Randomized Controlled Trial

A Randomized Controlled Trial of High Rate rTMS Versus rTMS and Amitriptyline in Chronic Migraine

Jayantee Kalita, MD, DM[1], Sumit Kumar, DM[1], Varun K Singh, DM[2], Usha K Misra, DM[3]

From: [1]Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh India; [2]Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Uttar Pradesh, India; [3]Department of Neurology, Vivekananda Polyclinic and Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Address Correspondence: Jayantee Kalita, MD, DM Professor Neurology Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow-226014 Uttar Pradesh India E-mail: jayanteek@yahoo.com; jkalita@sgpgi.ac.in

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 11-06-2020
Revised manuscript received: 01-28-2021
Accepted for publication: 01-29-2021

Free full manuscript: www.painphysicianjournal.com

Background: The patients with chronic migraine (CM) respond poorly to pharmacological agents including tricyclic antidepressants, β-blockers, anticonvulsants, calcium channel blockers, flunarizine, and melatonin. The combination of 2 or more pharmacological agents has not shown better efficacy but increased side effects. High rate repetitive transcranial magnetic stimulation (rTMS) has been reported effective in episodic migraine and converts CM to episodic migraine. A combination of high rate rTMS with a pharmacological agent may be more effective compared to rTMS alone.

Objectives: We evaluate the efficacy and safety of 10 Hz rTMS compared to rTMS and amitriptyline in CM.

Study Design: Randomized controlled trial.

Setting: Tertiary care teaching institute in India.

Methods: Patients with CM as per International Classification of Headache Disorder third edition (ICHD-3) beta criteria were included whose age was between 18 years and 55 years. CM was defined if there were 15 headache days per month and at least 8 of these attacks having migraine characteristics for a period of more than 3 months. Patients with major psychiatric, other neurological or systemic disease, and those on migraine prophylaxis were excluded. The demographic details, frequency of headache attacks and headache days per month, migraine triggers, and associated symptoms were noted. The severity of headache was noted using a 0-10 Visual Analog Scale and the number of abortive drugs per month was noted. CM patients were randomly assigned to rTMS (group I) or rTMS and amitriptyline (group II). 10 Hz rTMS was applied using a figure of eight magnetic stimulation coil. The coil was placed over the left frontal cortex corresponding to the hot spot of the right abductor digiti minimi, which is approximately 7 cm lateral from the midline and 2 cm anterior to interaural line. The motor threshold was measured, and 70% of it was used for rTMS. Ten trains of 10 Hz rTMS, each train comprising of 60 pulses with an inter-train interval of 45 seconds were delivered in one session. Three such sessions were delivered on an alternate day and were repeated every month for 3 months. Amitriptyline was prescribed in a dose of 10mg, increased to 25mg after 2 weeks; thereafter increase in dose to 50 mg was optional. The primary outcome was > 50% reduction in headache days, and secondary outcomes were the reduction in severity of headache, abortive drug, and side effects.

Results: Forty-one patients were included in group I and 42 in group II, and their baseline characteristics were comparable. A higher proportion of group II patients had more than 50% reduction in headache days at 3 months (76.2 vs 31.7%; $P < 0.001$) compared to group I. More than 50% reduction in headache severity was also greater in group II compared to group I at 3 months (47.6% vs 19.5%; $P = 0.01$). Side effects were comparable, and none had to be withdrawn.

Limitations: A higher proportion of patients was shifted from group I to group II.

Conclusion: Combination of rTMS and amitriptyline is safe and more effective in CM compared to rTMS alone.

Keywords: Headache, migraine, chronic migraine, transcranial magnetic stimulation, amitriptyline, prophylaxis, noninvasive stimulation, nonpharmacological treatment

