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Repetitive transcranial magnetic stimulation for prophylactive treatment of chronic migraine: A randomised, single-blind, parallel-group, sham-controlled trial

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Abstract

Background: Pilot studies suggest that repetitive transcranial magnetic stimulation could be effective in migraine. We studied its efficacy for prophylaxis of chronic migraine. *Methods:* We undertook a randomised, single-blind, sham-controlled study in patients with chronic migraine. Subjects were randomly allocated to sham, high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) or low-frequency repetitive transcranial magnetic stimulation (LF-rTMS). The primary outcome was the reduction of attacks at four weeks. In addition, reduction of severity of headache based on the Visual Analogue Scale score at two & four weeks and a functional disability score at four weeks was recorded. *Results:* One hundred and eight patients were allocated to sham stimulation (n=36), HF-rTMS (n=36) and LF-rTMS (n=36) groups. The number of attacks per month decreased to 7.05+/-1.45 at four weeks post-rTMS in the HF-rTMS ($p<0.001$) as compared to the LF-rTMS (10.61+/-1.69) and sham (10.83+/-3.37) groups. The VAS score in the HF-rTMS group was significantly lowered ($p < 0.001$) from 8.61+/-1.15 at baseline to 6.63+/-0.96, and 7.19+/-0.98 at two and four weeks respectively. The duration of headache in hours over 4 weeks reduced from 32.4+/-14.9 to 11.6+/-6.14 in the HF-rTMS group ($p<0.001$), but did not change significantly in the LF-rTMS (30.4+/-11.9 to 27.8+/-14, $p>0.05$) and sham (26.8+/-11.06 to 37+/-15, $p>0.05$) in sham groups. There was no significant difference in functional disability between all the study groups at four weeks.
Conclusion: High-frequency, but not low-frequency, repetitive transcranial magnetic stimulation may be useful in management of chronic migraine.

Keywords: Repetitive transcranial magnetic stimulation (rTMS), migraine, sham, visual analogue scale

INTRODUCTION

Migraine is a common disabling neurological disorder that affects up to 12% of the general population. Migraine has a cumulative lifetime incidence of 43% in women and 18% in men.[1] Episodic migraine transforms into a chronic pattern at the rate of 3-14% per year.[2] Chronic migraine is defined as a headache occurring on 15 or more days per month (with features of migraine headache on at least eight days per month) for more than three months.[3] The precise etiopathogenesis of migraine remains to be elucidated. Currently, cortical spreading depression (CSD) and trigemino-vascular activation are generally considered to be the likely pathophysiological mechanisms underlying aura and migraine pain respectively.[4] The trigemino-vascular system consists of trigeminal nerve endings on meningeal vessels, which become activated during the attack, releasing substance P, calcitonin gene-related peptide (CGRP), and other substances that induce vasodilation and trigger nociceptive neural transmission to the trigeminal nucleus caudalis, thereby producing pain.[5] Induction of cortical spreading depression is considered to be the pathophysiological basis of the migraine aura.[6]

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The dorsolateral prefrontal cortex (DLPFC) exerts an inhibitory control on the pain pathway in humans, Based on this, repetitive transcranial magnetic stimulation (rTMS) over the DLPFC has been tried in a pilot study.[7] If given in repeated pulses rTMS can produce long-lasting plastic effects depending on the stimulation frequency used: frequencies of 1 Hz or less i.e. low-frequency rTMS (LF-rTMS) reduce, whereas frequencies above 1 Hz i.e. high-frequency rTMS (HF-rTMS) increase cortical excitability. Waves of CSD can be inhibited by rTMS, reducing the severity of migraine attacks.[8] Through this study we explored the role of rTMS as a prophylactic treatment in patients with chronic migraine.

METHODS

Patients with chronic migraine age 18 years and above fulfilling the inclusion criteria were screened and included in the study. Written informed consent was obtained from patients. An appropriate sample size was calculated on the basis of findings of previous studies.[3,9,10] We expected that about 20% of participants in the sham group and about 25% of those in the rTMS group would respond to treatment. A minimum of 30 patients per treatment group was estimated to be needed to detect this magnitude of effect, with a two-sided χ^2 test, α of 0·05, and 90% power. Assuming a dropout rate of 10%, we needed to enrol a minimum of 90 individuals into the treatment phase of the study to ensure that at least 30 subjects in every group (total 90) would complete the study.

