Original Article

Role of Repetitive Transcranial Magnetic Stimulation in Treatment of Fibromyalgia: A Randomized Controlled Trial

Arvind Kumar Kankane, Atul Kumar Pandey, Patil Manish Ramesh, Arpit Agarwal
Department of Neurology, MLB Medical College Jhansi, Uttar Pradesh, India

Abstract

Background and Objective: Fibromyalgia syndrome (FMS) is a chronic disease characterized by widespread, persistent musculoskeletal pain in association with impaired health-related quality of life. Repetitive transcranial magnetic stimulation (rTMS) is an emerging tool for the management of fibromyalgia. There is no standardized protocol of rTMS for the treatment of FMS, and both low- and high-frequency stimulation of the dorsolateral prefrontal cortex (DLPFC) are described in the literature with variable efficacy. The objective of this study was to determine the effectiveness of rTMS in people with fibromyalgia and compare the response of low- and high-frequency stimulation with sham stimulation. **Materials and Methods:** This study was a single-blinded, randomized, placebo-controlled trial. Ninety patients with the diagnosis of FMS were randomly allocated into one of the following three groups: low-frequency (1 Hz) group, high-frequency (10 Hz) group, and sham group. Pain, depression, anxiety, and quality of life were measured using the Numerical Pain Rating Scale (NPRS), Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HDRS), and Revised Fibromyalgia Impact Questionnaire (FIQR) immediately following treatment as well as at 1 and 3 months after treatment. The data was statistically analyzed using Statistical Package for the Social Sciences version 23 software. *P* value < 0.05 was considered statistically significant. **Results:** Intergroup analysis revealed a significant improvement in NPRS, HAM-A, HDRS, and FIQR scores in both low- and high- frequency groups immediately following treatment and for 3 months after treatment. No significant difference in the efficacy of low- and high-frequency stimulation was noticed. **Conclusions:** rTMS is an effective mode of treatment in people with FMS. Both low and high frequencies of stimulation at DLPFC are equally effective in reducing pain and associated symptoms.

Keywords: Dorsolateral prefrontal cortex, fibromyalgia, high frequency, low frequency, rTMS

Introduction

Fibromyalgia syndrome (FMS) is a chronic condition characterized by widespread, noninflammatory, persistent musculoskeletal pain in association with impaired health-related quality of life (QoL). The prevalence of FMS is increasingly witnessed in women, afflicting approximately 2%–4% of the general population.[1,2] The etiopathogenesis of FMS is not completely understood, but recent studies have suggested a process of central hyperexcitability as one of the mechanisms.[3,4] This hyperexcitability at the central level results in a lowered threshold in the afferent sensory nerves and increased sensitivity toward pain stimuli.[5] The primary motor cortex (M1) and the dorsolateral prefrontal cortex (DLPFC) are pivotal in the release of endogenous opioids and management of central pain.[6] Studies have observed that the severity of central sensitization for pain is associated with a number of tender points.[7,8] Following treatment, a reduction in the number of tender points might be associated with improved central sensitization.[9] Based on variable pathophysiology, the recommended treatment strategies include pharmacologic and physical exercises along with psychologic interventions.[6] There is no single strategy that is completely effective in managing FMS; therefore, research is underway to find an effective mode of therapy. Repetitive transcranial magnetic stimulation (rTMS) is a safe and noninvasive method employed to manage fibromyalgia, movement disorders, and psychiatric illnesses.[10,11] Although the exact mechanism of rTMS remains unclear, the modulation of afferent neurons and activation of endogenous opioid analgesic mechanisms in the central nervous system are possible modes of action.[9,12] Therapeutic response of rTMS depends on the stimulation target as well as the frequency and intensity of stimulation.[13] A recent study has suggested that stimulation of the left DLPFC is more effective in the management of pain and physical role functioning in comparison to stimulation of M1.[14] There is evidence that rTMS of DLPFC affects the activity of a network of structures involved in the integration and modulation of pain signals, including the thalamus, brainstem, insular cortex, and cingulate cortex.[15] Neuroimaging studies have also established that

Address for correspondence: Prof. Arvind Kumar Kankane, Department of Neurology, MLB Medical College, Jhansi - 284 128, Uttar Pradesh, India.
E-mail: akankane2014@gmail.com

Submitted: 25-Nov-2023 **Revised:** 21-Mar-2024 **Accepted:** 03-Apr-2024
Published: 26-Apr-2024