Pain Physician 2021: 24:E733-E741

Pain is the cause of the worst morbidity of mankind, and headache is one of the common reasons to visit a physician. The lifetime prevalence of headaches is 66%, and about 90% of patients with migraine have moderate to severe headaches leading to functional impairment in 70% and work loss in 20% (1-4). According to the Global Burden of Disease study in 2012, migraine is the eighth most bothersome disease in the world (5). Migraine is a multifactorial disease having genetic predisposition and environmental influences. Various studies have reported the basis of neurovascular theory, impaired habituation, and sensitization of cortical, thalamic, and brainstem neurons (7-15). Chronic migraine (CM) is more disabling compared to episodic migraine (EM) in terms of household productivities, missing family activities, work loss, and direct cost of treatment. Headache-related disability in CM is 25% compared to 3% in EM. About 5% of migraineurs suffer from CM, which is three times more prevalent in females compared to males. Annually, about 3% of episodic migraineurs convert to CM (16). The prevalence of CM is likely to increase after the International Classification of Headache Disorder third edition (ICHD-3) beta criteria, in which medication overuse headache is not an exclusion criterion (17). Response to treatment is worse in CM compared to EM because of the difference in underlying pathophysiological mechanism. In CM, there is impaired nociceptive processing, impaired pain modulation, altered trigeminovascular and autonomic function, and abortive medication-induced central sensitization (18). Various pharmacological treatments including β-blockers, tricyclic antidepressants, anticonvulsants, and calcium channel blockers have shown not more than 50% efficacy in CM (19,20). A combination of pharmacological agents has shown mild or no additional benefit compared to a single drug, but increased side effects (21,22).

Various non-pharmacological treatments such as ketogenic diet, neutraceutical, cognitive behavioral therapy, biofeedback, psychotherapy, and noninvasive and invasive stimulation techniques are also used in CM (18). In recent years, transcranial magnetic stimulation (TMS) is not only used as a diagnostic tool but also used to understand the pathophysiology and treatment of various neurological diseases. Single-pulse TMS is mainly used for documentation of pyramidal pathway dysfunction for prognosticating stroke, multiple sclerosis, and myelopathy. Paired TMS has been used for understanding excitation and inhibition of cortical neurons in epilepsy and movement disorders. Repetitive TMS is mainly used as a therapeutic tool in migraine, stroke, refractory epilepsy, Parkinson disease and dystonia. A meta-analysis has reported the efficacy of single-pulse TMS in migraine, but its efficacy in CM was not significant (23). Repetitive TMS has shown variable results as a prophylactic treatment of migraine because of variability in the site of rTMS application, stimulation rate and duration, and the number of sessions (24-26). In chronic daily headache, 10 Hz rTMS on left frontal cortex resulted in more than 50% reduction in the frequency of headache attack in 45.7 % only (27). There is impaired modulation of serotonergic pathways in CM leading to the brainstem and cortical neuronal dysexcitability. Transcranial magnetic stimulation has resulted in elevated endorphin levels in migraineurs and has suppressed spreading depression and thalamic neurons in an experimental study (28,29). We hypothesized that combining high rate rTMS with amitriptyline may be able to suppress first, second, and third order neurons activated in CM pathophysiology, and thereby it may be more effective in reducing frequency and severity of headache compared to rTMS alone. In this study, we report the efficacy and side effects of 10 Hz rTMS and amitriptyline compared to amitriptyline alone in patients with chronic migraine.

Methods

This is an investigator initiated trial and conducted in a tertiary care teaching institute in India. The study protocol was designed by JK. The study was approved by the Institute Ethics Committee (2017-207-IP-100) and has been registered in the Clinical Trial Registry of India (CTRI/2018/06/014542). Patients with CM were recruited from the outpatient service of neurology from June 15, 2018, and the last follow up was October 4, 2019. We did not keep a placebo arm because of ethical concerns. Not prescribing any prophylactic treatment to the patients with CM may result in excessive analgesic intake producing health hazards. Ethics Committee did not have any objection regarding the application of rTMS as there are several reports on the safety of rTMS, and we also have done 3 studies on rTMS in migraine without any severe adverse event.

Inclusion Criteria

Patients with CM as per ICHD-3 beta criteria were included whose age was between 18 years and 55 years. Chronic migraine was defined if there were 15 headache days per month and at least 8 of these attacks having migraine characteristics for more than 3 months (17).

Exclusion Criteria

Patients with major psychiatric or neurological disease (stroke, epilepsy, head injury or tumor), malignancy, liver, or kidney failure, on migraine prophylaxis in the last 2 weeks or on immunotherapy, or those unwilling to give consent were excluded. Patients with hypertension, uncontrolled diabetes, bleeding disorders, or pregnancy were also excluded.

Clinical Evaluation

The demographic details (age, gender, education, and residence) and duration of illness were noted. Migraine triggers and allodynia were enquired using a questionnaire (30,31). The details of the frequency of headache and headache days in the previous month and duration of headache were noted. The severity of headache was assessed on a 0-10 Visual Analog Scale (VAS). The number of abortive medications in the previous month was also noted. A detailed medical and neurological examination was done including fundus examination.

