frequency and index considerably decreased. The severity of the headaches before treatment was similar between the intervention and control groups. Following therapy, the intervention group's headache severity dramatically decreased as compared to the control group.

Conclusion: Patients whom suffer from chronic migraines and tension headaches may be effectively treated and prevented using high-frequency rTMS. In light of this, it is advised that patients with chronic daily headaches, especially those who are not responding to therapy, consider high-frequency rTMS as a potential treatment.

Keywords: Chronic tension-type headache, Transcranial Magnetic Stimulation, Treatment, Chronic Daily Headache, Clinical trial, Alazhar University.

INTRODUCTION

A chronic daily headache is a headache that goes untreated for at least 15 days out of every month, for at least three months, and for at least four hours each day (CDH). Chronic tension-type headache and chronic migraine are examples of primary CDH, as are new-onset everyday pain and hemicrania continuous [(1)].

Chronic tension type headache (CTTH) is the most common type of headache. This is the basis for 80% of headache diagnoses [(2)]. CTTH is distinguished clinically by the lack of differentiating signs and symptoms, a mild headache that is never severe, and the absence of migraine features. Patients frequently exhibit minor phonophobia, photophobia, or none of these symptoms [(3)]. Aching, pressure, and the sense that a tight band is tightening around the head are all symptoms of pain. Migraine is a frequent neurological condition. Statistics show that 18% of men and 43% of women will suffer from a migraine at some point in their lives. The most common description of migraine is recurrent, pulsating or throbbing, moderate to severe, unilateral pain lasting 4–72 hours with complete relief in between attacks (episodic).In addition to the headache, nausea, and vomiting; there may be abnormalities in the senses of sight, sound, and smell [(4)].

Auras can cause unilateral sensory anomalies and/or deglutition difficulties. The most common sort of aura is visual, and it might manifest as zigzag lines or a large scintillating scotoma [(5)].

Transcranial magnetic stimulation (TMS) is a non-invasive and safe method of altering the cortical excitability of the brain by delivering brief magnetic pulses over the head. In animal models, TMS was observed to reduce cortical spreading depression, suggesting potential therapeutic use, particularly in migraine attacks accompanied by an aura. The repetition frequency of transcranial magnetic stimulation (rTMS), measured in hertz (Hz) or pulses per second [(6)].

Low-frequency (slow) and high-frequency (fast) rTMS are classified into frequency categories using frequencies of 1 Hz or less and bigger (ranging between 5 and 25 Hz). Another aspect connected with stimulation is the strength of stimulation, which is described as a percentage of each person's resting motor threshold. The underlying brain may be permanently altered as a result of recurrent TMS. The prefrontal cortex may be especially helpful in reducing the emotional, attentional, and affective components of pain [(7)].

Prior studies have indicated that prefrontal cortex rTMS has analgesic advantages. Although it is unknown how the left prefrontal cortex impacts pain, numerous theories maintain that left prefrontal activation actively

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modulates pain perception by modifying the cortico-subcortical and cortico-cortical circuits [8].

The purpose of the current study was to assess the effectiveness of repetitive transcranial magnetic stimulation in the management of chronic daily headache patients.

PATIENTS AND METHODS

A controlled clinical trial was carried out at Al-Azhar University Hospital in New Damietta. From July to December 2022, the study included 40 chronic patients. The patients were chosen from the Neurology Department, Faculty of Medicine, Al-Azhar University, New Damietta.

Before the study began, all participants received information about the purpose and methods. Each participant provided written informed consent and received thorough explanations of all potential consequences, such as hearing loss that may be avoided by using protective hearing equipment.

The chosen candidates were divided into 2 groups; the first was called Real (5 Hz) rTMS and applied to the 25 patients in the intervention group, while phoney (5 Hz) rTMS was applied to the 15 patients in the control group.

Patients from both groups were adults and older than 18 years old. They all suffered from everyday tension and migraine headaches for at least 3 months without receiving any medication for pain relieve.

Patients with abnormal brain computed tomography (CT), abnormal brain magnetic resonance imaging (MRI), or abnormal conventional EEG readings were excluded.

The Hamilton Depression Scale was used to determine the depression in research participants; as a result, patients were not depressed (their score is 0–7 to exclude depression). Those with other primary headache subtypes, secondary headache causes, epilepsy, or a family history of epilepsy were also excluded from the clinical trial, as were women who were pregnant, had pacemakers, intracranial metal implants, or metal dental implants.

The patients were subjected to clinical examinations, which comprised a comprehensive history-taking procedure and a complete neurological examination. Patients were given a headache diary to complete after their initial appointment. They were required to rate it before and after finishing all of their therapy sessions based on a number of headache-related parameters. The scale considered the frequency of episodes each month, the length of the headaches, the degree of the pain (measured on a scale of 0 to 3, with 0 representing no pain, 1 denoting mild pain, 2 denoting moderate pain, and 3 denoting severe pain), and the headache index (frequency and intensity) [9].