DOI: 10.4103/aian.aian_1041_23

DLPFC might play a role in top–down patterns of inhibition and modulating pain perception through descending fibers of the prefrontal cortex.[16] Long-term changes in brain activity induced by rTMS depend on the frequency of stimulation. Low-frequency (typically 1 Hz) or high-frequency (typically 10 Hz or more) rTMS protocol leads to decrease or increase in cortical excitability, thought to result from the mechanism of long-term depression (LTD) or long-term potentiation (LTP), respectively.[13] Intensity of stimulation is typically individualized and based on resting motor threshold (RMT). The protocols for rTMS in different diseases are designed based on the cumulative evidence gained from multiple clinical trials, meta-analyses, expert opinions, and recommendations. The US Food and Drug Administration (US FDA) has approved high-frequency (10 Hz) stimulation of left DLPFC for treatment of depression.[13] Low-frequency (1 Hz) rTMS on the right DLPFC is also recommended in patients of depression associated with comorbid anxiety and obsessive–compulsive disorder. There is no standard protocol of rTMS for the treatment of FMS. In various previous studies, the researchers have employed high-frequency rTMS on the left DLPFC[17] and low-frequency rTMS on the right DLPFC,[6] with variable responses on pain and associated symptoms of FMS. Based on these previously used rTMS protocols as references, we conducted this randomized controlled trial to evaluate the effectiveness of rTMS in people with FMS by comparing the response of low- and high-frequency stimulation with a parallel sham-controlled group.

Study design

The study was a randomized, single-blinded, sham-controlled trial that was conducted to evaluate the efficacy and safety of low- and high-frequency rTMS in people with FMS. The study was conducted in the Department of Neurology and Psychiatry at Maharani Laxmi Bai (MLB) Medical College, Jhansi, Uttar Pradesh, India, after receiving ethical approval from the Institutional Ethics Committee (Ref. No: 44/IEC/1/2021 Dated 05/04/23). The study was registered at the Clinical Trials Registry- India (CTRI/2023/04/051395) before initiation. All the patients involved in the study provided written informed consent for their voluntary participation before their enrollment in the study. The guidelines of Consolidated Standards of Reporting Trials (CONSORT) were adhered to.

Study population

People aged 18-80 years with FMS, as defined by the American College of Rheumatology guidelines 2010, were selected from the outpatient department of neurology and psychiatry, MLB Medical College, Jhansi, Uttar Pradesh, India, between April 2023 and September 2023. Patients were excluded if they (i) were unable to give written informed consent; (ii) had a history of trauma, seizures, tinnitus, or any illness involving the brain; (iii) were under medications which reduced the threshold of seizures, such as tramadol, acetylcholinesterase inhibitors, anticholinergics, antiemetics, antihistamines, baclofen, ß-blockers, cephalosporins, cyclosporine, etc.; (iv) had implants of defibrillators, neurostimulators, or cardiac pacemakers; (v) were pregnant or lactating women; (vi) had chronic systemic disease, inflammatory joint diseases, or other secondary FMS, that is, hypothyroidism, nutritional deficiency, diabetes mellitus, connective tissue disorder; (vii) were substance dependent; or (viii) had psychiatric disorder, that is, schizophrenia and other psychotic disorder, bipolar disorder, or personality disorder.

Randomization, blinding, and intervention

People diagnosed with FMS underwent a screening process for the inclusion and exclusion criteria. The demographic characters and medical history were recorded, along with physical and vital examinations. Following screening, eligible patients were randomized through an allocation-concealed randomization list to one of the three treatment groups: group A (high-frequency rTMS), group B (low-frequency rTMS), or group C (sham rTMS). To maintain privacy, an identification number was assigned to each patient based on his or her sequence of enrollment. The patients were blinded to the treatment interventions (single blinded) until the completion of the study. They were treated according to their assigned groups as presented in Table 1. All patients were advised to follow a prescribed medical treatment plan in terms of physical therapy, psychotherapy, and pharmacotherapy as per recommendations.[18] Pharmacotherapy employed in these patients included tricyclic compounds (amitriptyline 10–25 mg/day), gabapentinoids (pregabalin 75–300 mg/day and gabapentin, 300–1200 mg/day), and serotonin–norepinephrine reuptake inhibitors (duloxetine 30–60 mg/day). Analgesics and other supportive treatments were prescribed according to requirements.