Investigations

Blood counts, hemoglobin, erythrocyte sedimentation rate, fasting and 2-hour postprandial blood sugar, serum creatinine, albumin, and calcium were measured. Electrocardiogram, HIV serology, and pregnancy test were done. Cranial computerized tomographic scan (CT) scan was done using third generation CT scan machine. Patients were advised to take paracetamol 650 mg as and when necessary.

Sample Size Calculation

Sample size calculation was done using two-sided z test with pooled variance. The sample size in each group was 41 with 80% power to detect a difference of group proportion of 0.3. A significance level of the test was targeted to 0.05. The proportion of efficacy in rTMS was considered 0.3 and that of rTMS and amitriptyline 0.7. We planned to recruit 45 in each group presuming about 10% drop out.

Randomization

The patients fulfilling the inclusion criteria were randomized to rTMS (group I) or rTMS and amitriptyline (group II) using computer-generated random number by one investigator (JK) and the evaluation (SK) was done by the other. It was an open-labeled randomized controlled trial. The patient was advised to lie on a couch in a right lateral position and 10 Hz rTMS was applied using Magstim Rapid-2 (Whiteland, Walsh, UK) with an air-cooled figure-eight coil of 7 cm diameter. The stimulator was placed anterioposteriorly parallel to midline over the left frontal cortex corresponding to the hot spot of the right abductor digiti minimi, which is approximately 7 cm lateral from the midline and 2 cm anterior to interaural line. The motor threshold was measured and 70% of it was used for rTMS. Ten trains of 10 Hz rTMS, each train comprising of 60 pulses with an inter-train interval of 45 seconds were delivered in one session. Each session comprised of 600 pulses and rTMS was completed in 412.4 seconds. Three sessions of rTMS were delivered on an alternate day and were repeated every month for 3 months. Amitriptyline was started in a dose of 10 mg at bed time and increased to 25 mg at 2 weeks. Thereafter, an increase to 50 mg was optional. Amitriptyline was chosen because of its reported efficacy in migraine, low cost, easy availability, time-tested record, predictable side effects, and not needing laboratory follow-up.

Follow-up

Patients were advised to maintain a headache diary. They were evaluated at 1, 2, and 3 months and their headache days, severity, and number of abortive drugs per month were noted from their headache diary.

Outcome Measure

The primary outcome was ≥ 50% reduction in headache days. The secondary outcomes were the reduction in severity, number of abortive medications, and side effects. The exact frequency of headache, VAS score, and number of abortive medications have also been evaluated in both groups. We have considered 50% reduction in the frequency of headache for a meaningful robust primary outcome. Moreover, the influence of the placebo response could be reduced by considering more than 50% reduction. This may however undermine mild improvement.

Statistical Analysis

Continuous and normally distributed data are presented as mean ± standard deviation (SD), and categorical or skewed continuous variables are expressed as median (range). The baseline characteristics between the 2 groups were compared by chi-square for categorical variables and independent or Mann-Whitney U test for continuous variables. Reduction in headache days, severity, and the number of abortive medications at 1, 2, and 3 months were compared to the baseline within

the group and between the groups using one way analysis of variance (ANOVA). Intention to treat (ITT) and per protocol analysis (PPA) were done for the primary outcome. Reduction in severity and number of abortive medications were compared between the groups at 1, 2, and 3 months by independent t or Mann-Whitney U test. The frequency of side effects between the two groups was compared by chi-square test. A variable having a 2-tailed *P* value of < 0.05 in the test statistics was considered significant. Statistical analysis was done using SPSS software Version 18.0 (IBM Corporation, Chicago, IL) and graphs were prepared using GraphPad Prism 5. The data will be available if needed from JK, VKS and SK.

Results

Ninety patients were screened, and 7 patients were excluded (Fig. 1). This study, therefore, is based on 83 patients. Forty-one patients received rTMS (group I) and 42 both rTMS and amitriptyline (group II). The baseline characteristics were comparable between group I and group II (Table 1).

Follow-up

Six patients in group I and 5 in group II were lost to follow-up. In group II, the remaining 37 patients adhered to treatment protocol. In group I, however, 22 patients shifted to group II due to inadequate response; 17 left the group after one month and 5 after 2 months. These patients were considered as non-responders in intention to treat analysis.