The inclusion criteria were: 1) Adult patients with chronic migraine fulfilling the definition of International Classification of Headache Disorder (ICHD) 3B; 2) Failure to respond to at least one or two prophylactic drugs at an optimal dosage, either one or both at a time for at least three months after starting of medication, but still having more than four attacks per month (with attacks lasting from 4 hrs to 72 hrs).

The exclusion criteria were: Patients with pregnancy, liver and kidney disorder, malignancy, severe hypertension, a pacemaker or metallic implant, and family or past history of seizure or any structural brain lesion.

All patients underwent detailed history, clinical examination, and investigations which were recorded on a pre-designed questionnaire. All patients maintained a headache diary. rTMS was performed by using a (Magstim Rapid, Whitland, Wales, UK) figure-of-8 magnetic stimulator coil 7 cm in diameter. The stimulator was placed over the DLPFC, which corresponds to site of activation of the right abductor digit minimi. The motor threshold was determined to be the stimulus intensity that was able to elicit motor unit potentials of about 50 microvolts in five or more out of 10 consecutive stimuli. Seventy percent of the motor threshold stimulus strength was then used for rTMS.

Each course of treatment consisted of:

- High-frequency r-TMS for three sessions on alternate days, comprising 584 pulses in 10 trains separated by an inter-train interval of 45 sec at a frequency of 8Hz.
- Low-frequency r-TMS for three sessions on alternate days, comprising 500 pulses in two trains separated by an inter-train interval of 1min at a frequency of 1Hz.
- For sham therapy, the same type of coil was placed over the vertex, and 100 pulses at 30% motor threshold stimulus intensity at a frequency of 1Hz were delivered in three sessions on alternate days, and results evaluated similarly as the treatment groups.

Subjects were randomized by using computer-generated randomisation according to a 1:1:1 ratio into the three study groups. All subjects were blinded to the treatment received by our using the same colour and type of probe in each group. All patients continued their usual prophylactic medications during the study.

Outcome measure: The frequency of headache, and Visual Analogue Scale (VAS) scores on a 0–10 scale were noted at the end of the rTMS session, and two and four weeks after the rTMS session. Functional disability scores were assessed at four weeks. All subjects were followed up in the outpatient clinic, or with telephonic interviews.

Primary outcome: Reduction of attack frequency from the baseline at four weeks post-rTMS.

Secondary outcomes: 1) The severity of headache based on VAS assessed at two and four weeks from baseline; 2) The functional disability (MIDAS) score at four weeks from baseline.

Safety outcomes in the form of any side-effects were noted. Outcomes from HF rTMS, LF rTMS, and sham treatment were determined at the end of the study. Statistical analysis was done with STATA/SPSS software. All categorical data were

analyzed using the Chi-square test or Fisher exact test. Continuous variables were analyzed using Student's t-test &/or ANOVA. Normality of data was tested by the Kolmogorov-Smirnov test. Non parametric tests were used in non-normally distributed data. The level of significance was set at a p-value <0.05. This trial is registered with CTRI, number REF/2016/08/012053.

RESULTS

This study was conducted at the Army Hospital (Research & Referral) New Delhi. The mean age was 31 years. Among them 84.25% were females and 15.75% were males with an F:M ratio of 5:1. One hundred and eight patients with a history of chronic migraine were identified and divided into three groups using computer-based block randomisation. Group A consisted of 36 patients who received HF-rTMS, Group B consisted of 36 patients who received LF-rTMS, and Group C consisted of 36 patients who received sham therapy. The baseline characteristics were similar in all three groups (Table 1). The consort diagram is depicted in Figure 1. Significantly fewer attacks post rTMS were observed in the HF (<0.001) group at four weeks as compared to the baseline

