ORIGINAL ARTICLE

Efficacy of Repetitive Transcranial Magnetic Stimulation in Migraine Prophylaxis in Drug Resistant Migraine

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Abstract

Background: ***Around fourteen percent of the global population suffers from migraines, making it one of the most prevalent neurological disorders. Migraine prevention and abortive treatment options are extensive. All of these medications come with a plethora of adverse effects, and none of them work perfectly.***

Aim and objectives: ***To determine whether drug-resistant migraine sufferers can benefit from rTMS, a form of high-frequency repeated transcranial magnetic stimulation, for migraine prevention.***

Patients and methods: ***Fourty-two patients diagnosed with migraine were recruited for this prospective interventional trial from the Outpatient Clinic of the Neurology Department at Al-Azhar University Hospitals(Al-Hussein and Bab-Elshaarya University Hospitals) between August 2023 and March 2024. All patients were subjected to detailed medical and neurological history, CT brain, and/or MRI brain.***

Results: ***There was a statistically significant difference in the number of migraine attacks in the first two weeks after rTMS, with the greatest improvement shown in the first two weeks of the current trial, which involved 42 patients. Statistical analysis revealed that migraine episode duration varied significantly across weeks, with the first two weeks showing the greatest improvement.***

Conclusion: ***In patients suffering from chronic migraines, the use of high-frequency rTMS over the left motor cortex has been shown to alleviate pain, lessen the impact of headaches on daily life, and alleviate anxiety. The most notable improvements were noted in the first and second weeks of treatment with regard to functional disabilities, attack duration, severity, and number of attacks.***

Keywords: High frequency rTMS; Migraine prophylaxis; Drug resistant

1. Introduction

Worldwide, approximately 14% of the population suffers from migraines, a prevalent neurological condition.[1]

Because migraines have a negative impact on quality of life and everyday activities, particularly between the ages of 14 and 50, when people are at their most productive, it is crucial to find effective treatments.[2]

For the prevention and abortive treatment of migraines, there is a wide selection of medications available. There is a wide range of negative effects associated with these medications, and none of them work perfectly.[3]

An estimated 5.1% of the general population suffers from migraines that are resistant to medical treatment.[4]

Research using visual and somatosensory evoked potentials has shown that migraineurs do not have adequate cortical inhibition.[5]

One effective method for treating both short-term and long-term migraines is transcranial magnetic stimulation (TMS).[6]

Using intense magnetic pulses administered to the scalp, transcranial magnetic stimulation (TMS) is a non-invasive way to activate the cerebral cortex.[7]

Pulse trains used in recurrent transcranial magnetic stimulation (rTMS) have the potential to modulate both neuronal excitability and cortical function.[8]

The usual way that these changes have been noticed is that low-frequency stimulation (≤1-Hz) reduces cortical excitability, and high-frequency rTMS (≥5-Hz) increases it.[9]

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Today, transcranial magnetic stimulation (TMS) is thought of as an intervention that is both safe and well-tolerated.[10] The dopamine levels in the hippocampus were raised, and the glutamate/glutamine levels in the dorsolateral prefrontal cortex were altered by high-frequency frontal stimulation. Consequently, these alterations restore normal cortical excitability, which in turn lessens the frequency of migraine episodes.[11]

The purpose of this research is to determine whether drug-resistant migraineurs can benefit from using high-frequency rTMS as a migraine preventive measure.

2. Patients and methods

Between August 2023 and March 2024, 42 patients were randomly chosen from the outpatient clinics of the neurology departments of Al-Azhar University Hospitals(Al-Hussein and Bab-Elshaarya University Hospitals). The study was an interventional prospective design.

In accordance with the principles laid out in the Declaration of Helsinki, this research was carried out. The Al-Azhar University Faculty of Medicine's ethical committees gave their stamp of approval, and the study was subsequently approved by the Institutional Review Boards. All patients who were enrolled were asked to sign an informed consent document when they were enrolled.

Inclusion criteria:

Patients with medication resistance, as well as those in the 12–50 age range (medication-resistant migraineurs with more than five attacks monthly who have not shown improvement after two months of treatment with each preventative medication).[3]

Exclusion criteria:

People who have a history of seizures or structural brain lesions, people who have electronics or metal devices implanted (such as a pacemaker, a coil or clip for aneurysms, a stent in the neck or the brain, a deep brain stimulator, electrodes to record brain activity, metal in their ears or eyes, a piece of bullet in or near their head, or any other metal device or object)

Methods:

The following studies were performed for all cases:

The patient's complete medical and neurological history, including all relevant medical conditions, past medical procedures, and current symptoms, including the frequency, severity, and length of migraine attacks. The length, intensity, and regularity of the episodes. The quantity of rescue medication administered and the reaction. Relevant medical history, substance use history, and family medical history are examples of associated symptoms.