Outcome

On ITT analysis, greater proportion of group II patients had more than 50% reduction in headache days at 2 months (69% vs 29.3%; *P* < 0.001) and 3 months (76.2 vs 31.7%; *P* < 0.001) compared with group I. At one month, 30% of patients converted to EM in group I and 41% in group II. More than 50% reduction in headache severity was also greater in group II compared with group I at one month (21.4% vs 4.9%; *P* = 0.048), 2 months (33.3% vs 12.2%; *P* =0.035), and at 3 months (47.6% vs 19.5%; *P* = 0.01). A reduction in the number of abortive drugs was observed following both treatment modalities. The details of primary and secondary outcomes are presented in Table 2. In group II, a higher proportion of patients on 25 mg of amitriptyline had reduction in headache days (> 50%) compared to those on 50 mg [23/23 (100%) vs 9/14 (64.2%); *P* = 0.002].

Comparison of Outcome Parameters Within and Between the Groups

The number of headache days and severity of headache were reduced at one and 2 months in both group I

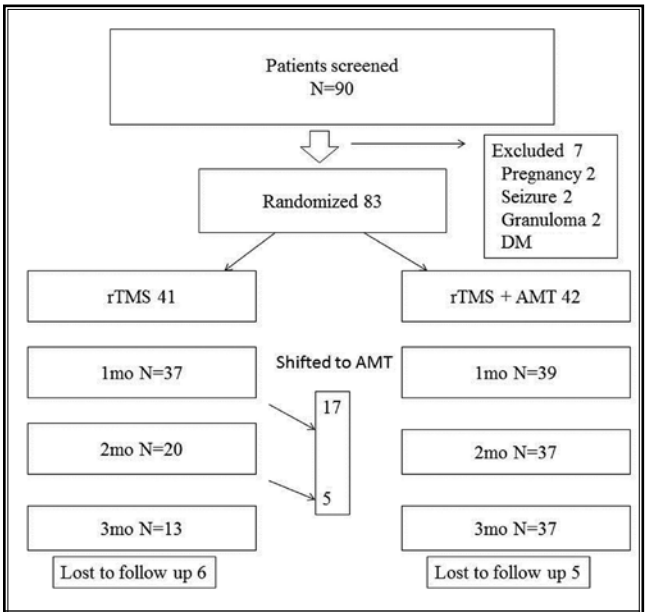

Fig. 1. *Flow chart shows number of patients screened, randomized and number of patients crossed over from group I to group II.*

Table 1. *Comparison of baseline characteristics of CM patients receiving rTMS vs rTMS and AMT.*

Baseline characteristics	rTMS only (n = 41)	rTMS + AMT (n = 42)	*P* value
Age (yrs)	29.85 ± 9.15	32.38 ± 9.64	0.22
Gender (female)	37 (90.2%)	35 (83.3%)	0.35
Rural dwelling	9 (21.9%)	25 (59.5%)	0.001
Total duration (yrs)	6.17 ± 3.64	7.29 ± 4.44	0.21
CM duration (yrs)	1.38 ± 1.23	1.45 ± 1.36	0.48
Nausea	29 (70.7%)	26 (61.9%)	0.70
Photophobia	34 (82.9%)	37 (80.9%)	0.50
Phonophobia	39 (95.1%)	41(97.6%)	0.54
Total no. of triggers	8.27 ± 2.39	8.57 ± 2.67	0.59
Headache days/mo	27.56 ± 5.13	27.02 ± 5.52	0.58
VAS score	8.15 ± 1.31	8.0 ± 0.98	0.56
Number of abortive drug intake	15.90 ± 11.33	18.76 ± 14.21	0.31

Abbreviations: CM = chronic migraine, rTMS = repetitive transcranial magnetic stimulation, AMT = amitriptyline, VAS = Visual Analogue Scale.
Data presented as mean ± SD. SD, Standard deviation or numbers (%)

and in group II. Thereafter their improvement was not significant. The numbers of abortive drug were also significantly reduced in both the groups. The details are presented in Fig. 2. Comparing the headache days, VAS score, and number of abortive drugs did not differ significantly, except headache days and VAS scores at one month were lower in group II when compared with group I (Fig. 3).

Subanalysis of Patient Dropouts from group I

Twenty-two patients who shifted from group I to II were analyzed separately. Twelve patients received 25 mg and 10 received 50 mg of amitriptyline. At 3 months (2 months of amitriptyline), 16 (73%) patients had > 50 % reduction in headache days and 12 (54%) had > 50% reduction in severity.