After receiving rTMS, patients were observed for a month to make sure that results were constant. Before and after each treatment session, the scale was used with all patients.

Common laboratory tests included erythrocyte sedimentation rate (ESR), complete blood count (CBC), fasting blood sugar and 2 hours post prandial levels, liver and kidney functions tests, and collagen vascular profile.

A brain CT or MRI was used to perform a radiographic scan of the brain to diagnose any secondary headache causes.

Treatment methods High-frequency repetitive TMS was attached to a figure-of-eight coil with a diameter of 70 mm. Prior to the first session, a typical EMG machine and surface electrodes were used to deliver a single pulse of stimulation to the primary motor cortex over the hot spot of the first dorsal interosseous (FDI) muscle in order to determine each participant's motor threshold (MT).

The minimal stimulus level, or MT, is the stimulus level required to elicit a motor-evoked potential in 50% of subsequent trials or to cause a thumb, wrist, or finger to move noticeably in at least half of ten stimulations in a fully relaxed muscle [9]. The left DLPFC cortex was located on the skull and was covered by the handle of the figure-of-eight coil, which was positioned posteriorly and perpendicular to the mid-sagittal axis of the head. 5 cm in front of this position was where the FDI muscle's hot spot was [10].

The intervention group got 12 sessions of high-frequency rTMS every other day, except weekends, for a total of 4 weeks. In each rTMS session, ten trains of ten stimulation pulses lasting 2 seconds each, delivered at a frequency of 5 hertz (Hz), and 90% as powerful as MT, were used to target the left DLPFC [9].

In the control group, the same technique and intensity as true rTMS were applied, but the coil was applied to the same area of the skull while being turned 90 degrees away from the scalp. This method produced a sound resembling active stimulation and certain physical sensations with hardly any direct cerebral repercussions [11].

Ethical Approval:

The study was approved by the Ethics Board of Al-Azhar University and the patients were given all the information they need about the trial. An informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by using the Statistical Package for Social Sciences (SPSS) program version 24 for windows. Qualitative data were defined as numbers and percentages.

Chi-Square test/Fisher's exact test was used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test.

Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test/Paired t-test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS

No remarkable variations among the studied candidates related to age, sex, BMI, and duration and types of headaches (Table 1).

Table 1: Basic characteristics of the studied groups.

Variable	Study (n=25)	Control (n=15)	P-value
Age (years)	36.87 ± 8.32	35.13 ± 7.76	0.516
Sex			
Male	4 (16%)	3 (20%)	0.747
Female	21 (84%)	12 (80%)	
BMI (kg/m^2)	26.47 ± 2.59	27.38 ± 3.22	0.333
Duration of disease (months)	22.86 ± 35.17	32.25 ± 41.59	0.455
Types			
Migraine	14 (56%)	8 (53.3%)	0.870
Tension	11 (44%)	7 (46.7%)	

Table 2 demonstrates that there was no statistically significant difference in headache frequency or index before treatment between the study and control groups. However, there is a significant difference between the groups regarding after frequency of headache treatment and index.

Table 2: Headache data of the patients before and after treatment.

Variable	Study (n=25)		Control (n=15)		P-value
	Before	After	Before	After	
Frequency	24.36 ± 5.92	5.26 ± 2.73	23.14 ± 6.35	21.63 ± 7.11	P1 0.543 P2 <0.001
P (within the same group)	**<0.001**		0.251		---
Headache index	57.66 ± 20.88	4.35 ± 3.98	60.87 ± 23.72	51.46 ± 16.75	**P1 0.614** **P2 <0.001**
P (within the same group)	**<0.001**		0.092		---

P1: Study vs. Control before treatment. P2: Study vs Control after treatment.

Meanwhile, there was a significant decrease in headache frequency and index after treatment in the study group, but not in the control group (**Figures 1 and 2**).