The patient underwent a comprehensive neurological and general medical evaluation. International Headache Society criteria were used for the migraine diagnosis.[12]

Patients were advised to refrain from taking migraine preventive medication during treatment and follow-up; rescue medicine should only be used in extreme cases. In a headache journal, the patient keeps track of the amount of tablets taken weekly for acute therapy, the duration and frequency of attacks, and more. The basic diagnostic headache diary (BDHD) was used one week prior to and four weeks following TMS sessions.[13]

Following the guidelines laid out by Piovesan and Silberstein, headaches were rated from 0 (none), 1 (mild), 2 (moderate), and 3 (severe).[14]

Using a scale from 1 (little or no disability) to 4 (severe disability), the functional disability was determined using the migraine disability assessment.[15]

The Migraine Disability Assessment Scale (MIDAS):

A common tool for assessing impairment due to migraines is a set of particular questionnaires. The seven-item MIDAS assesses the effects of migraine on three types of activities: work/school, household, and social and leisure. Over the last three months, all of these have been assessed. A four-point scale is used by MIDAS: Level-I: minimal or no impairment (scores ranging from 0 to 5); Level-II: moderate impairment (scores from 6 to 10); Level-III: moderate impairment(scores from 11 to 20); Level-IV: severe impairment(scores of 21 or more).

Investigations:

Serum chemistry, erythrocyte sedimentation rate, hemoglobin, and blood counts. Brain MRI and CT scans, which are examples of radiological studies, were also performed.

rTMS sessions protocol for migraine:

Drug-resistant patients: Migraine patients not responding to at least two prophylactic drugs taken for at least 2 months each and having more than five attacks per month.[16]

Three sessions don't consume much time or money, make great results, and make patients more compliant with treatment.[17]

The Magstim Rapid², an angular figure of eight-shaped coil, and two channels of the Neuro-EMG digital system© were utilized in three sessions of alternate-day rTMS treatment(Figure 1). Every session includes a 10-Hz rTMS that is divided into 10 trains with 45-second intervals between each train. The stimulation intensity is set to the "visual motor threshold" of the dominant hand, which is about the same as the resting motor threshold. The left frontal cortex is targeted during these cycles. We found the stimulator intensity that, in five out of ten trials, caused the target muscle to contract to a

minimally perceptible degree(visual motor threshold). Patients underwent follow-up for 4 weeks.

Assessment of visual motor threshold(VMT):

The stimulator intensity produced a visually detectable minimal muscle contraction in the target muscle in at least 5 out of 10 trials. The stimulation intensity is set to 'the visual motor threshold of the dominant hand, an intensity that corresponds approximately to the resting motor threshold.

It was requested that the patient sit up straight. To begin, we visually examined each subject's first dorsal interosseous muscle motor thresholds to get a general idea of their cortical excitability. In order to do this, the figure eight probe was placed on the patient's head in the area of the right-hand motor cortex. Then, single pulses of varying intensity were administered. In order to detect when the patient's hand contracts, we had him abduct his index finger and then ask him to stretch his right hand fingers. Estimations of migraine attack length, frequency, severity, functional handicap, and accompanying symptoms were used to quantify effectiveness, along with the number of analgesics used each week. At the conclusion of the final session and on a weekly basis for four weeks, the reaction was assessed.

Figure 1. Magstim Rapid 2-TMS Device.

Statistical Analysis

The data was coded, processed, and analyzed using the Windows version of the SPSS program (Version 24). When necessary, we utilized the proper statistical tests. Statically significant results were defined as p-values below 0.05 or 5%. The normality of the data distribution was tested using the Shapiro-Wilk test. Statistics measures such as median, range, standard deviation, and standard error are presented for numerical data. Frequency and percentage of non-numerical data. To determine whether the difference in means of the parametric variables between the two groups was statistically significant, the Student T-Test was employed. For the purpose of determining if a non-parametric variable differed significantly between the two research groups, the Mann-Whitney Test(U-test) was employed. To determine if a non-parametric variable's difference between more than two research groups was statistically significant, the Kruskal-Wallis Test was employed. The correlation between the two qualitative variables was investigated using a chi-square test. Analyzing correlations: In order to measure the degree of correlation between two numerical variables.

3. Results

Table 1. Patient demographics used in the research.