Adverse Events

Adverse events were milder, and none had to be withdrawn from the treatment protocol. Noise and headache during rTMS were experienced by the majority. Dry mouth was more commonly experienced by the patients receiving amitriptyline (11 vs 5). The details are presented in Table 3.

Discussion

In CM, adjunctive amitriptyline with high rate rTMS was better in terms of reduction in headache days (76.2% vs 31.7%) and VAS score (47.6% Vs 19.5%) at 3 months compared with rTMS alone. More than 50% of patients in the rTMS group shifted to adjunctive amitriptyline treatment after one month due to inadequate response. At one month, 30% of patients in group I and 41% in group II converted to EM. This study highlights the role of adjunctive amitriptyline treatment with rTMS in CM. In our earlier study on chronic daily headache, patients receiving 3 sessions of 10 Hz rTMS on the left frontal cortex, monthly for 3 months had a marginal reduction in headache frequency (59.6% vs 52.2%) compared with a single session monthly for 3 months. Chronic daily headache converted to episodic headache of 74.4% in the patients who

Table 2. *Comparison of primary and secondary outcomes at 1, 2, and 3 months in CM patients receiving rTMS vs rTMS and AMT on intention to treat analysis.*

Primary outcome	rTMS (n = 41)	rTMS +AMT (n = 42)	*P* value
1 month			
> 50% freq ↓	11 (26.8%)	20 (47.6%)	0.069
> 50% VAS ↓	2 (4.9%)	9 (21.4%)	0.048
2 months			
> 50% freq ↓	12 (29.3%)	29 ((69%)	0.0004
> 50% VAS ↓	5 (12.2%)	14 (33.3%)	0.035
3 months			
> 50% freq ↓	13 (31.7%)	32 (76.2%)	< 0.0001
> 50% VAS ↓	8 (19.5%)	20 (47.6%)	0.01

Abbreviations: CM = chronic migraine, rTMS = repetitive transcranial magnetic stimulation, AMT = amitriptyline, Freq = frequency, VAS = Visual Analog Scale.