Table 1: Baseline characteristics

Variables	HF-rTMS	LF-rTMS	Sham	P value
Age (in years)	31.02±7.24	32.08±7.75	31.47±7.87	0.84
Female sex	32(88.8 %)	29(80.5 %)	30(83.33%)	0.61
Duration of Headache (in years)	3.02±1.9	3.1±1.87	2.41±0.69	0.13
No of attack per month	13.7±4.43	13.44±3.53	12.47±3.51	0.35
Duration of attack(hrs) per month	32.4±14.9	30.4±11.9	26.8±11.06	0.16
Aura	3(8.3%)	1(2.7%)	2(5, 5%)	0.59
Time to peak intensity(mins)	23.8±19.7	24.5±22.8	23.6±20	0.97
Severity mode pre TMS moderate to severe no (%)	32(88.8%)	30(83.3%)	31(86.1%)	0.79
Character of headache (Dull)	6(16.6%)	4(11.6%)	5(13.8%)	0.79
Character of headache (Throbbing)	30(83.4%)	32(88.4%)	31(86.2%)	
Vomiting	24(66.6 %)	18(50%)	22(61.1%)	0.34
Photophobia	34(94.4%)	29(80.5%)	33(91.6%)	0.14
Phonophobia	27(75%)	29(80.5)	34(94.4)	0.07
Lacrimation	6(16.6%)	4(11.1%)	4(11.1%)	0.72
Nasal congestion	3(8.3%)	2(5.5%)	1(2.7%)	0.58
Menstrual association	6(16.6%)	4(11.1%)	6(16.6%)	0.74
Depressed mood	9(25%)	10(27.7%)	7(19.4%)	0.70
Stressor	8(22.3%)	10 (27.8%)	8 (22.2%)	0.9
Past history of headache	6(16.6%)	7(19.4%)	3(8.3%)	0.38
Addiction	2(5.5%)	2(5.5%)	1(2.7%)	0.81
Dietary habits(mixed)	27(75%)	30(83.3%)	30(83.3%)	0.58
Family history of headache	4(11.1%)	2(5.5%)	3(8.3%)	0.69
Treatment history of analgesics Naproxen + domperidone + PCM	17(47.2%)	11(30.5%)	15(41.6%)	0.33
Sumatriptan + naproxen + ibuprofen	19(52.7%)	25(69.4%)	21(58.3%)	
Prophylactic with topiramate	15(41.6%)	15(41.6%)	13(36.1%)	0.85
Others*	21(58.4)	21(58.4)	23(63.9)	
Duration of prophylaxis (years)	1.75±0.9	1.83±0.91	1.58±0.84	0.47
Pre-TMS VAS	8.61±1.15	8.1±1.36	7.9±1.3	0.07
Pre-TMS MIDAS	16.7±2.1	16.6±2.01	15.9±1.6	0.15