		N	%
Age	Mean±SD	30.24±8.8	
Gender	Female	28	66.7
	Male	14	33.3
Occupation	Doctor	3	7.1
	Housewife	12	28.6
	Manual Worker	5	11.9
	Nurse	5	11.9
	Student	8	19.0
	Others	2	4.8
Residency	Behira	3	7.1
	Cairo	24	57.1
	Giza	4	9.5
	Others	3	7.1

There were 28-females(66.7%), while males constituted 33.3% of patients. The most common occupations of them included housewives 28.6%, students 19%, nurses and workers 11.9%, and doctors 7.1%.

Table 2. Baseline assessment of clinical data of patients per week.

	Number of Prophylactic drugs	Number of attacks	Duration of attacks(days)	Severity of attacks 0-3	Functional Disability 1-4	Number of rescue medications	Associated symptoms(numbers)
Mean	3.05	5.10	5.95	2.43	3.19	19.07	1.69
SD	0.582	1.462	0.854	0.501	0.455	7.090	0.643
Min	2	3	4	2	2	12	1
Max	4	9	7	3	4	42	3

The mean number of used prophylactic drugs was 3.05±0.5, min=2, max=4, the mean number of attacks per week was 5.1±1.4, min=3, max=9, the mean severity of attacks was 2.4±0.5, min=2, max=3, the mean functional disability grade according to MIDAS was 3.1±0.4, min=2, max=4, the mean number of rescue medications per week was 19.07±7, min=12, max=42, while the mean associated symptoms was 1.6±0.6, min=1, max=3, table(2), figure(2).

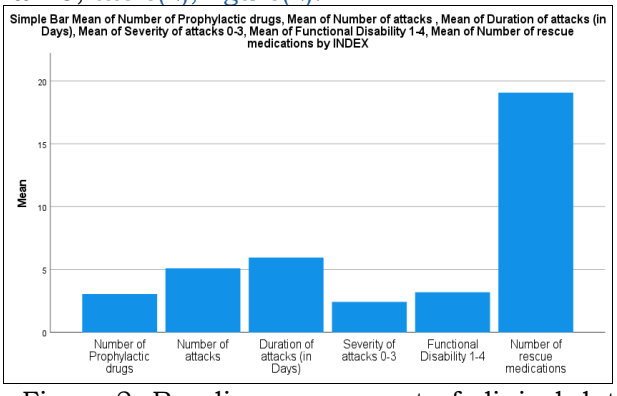

Figure 2. Baseline assessment of clinical data per-week.

Table 3. First-week assessment of clinical data of patients.

	Number of Prophylactic drugs	Number of attacks	Duration of attacks(days)	Severity of attacks 0-3	Functional Disability (1-4)	Number of rescue medications	Associated symptoms (numbers)
Mean	0.00	0.48	0.52	0.24	0.26	1.90	0.12
SD	0.000	1.596	1.671	0.759	0.857	6.669	0.395
Minimum	0	0	0	0	0	0	0
Maximum	0	7	7	3	4	30	2

The mean number of attacks was 0.4±1.5, min=0, max=7, the mean duration of attacks in days was 0.5±1.6 days, the mean severity of attacks was 0.2±0.7, min=0, max=3, the mean functional disability was 0.2±0.8, min=0, max=4, the mean number of rescue medications was 1.9±6.6, min=0, max=30, while the mean associated symptoms was 0.1±0.3, min=0, max=2, table(3), figure(3). On the other hand, there was no prophylactic drugs had been used.

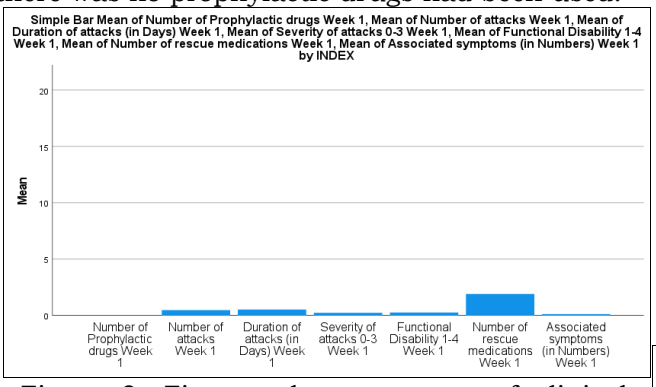

Figure 3. First week assessment of clinical data.

Table 4. Second-week assessment of clinical data of patients.