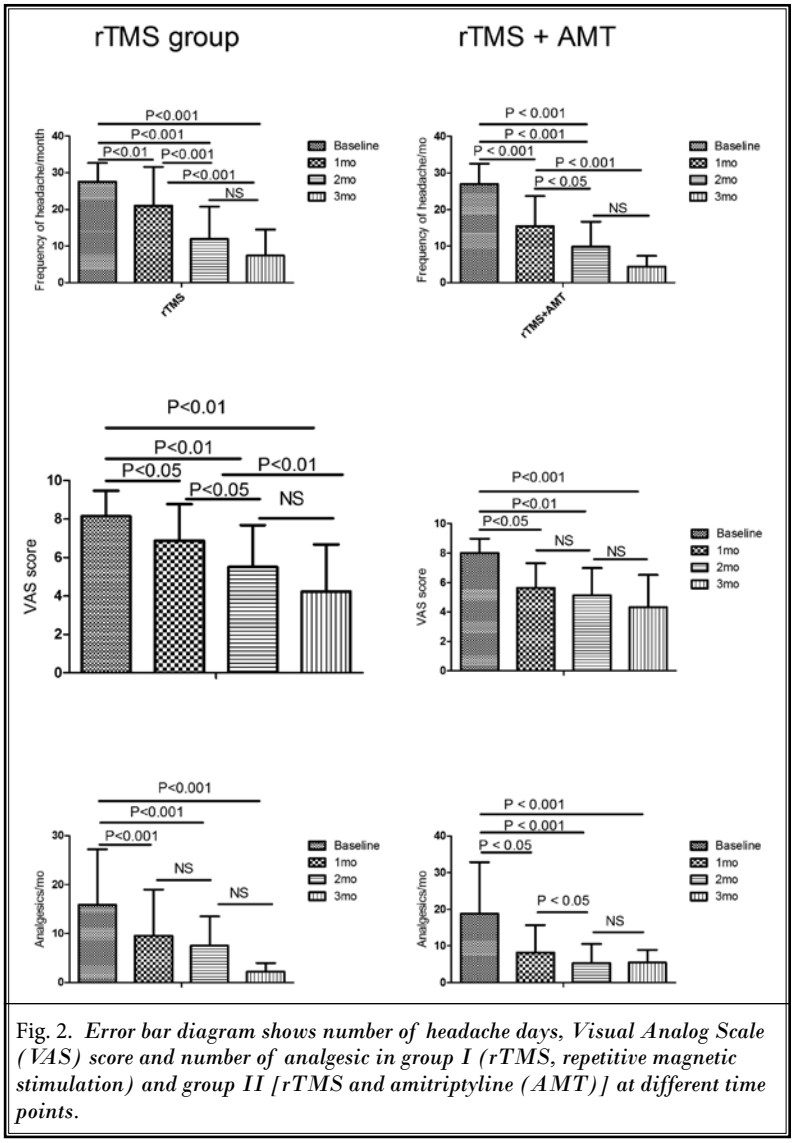

Fig. 2. *Error bar diagram shows number of headache days, Visual Analog Scale (VAS) score and number of analgesic in group I (rTMS, repetitive magnetic stimulation) and group II [rTMS and amitriptyline (AMT)] at different time points.*

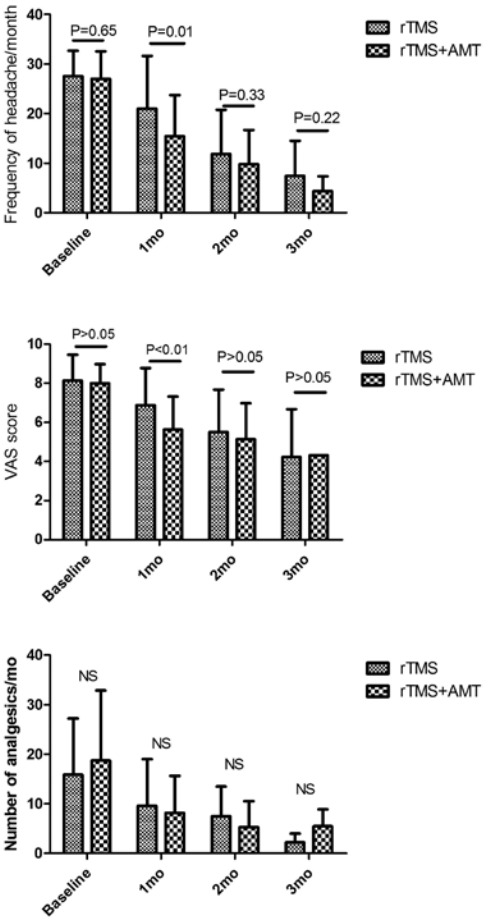

Fig. 3. *Error bar diagram shows comparison of headache days, Visual analogue Scale (VAS) score and number of abortive medications in group I (repetitive transcranial magnetic stimulation, rTMS) compared to group II [rTMS and amitriptyline (AMT)].*

Table 3. *Comparison of side effects of rTMS group vs rTMS and AMT group in patients with CM.*

Side effects	rTMS (n = 41)	rTMS + AMT (n = 42)	*P*
Rhinorrhea	4	4	0.97
Tearing	14	7	0.07
Pain	36	32	0.17
Noise	22	23	0.92
Dry mouth	5	11	0.64
Sedation	3	6	0.85

Abbreviations: CM = chronic migraine, rTMS = repetitive transcranial magnetic stimulation, AMT = amitriptyline.

received 3 sessions of rTMS compared to 59. 2 % receiving a single session (27). In this study, we therefore used 3 sessions on alternate days per month rather than a single session per month, although it has caused more frequent visits to the hospital. Deen et al have reported results of controlled trials in CM. Out of 16 studies, 13 were randomized controlled trials (double-blind, placebo-controlled); 6 of these studies evaluated efficacy of oral medicine, 5 evaluated injectable medications (4 calcitonin gene-related peptide [CGRP] monoclonal antibody, one botulinum toxin), 5 nerve block, and no combined rTMS and pharmacotherapy (32). CM is a disabling disease incurring a higher economic loss, work loss, visit to the physician and lower productivity, but only few studies have evaluated efficacy of a combination of prophylactic treatment (21,22). Silberstein et al conducted a randomized double-blind trial in which patients with CM were randomized to topiramate (50 to 100 mg/day), topiramate and propranolol (240 mg/day) or topiramate and placebo. The addition of propranolol did not result in better efficacy compared to placebo (21). In another study, CM patients either on nortriptyline or propranolol were randomly prescribed melatonin (3 mg/day), valproate (200 mg/day) or placebo. Adjunctive melatonin or valproate was significantly effective in reducing attack frequency, severity, duration, number of abortive medications, and headache-induced disability. Melatonin was superior to valproate (22). In a study on 62 patients with CM, a comparison of topiramate and flunarizine revealed better efficacy of flunarizine in reducing total migraine days (-4.3 vs -1.4) and abortive medication (-4.6 vs -0.5) compared with topiramate. In the flunarizine group, 58.6% of patients had > 50% reduction in headache frequency compared to 25.9% in the topiramate group. Adverse effects were noted in 37.9% in the flunarizine group, and 51.9% in the topiramate group (33). The adverse effects of topiramate at recommended dose of 100 mg ranges between 66% and 82.5% (34-36). Better efficacy of flunarizine has been attributed to dopa blockade and serotonin modulation. The responder rate of various monoclonal antibodies against CGRP ranges between 50% and 75% with side effects comparable to placebo (37). Pooled analysis of 2 studies on onabotulinum toxin A in chronic migraine has revealed > 50% reduction in headache days in 49.3% after the first cycle, 11.3% after the second cycle, and 10.3% after third cycle of injections (38). This study highlights that a repeat injection may improve the responder rate in CM who fails to respond after the first cycle. We also ob-