*Propranolol, valproate, amitriptyline, nortriptyline, flunarizine

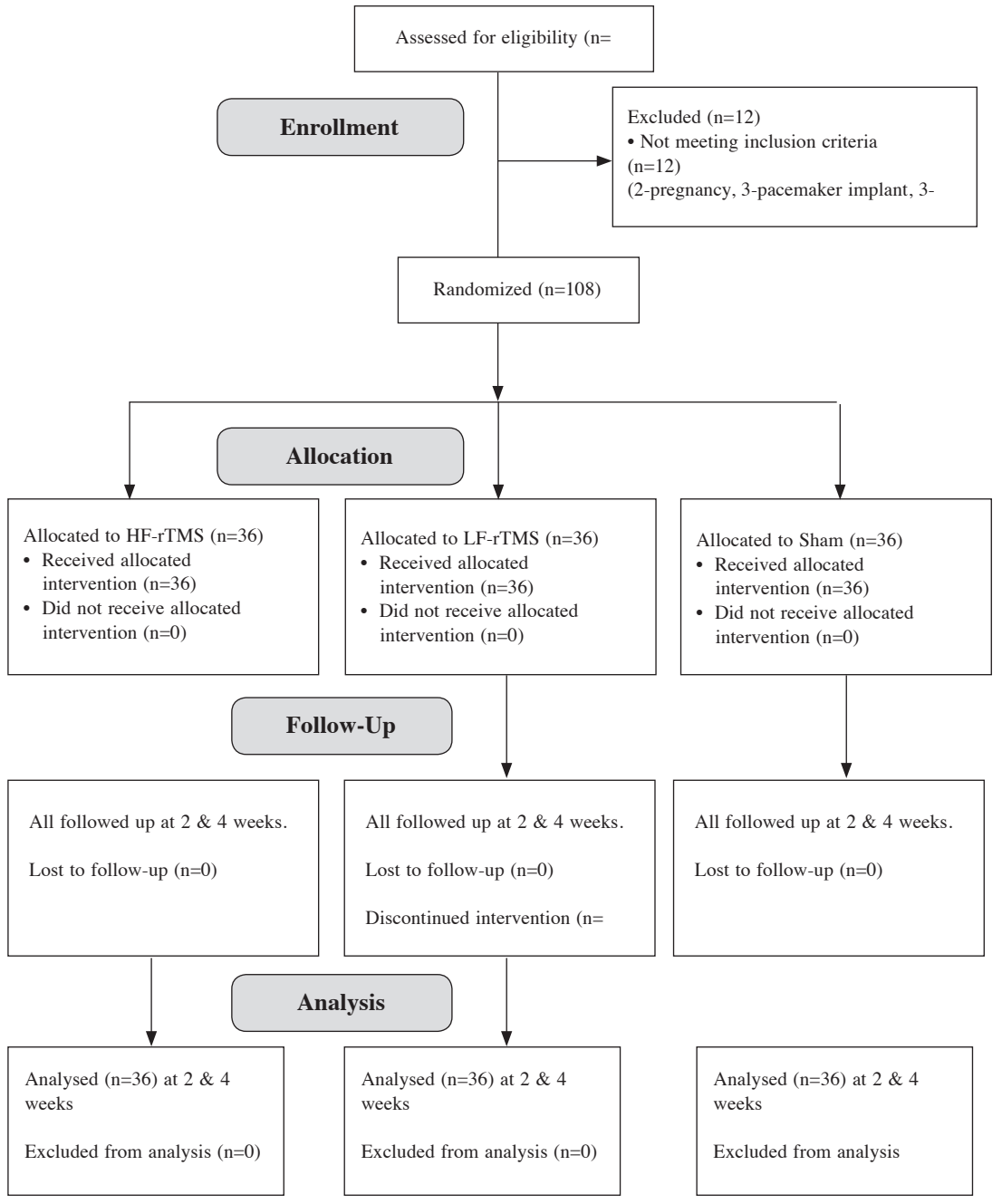

Figure 1. Consort flow diagram.

(Table 2). A statistically significant difference in the number of attacks per month was present at four weeks between the HF-rTMS and LF-rTMS groups (P<0.001), as well as between the HF-rTMS and sham groups (P<0.001) (Figure 2). There was no statistically significant difference in the number of attacks per month at four weeks between the LF-rTMS and sham groups (P= 0.99). One way ANOVA analysis showed a statistically significant difference in VAS scores at two weeks (P <0.001) and four weeks between study groups (P <0.045) (Table 3). However, a greater than 50% reduction rate in VAS scores from the baseline was not achieved. There was a statistically significant improvement in the VAS score at two weeks in the HF-rTMS group as compared to the sham group (P < 0.001) and the LF-rTMS group (P<0.001) (Figure 3). We

Table 2: One way ANOVA analysis: Reduction of number of attacks post TMS at four weeks

Variable	HF-rTMS	LF-rTMS	Sham	P value
No. of attacks in the four weeks post-intervention	7.05±1.45	10.61±1.69	10.83±3.37	<0.001