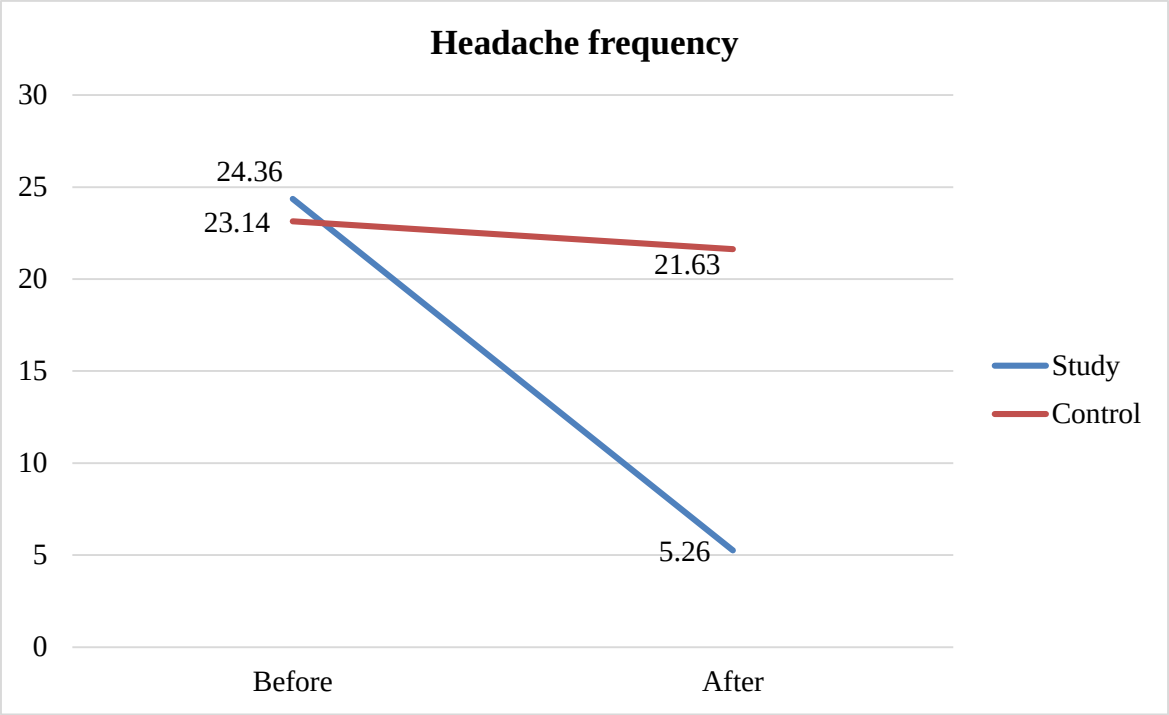

Figure 1: Headache frequency of the patients before and after treatment.

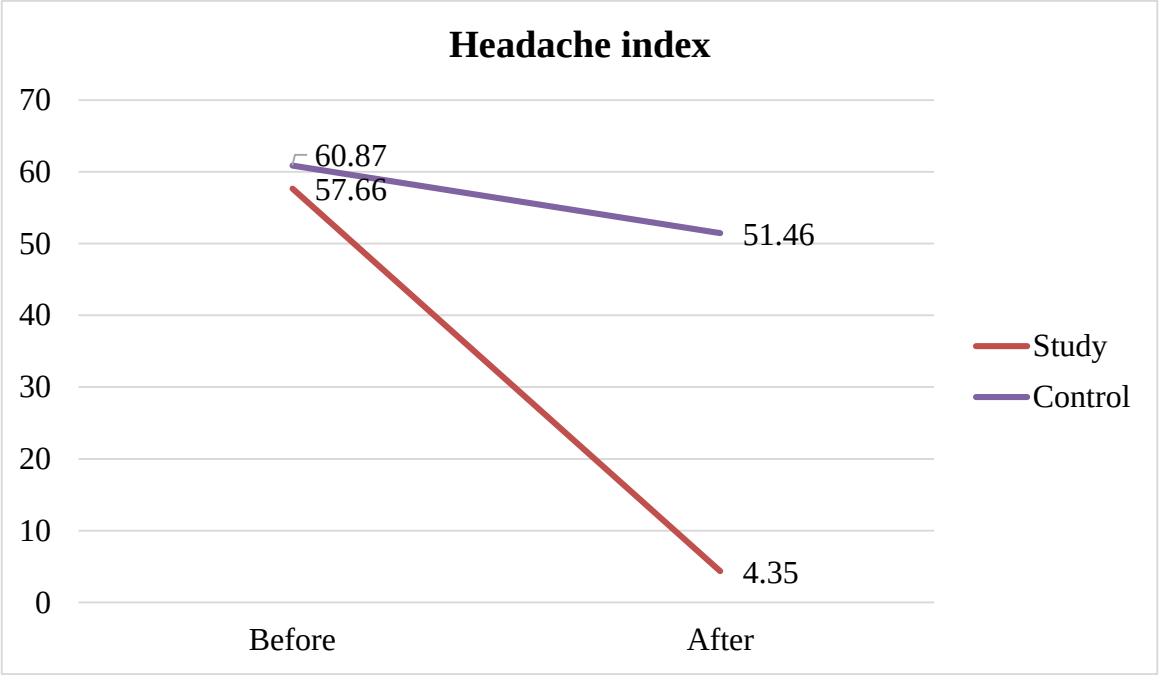

Figure 2: Headache index of the patients before and after treatment.