served increasing responder rates in terms of headache days at second and third months in both groups. The efficacy of amitriptyline has been also been reported in migraine prophylaxis (39-41). In a study, divalproate resulted in faster response, but at 6 months amitriptyline was equally effective in the reducing frequency of headach (39). We have used 25-50 mg of amitriptyline, because the pain modulating effect of amitriptyline is observed at a lower dose, and at a higher dose, it works as an antidepressant.

Low-frequency rTMS (1Hz) reduces neuronal excitability and high-frequency rTMS increases neuronal excitation. In a recent systematic review and meta-analysis, the pooled analysis of 3 studies on high rate rTMS over left motor cortex in migraine favored a positive effect with a median effect size of -0533, 95% CI 0.940 to -0.126 (27,31,42,43). Two other studies using 5 Hz over the dorsolateral prefrontal cortex have reported contradictory results. The pooled analysis of 2 other studies using 5 Hz in one (44) and theta-burst in another (45) over the left dorsolateral prefrontal cortex did not favor a positive effect (43).

Multiple mechanisms of TMS have been attributed to migraine relief. In CM, there is a deficit in serotonergic response from the brainstem to thalamus to cortex, reduced level of endorphin, increased glutaminergic and reduced GABAergic pathway along with imbalance of various ion channels (9,14,15,29,46,47). High rate rTMS may result in structural remodeling of dendritic spines by remodeling postsynaptic gephyrin scaffolds along with modifying synaptic GABAergic strength. High rate rTMS also increases endorphin level in patients with migraine (24). Repetitive TMS influences brain excitability on target and distant region belonging to the same network varying in structural connectivity between long-range areas. We have stimulated left frontal region corresponding to hotspot of abductor digiti minimi due to our earlier experience (24,27), and report on experimental and human studies in reducing pain (48). Thalamus is consistently active during a migraine and is a pivotal area for hypersensitivity to various sensory stimuli especially to visual and mechanical allodynia. In an experimental study of migraine, a single TMS was able to suppress propagation of cortical spreading depression, and spontaneous or evoked firing rate of third order neuron, but not able to suppress the second order neuron (trigeminothalamic tract). C-fiber activation during TMS also inhibits corticothalamic neurons thereby suppressing third order neuron (28). Modulation of trigeminocervical complex and trigeminothalamic tract is important for management of migraine headache and may be modulated by CGRP blockers or tricyclic antidepressant.

None of our patients had severe adverse effects necessitating withdrawal of rTMS or amitriptyline. More than half the patients in both the groups had mild to moderate discomfort due to noise and contraction of muscles during rTMS, but none opted out.

Limitation

We did not have placebo arm due to ethical issues because all the patients had more than 15 headache days monthly and giving them frequent abortive medications may not be appropriate. Eleven patients were lost to follow up, which is comparable in both arms. About 50% of patients opted for additional amitriptyline treatment due to inadequate headache relief and 73% of them had significant reduction in headache days following combination treatment.

Conclusion

In CM, three sessions of 10 Hz rTMS monthly for 3 months on the left primary motor cortex in combination with amitriptyline is better in reducing headache days and severity compared to rTMS alone. These results are applicable to the patients with CM in general.

Acknowledgement

We thank Mr. Shakti Kumar for secretarial help.

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