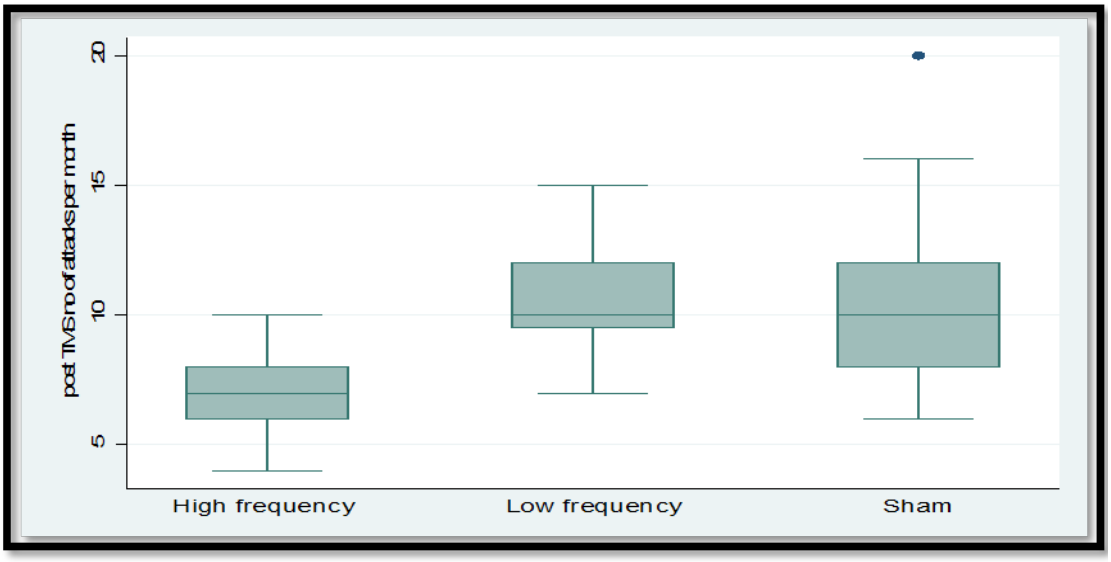

Figure 2. Post hoc analysis of reduction of number of attacks post TMS at four weeks.

Table 3: One-way Anova analysis for differences in VAS score among the study groups.

Variables	HF-rTMS	LF-rTMS	Sham	P value
VAS at two weeks	6.63±0.96	7.86±1.31	7.91±1.27	<0.001
VAS at four weeks	7.19±0.98	7.75±1.22	7.83±1.27	0.045

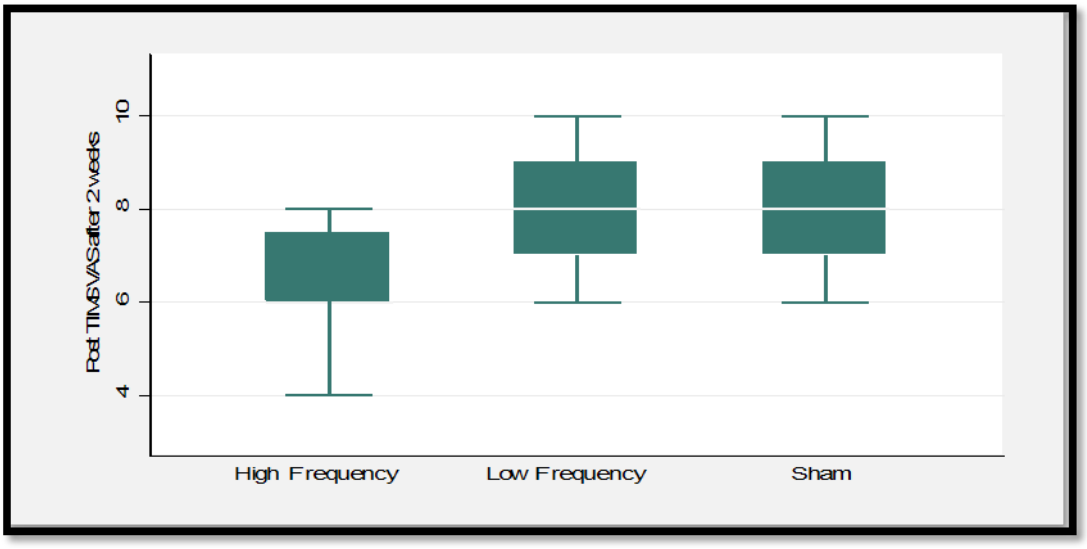

Figure 3. VAS scale after two weeks of intervention.

observed a non-significant trend towards greater pain reduction in the HF-rTMS group compared to the sham group at four weeks post rTMS (P =0.06). There was no statistically significant difference in VAS scores between the HF-rTMS and LF-rTMS groups at four weeks post rTMS (P = 0.13) (Figure 4). One-way ANOVA analysis showed no statistically significant differences in functional disability (MIDAS) between the 3 study groups (P = 0.16) (Table 4). MIDAS scores did not differ significantly at four weeks between HF-rTMS and LF-rTMS (P= 0.17), HF-rTMS and sham (P= 0.99), and LF-rTMS and sham groups (P= 0.67).

Four weeks after treatment, the duration of attacks was shorter (hours) per month in the HF-rTMS group (11.6 ± 6.14) as compared to LF-rTMS (27.8 ± 14) and sham (37 ± 15) groups (P < 0.001). There was a statistically significant difference in duration of attacks in hours at four weeks between the HF-rTMS and LF-rTMS (P<0.001) groups, between the HF-rTMS and sham (P < 0.001) groups, and between the LF-rTMS and sham (P = 0.007) groups (Figure 5).