Table 3: demonstrates that there was no statistically significant difference in pre-treatment headache intensity between the study and control groups. However, there is a substantial difference between the groups regarding to post-treatment headache intensity. Meanwhile, there is a significant improvement in headache intensity after treatment in the study group but not in the control group.

Table 3: Headache intensity of the patients before and after treatment.

Variable	Study (n=25)		Control (n=15)		P-value
Intensity					
Mild	2 (8%)	21 (84%)	1 (6.7%)	1 (6.7%)	
Moderate	11 (44%)	4 (16%)	5 (33.3%)	6 (40%)	**<0.001**
Severe	12 (48%)	0 (0%)	9 (60%)	8 (53.3%)	
P-value (within the same group)	**<0.001**		0.729		

DISCUSSION

Headache issues, one of the most prevalent neurological illnesses that affect 66% of people worldwide, are considered a major health issue. Patients' quality of life is significantly impacted by the fact that 75% of them claim they were unable to finish their jobs during the assault and that 50% need support from family members [12].

In our study, the study group age was 36.87 (SD 8.32) years and the control group age was 35.13 (SD 7.76) years. In a prior study done by **AbdElkader *et al*.** [5] the patients' ages ranged from 20 to 45 years, despite the fact that migraine normally affects individuals between the ages of 25 and 55 and CTTH commonly affects people between the ages of 30 and 39 [13].

Furthermore, overall, there were 4.7 more women than men in our study. The male to female ratio in a previous study by **AbdElkader *et al*.** [5] was 1:4.4, with 22 patients being female (81.5%) and 5 (18.5%) patients being male. This study confirmed previous findings that women are more likely than men to develop CDH [14].

This age and gender disparity in migraine prevalence rates may be a sign that hormonal factors play a role in migraine development. In the current study, those whom got real rTMS had less severe headaches, fewer headaches overall, and a lower headache index.

These outcomes supported by the findings of **Kumar *et al.*** [15], they discovered that rTMS treatment lowered headache frequency and headache index considerably. The precise pace at which magnetic stimulation of the left frontal lobe improves chronic headaches remains unknown. Recent study has shown that high-frequency rTMS therapy can restore DLPFC activity to normal or near-normal levels [16].

Fronto-limbic sensitization has been associated to migraine and chronic pain symptoms. As a migraine attack persists, the pain is usually unrelated to the initial triggers and is frequently accompanied by "limbic" symptoms such as sleep problems, weariness, reduced memory and attention, and decreased libido. Consequently, DLPFC activation may limit or reset decreased fronto-limbic dysfunction, resulting in clinical improvement. While rTMS was only employed on the prefrontal region, its distant effects, also known as network effects, may have an impact on distant, related locations [17].

Frequent TMS may enhance long-term plastic changes that reconfigure the function of the underlying cortex. Several mind networks that are practically connected to the visual framework may be involved in the effects of single-beat TMS on headache [18,19].

According to this study, treating CM and CTTH patients with high-recurrence rTMS applied to the left DLPFC was quite beneficial. Furthermore, the reduction in pain caused by left DLPFC stimulation may have contributed to the improvement of CTTH patients. These results agreed with **AbdElkader *et al.*** [5]. These results also agreed with the findings of **Brighina *et al.*** [20], They discovered that applying capsaicin to the dorsal surfaces of the right or left hands on a 2 cm square for 10 or 20 minutes reduces unrestricted pain in two hands [18].

Similar settings were used to get the right DLPF C, but there wasn't much difference in how annoying it was. These findings support the left DLPFC's essential antinociceptive capability by demonstrating that activation of this region prompted the two-sided guidelines of the aggravation framework. Patients with persistent headaches who qualified for certifiable rTMS in the current review encountered a critical decrease in cerebral pain side effects after treatment.

Misra *et al.* [21] discovered that headache relief improved with three meetings of high-recurrence (10 Hz) rTMS controlled to the left frontal cortex every other day, totaling 600 heartbeats in ten trains. At the end of the first and subsequent weeks after receiving rTMS, nearly 98% of patients experienced a 50% reduction in assault recurrence, and in 80.4% of cases, the improvement continued into the fourth week.

A total of 14 patients with headache and unipolar wretchedness were remembered for a concentrate by **Kumar *et al.*** [22]. The Hamilton wretchedness score and the MIDAS score both superior after 15 meetings of rTMS over the DLFC. As per a new report by Kumar and partners, animating the left front facing mind diminishes both cerebral pain recurrence and force in individuals who have ongoing headache migraines [15]. Since the engine cortex is a part of the nociceptive circuit, the past finding can be made sense of by this reality [22].

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CONCLUSION

Chronic migraines and tension headaches can be effectively treated and prevented by using high-frequency rTMS. As a result, individuals with chronic daily headaches, particularly those who are not responding to therapy, may investigate high-frequency rTMS as a viable treatment.

Conflict of interest: The authors declare no conflict of interest.

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