	Number of Prophylactic drugs	Number of attacks	Duration of attacks (days)	Severity of attacks 0-3	Functional Disability (1-4)	Number of rescue medications	Associated symptoms (numbers)
Mean	0.00	0.52	0.57	0.26	0.29	2.07	0.17
SD	0.000	1.700	1.796	0.828	0.918	7.151	0.537
Minimum	0	0	0	0	0	0	0
Maximum	0	7	7	3	4	32	2

The mean number of attacks was 0.5 ±1.7, min=0, max=7, the mean duration of attacks in days was 0.5±1.7 days, the mean severity of attacks was 0.2±0.8, min=0, max=3, the mean functional disability was 0.2±0.9, min=0, max=4, the mean number of rescue medications was 2.07±7.1, min=0, max=32, while the mean associated symptoms was 0.1±0.5, min=0, max=2, table(4), figure(4). On the other hand, there was no prophylactic drugs had been used.

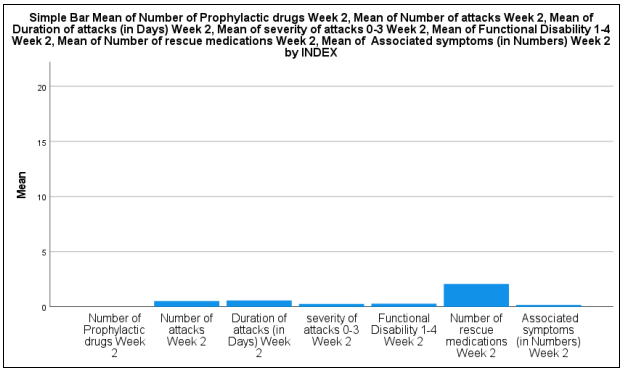

Figure 4. Second-week assessment of clinical data.

Table 5. Correlation of duration of attacks among different times.

		Mean	SD	Corr	P
Pair-1	Duration of attacks(days) baseline	5.95	0.854	0.337	0.001
	Duration of attacks(days) session week	2.07	1.536		
Pair-2	Duration of attacks(days) Week-1	0.52	1.671	0.955	0.001
	Duration of attacks(days) Week-2	0.57	1.796		
Pair-3	Duration of attacks(days) Week-3	0.7679	1.90426	0.987	0.001
	Duration of attacks(days) week-4	1.3214	1.72966		

There was statistically significant difference regarding duration of migraine attacks between different weeks table(5), figure(5).

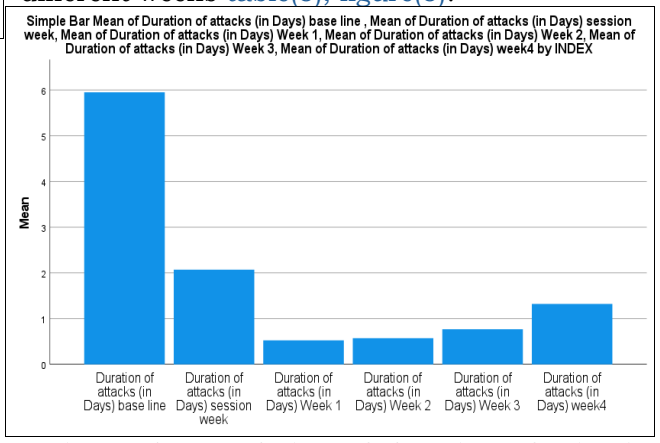

Figure 5. Correlation of duration of migraine attacks.

Table 6. Correlation of severity of attacks among different times.

		Mean	SD	Corr	P
Pair-1	Severity of attacks 0-3 base line	2.43	0.501	0.477	0.001
	Severity of attacks 0-3 session week	1.64	0.656		
Pair-2	Severity of attacks 0-3 Week-1	0.24	0.759	0.985	0.001
	severity of attacks 0-3 Week-2	0.26	0.828		
Pair-3	Severity of attacks 0-3 Week-3	0.60	0.912	0.866	0.001
	Severity of attacks 0-3 week-4	1.19	0.594		

There was statistically significant difference regarding severity of migraine attacks between different weeks, table (6), figure (6).

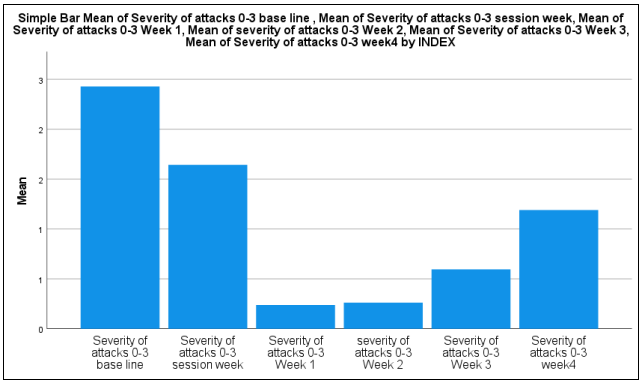

Figure 6. Correlation of severity of migraine attacks.