No serious adverse side effects were noted in any of the groups. Only minor side effects in the form of transient giddiness were noted in 27.7% of the HF-rTMS, 19.4% in the LF-rTMS and 16.6% in the sham groups. These differences were not statistically significant (P value = 0.48).

DISCUSSION

rTMS has been studied as a non-pharmacologic therapy in prevention of chronic migraine with good outcome.[10] Our study also shows significant response with HF-rTMS in comparison to sham stimulation in terms of improvement in VAS scores two weeks after treatment as well as in the number and duration of attacks four weeks after treatment. Only mild side effects were observed which did not cause dropouts from the study. Misra *et al*. also observed that the VAS score improved with a maximum response at the end of the first week. Greater than 50% improvement in VAS scores was present in 80% of the patients even at the end of the fourth week. Severe headache was not recorded after the second week. Improvement was noted in migraine frequency (P < 0.0001), severity (P < 0.0001), and functional disability (P < 0.0001).[11] The treatment was well tolerated. These results were similar to what we observed in our study.

Brighna *et al*. compared HF-rTMS (n=6) and

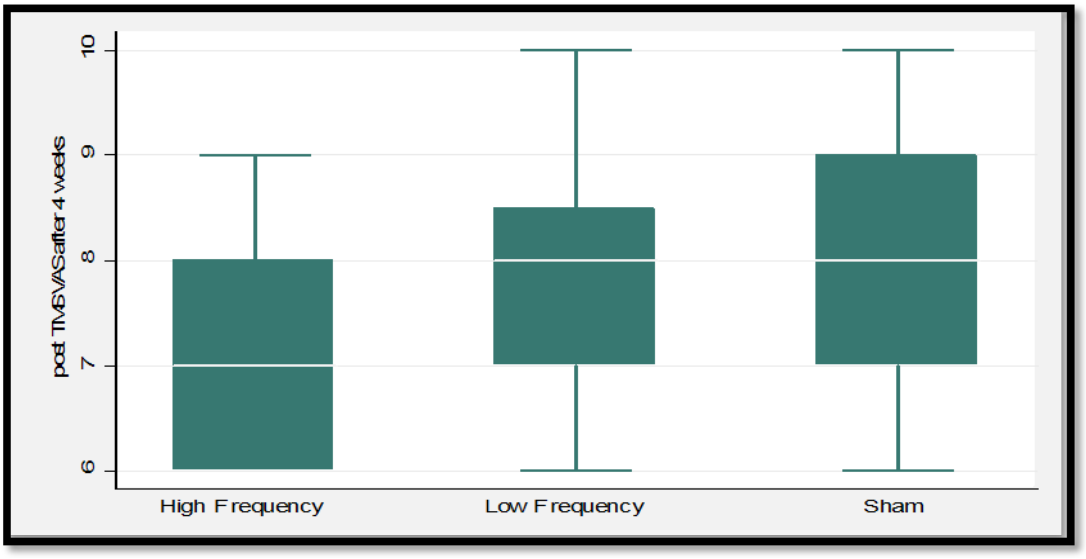

Figure 4. VAS scale after four weeks of intervention.

Table 4: Differences in the Secondary Outcomes analysis (MIDAS) among the study groups

Variable	HF-rTMS	LF-rTMS	Sham	P value
Functional disability (MIDAS) at four weeks	15.58±1.42	16.36±1.82	15.86±1.91	0.16

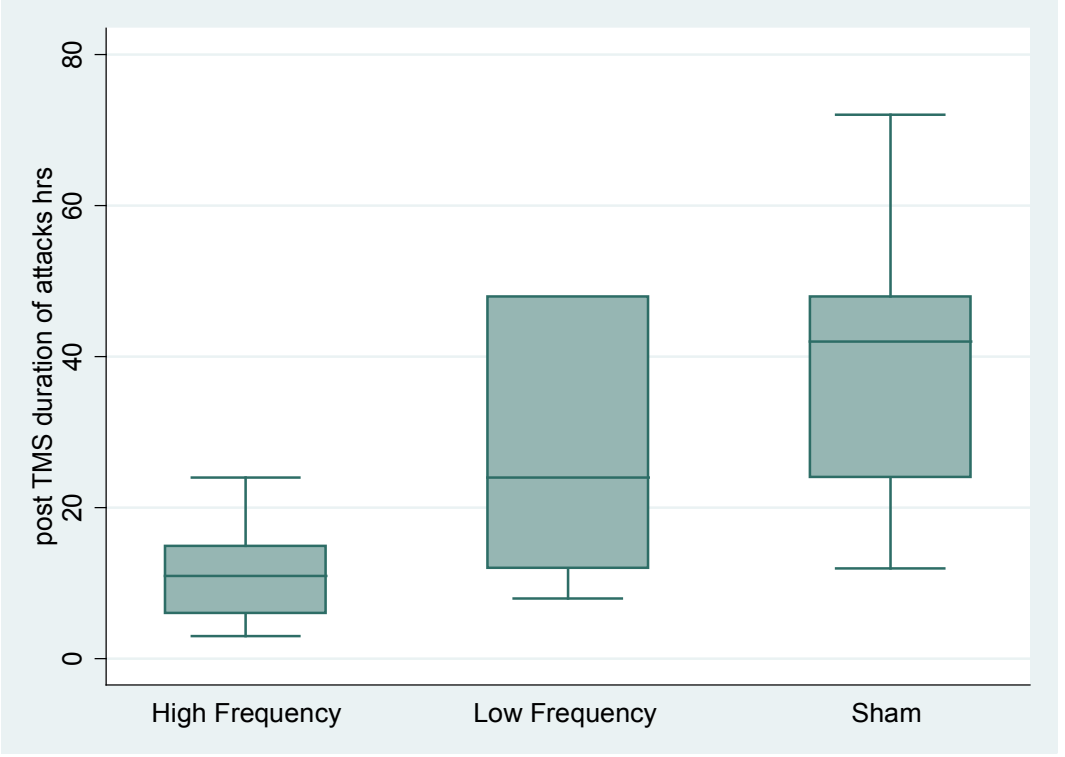

Figure 5. Post hoc analysis of post-TMS duration of attacks

sham stimulation (n=5) and observed that there was significant benefit in the high-frequency TMS group.[7] Their results showed significant reduction of attack frequency and the number of abortive medications used. rTMS at high-frequency had a sustained effect in reducing attack frequency and the number of medications. This was statistically significant at four weeks and eight weeks ($p<0.0005$). Patients tolerated the therapy though they used a higher stimulation frequency (20 Hz vs. 8 Hz) than that used in our study. Zardouz *et al*. also evaluated the role of rTMS in prophylaxis of chronic migraine.[12] Five patients received five repetitive transcranial magnetic stimulation sessions over a two-month period. These patients responded in the form of reduction of the intensity, frequency, and duration of headaches to the tune of 37.8%, 32.1%, and 31.2%, respectively. This result is consistent with our study findings.

The results in our study and Mishra *et. al*. are similar.[11] They also used a similar type of coil, with a similar frequency (8 Hz for HF-rTMS). Though we used a lower frequency (8 Hz) compared to Brighna *et al*. (20 Hz), and Zardouz *et al*. (10 Hz), and fewer sessions (3 alternate day sessions in our study vs. 12 alternate day sessions in the study by Brighna) and fewer pulses per session (584 pulses in our study vs 2000 pulses in the study by Zardouz), we obtained similar results. [7,12] The results of our study, and the study done by Lan *et al*. are also similar.[10] We found no statistically significant difference in effect between the LF-rTMS group and sham TMS group. We also found that VAS at two weeks was better than VAS at four weeks in the HF-rTMS group. This is most likely because the effect of treatment peaks at two weeks.

Our study was limited by a short follow-up period and a relatively low number of subjects. Multicenter randomised controlled trials with long follow-up periods are needed to confirm the dose, side and location of stimulation, type of coil, and number and frequency of session for standardised treatment.

In conclusion, HF-rTMS is a treatment option for chronic migraine. HF-rTMS of 8 Hz with 584 pulses on left DLPFC in three alternate day sessions is useful in reducing the number of migraine attacks. For a good sustained effect, rTMS sessions may have to be repeated. Our study also reveals that LF-rTMS and sham therapy have no significant role as prophylactic therapy in chronic migraine.

DISCLOSURE

Conflict of interest: None.

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