4. Discussion

From baseline to 1-month follow-up, our study found that rTMS significantly improved the frequency, length, and intensity of attacks, as well as the number of rescue drugs taken, functional impairment, and related symptoms. Compared to the baseline, there was a considerable improvement during the application week, which peaked in the first week following TMS and then fell in the third and fourth weeks. However, the improvement was still there.

Contrary to what we found, earlier research by Misra et al.,[17] Forty-eight percent of patients reported a decrease in headache frequency of more than 50% between the last session and one week after rTMS, and eighty-four percent stated that the improvement lasted until the fourth week.

Although there was a steady decrease in headache frequency, intensity, functional disability, migraine index, and rescue drug use throughout the trial, the benefits were greatest in the first two weeks. They found that high-rate rTMS in the left frontal brain was efficacious and well-tolerated for migraine prophylaxis, and there were no major side effects.

Also, our findings were in line with Brighina et al.,[18] who sought to address chronic migraine by studying the efficacy of high-frequency rTMS over the left dorsolateral prefrontal cortex(DLPFC). In their study, eleven migraine patients were randomly assigned to either a sham treatment group or an active group that received twelve sessions of rTMS on the left dorsolateral prefrontal cortex. The results showed that six of the active group patients had a 50% reduction in headache frequency and analgesic intake at one and two months, while none of the five sham group patients showed any improvement in their migraine symptoms. The researchers concluded that high-frequency rTMS over the left DLPFC could alleviate chronic migraine.

The study group's patients demonstrated a 94.5% improvement in headache parameters(headache frequency, intensity, and index) following real rTMS stimulation, as compared to the control group(P-value<0.001).

Similarly, this study agreed with Sahu A et al.,[19] who came to the conclusion that the left DLPFC could be safely and effectively stimulated with adjunctive active intermittent theta-burst repetitive transcranial magnetic stimulation to lessen the prevalence, length, and intensity of migraine headaches as well as the disability that comes with the disease. This is because stimulation of the DLPFC can change glutamate/glutamine levels and induce dopamine release. In addition, normalizing brain excitability and modulating thalamocortical signals are two additional potential benefits of rTMS for migraine sufferers.

The opposite was true: our findings ran counter to Teepker et al.,[20] who studied the efficacy of low-frequency rTMS for migraine treatment. Both the treatment and placebo groups showed a statistically insignificant decrease in migraine attack frequency relative to baseline.

When comparing the rTMS group to the placebo group, we did not find any statistically significant differences in migraine attack frequency, headache duration, pain intensity, or rescue drug usage. Possible explanations for the discrepancy in findings include variations in study design, stimulation parameters, and stimulation site.

Three treatments were administered to each patient on a daily basis. Each session included 10-Hz rTMS, which was delivered to the left frontal cortex in 10 trains and comprised 600 pulses. Whereas Teepker et al.,[20] administered 500 stimuli at 1 Hz for 5 days over the vertex.

Based on our findings, rTMS is likely a key factor in migraines that do not respond to conventional treatment. In addition, our patients were simply instructed to take rescue analgesics and did not receive any preventative medication before, during, or after the rTMS.

Predicting where stimulation will alleviate pain is crucial. The participants in this study were asked to endure pain by having capsaicin injected into the backs of their hands, and then they were given rTMS to apply to the matching deep-layer pressure fibers(DLPFC). Both hands had pain relief upon stimulation of the left DLPFC, whereas stimulation of the right side had no such effect. Stimulating the left dorsolateral prefrontal cortex(DLPFC) may have a crucial anti-nociceptive function and appear to exert a bilateral regulation of pain.[21]

Rollnik et al.,[22] The study found that the figure-eight coil was more effective in reducing pain severity than the circular coil. Specifically, when the circular coil was used, there was no

significant difference between the reductions in pain severity ratings after rTMS and those after sham.

The propagation of magnetic stimulation to nearby regions of the cortex might explain this reaction. While electrical stimulation increases spread via activating corticospinal neurons' axons in white matter, magnetic stimulation increases spread through activating neurons trans-synaptically. rTMS has the potential to reduce migraine frequency by altering neurotransmitters or causing a long-term shift in neuronal excitability.[23]

4. Conclusion

In patients suffering from chronic migraines, the use of high-frequency rTMS over the left motor cortex has been shown to alleviate pain, lessen the impact of headaches on daily life, and alleviate anxiety. The most notable improvements were noted in the first and second weeks of treatment with regard to functional disabilities, attack duration, severity, and number of attacks.

Disclosure

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Authorship

All authors have a substantial contribution to the article

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