rTMS protocol

Magstim Super rapid^2 Plus^1 (Minnesota, USA) TMS was utilized for repetitive magnetic stimulation of the brain. Real rTMS was administered using a butterfly coil, and sham stimulation was delivered with a sham coil provided by the manufacturer. RMT was determined using a single-pulse stimulation over M1 to locate an optimal stimulation area on the scalp. RMT was defined as the lowest stimulus intensity that could elicit at least five twitches in the abductor pollicis brevis muscle out of 10 consecutive stimuli given over M1. For the determination of DLPFC, the TMS coil was aligned in a parasagittal line 5 cm anterior from the "motor hot area" M1. rTMS was delivered at DLPFC for 5 days a week for two successive weeks (a total of 10 sessions). The rTMS protocol employed in different groups is presented in Table 1.

Sample size calculation

Following adjustment of the alpha error multiple comparisons among the three groups and assuming 80% power of the study and a 95% confidence interval, the sample size was found to be 74 patients in each group ($N = 222$). We predicted that only 150 patients satisfying the inclusion criteria might be available for the study during the data collection period at our study center. Based on finite population correction, a total of 90 patients, 30 in each group, were considered for the study.

Table 1: Details of rTMS protocol in different groups

Group	Frequency (Hz)	Stimulus intensity to evoke MEP (% RMT)	Number of stimulations per train	Pause between runs (s)	Total duration (minutes)	Number of sessions	Site of stimulation (DLPFC)
A	10	80	10	20	20	10	Left
B	1	80	150	60	27	10	Right
C	1	80	150	60	27	10	Right

DLPFC=Dorsolateral prefrontal cortex, MEP=Motor evoked potential, RMT=Resting motor threshold, rTMS=Repetitive transcranial magnetic stimulation

Outcome measures

To evaluate the long-term effectiveness of the intervention, both primary and secondary outcomes were measured at 1 and 3 months.

Primary outcomes

The primary outcome was the change in the intensity of pain from baseline to immediately posttreatment and 1 and 3 months after treatment, which was assessed using the Numerical Pain Rating Scale (NPRS).[19]

Secondary outcomes

The secondary outcomes were the assessment of depression, anxiety, and QoL using the Hamilton Depression Rating Scale (HDRS),[20] the Hamilton Anxiety Rating Scale (HAM-A),[21] and the Revised Fibromyalgia Impact Questionnaire (FIQR),[22] respectively, from baseline to immediately posttreatment and 1 and 3 months after treatment.

Safety assessment

Safety of rTMS was assessed immediately posttreatment and 1 and 3 months after treatment. The patients were advised to contact the investigator or the research team immediately in the event of adverse effect (s).

Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences version 23 (IBM Statistics for Windows, Chicago, IL, USA). One-way analysis of variance (ANOVA) and paired t-test were employed for normally distributed data, while the Kruskal–Wallis test was used to compare variables with non normal distribution. The Chi-squared test and the Fisher's exact test were utilized for categorical values. P value < 0.05 was considered statistically significant.

Results

A total of 340 patients were screened for eligibility. Out of them, 90 were randomized, 30 in each group, and all were females. The CONSORT flow chart is shown in Figure 1. The mean age ± standard deviation was 41.38 ± 11.35, ranging from 18 to 75 years. The median (interquartile range) of age was 40.00 (34.00–50.00) years. There was no comorbidity among patients in each group. The baseline demographic data is presented in Table 2.

NPRS score

The NPRS score was significantly decreased in low-frequency, high-frequency, and sham groups immediately post-rTMS ($P < 0.001$). Furthermore, the change (percent change from baseline) in NPRS was significant at 1 and 3 months ($P < 0.001$) in both low- and high-frequency groups, but not in the sham group [Table 3].

HDRS score

The HDRS score was significantly decreased in the low-frequency rTMS group at 1 month ($P = 0.003$) in comparison to the high-frequency group ($P = 0.088$) and the sham group. However, the change (percent change from baseline) in HDRS was observed at 3 months in both low-frequency ($P < 0.001$) and high-frequency ($P = 0.008$) groups, while the phenomenon was not observed in the sham group [Table 3].

HAM-A score

The HAM-A score was significantly decreased in the high-frequency group immediately post-rTMS ($P = 0.030$) in comparison to the low-frequency group ($P = 0.166$) and the sham group. The change (percent change from baseline) in HAM-A was observed at 1 and 3 months in both low-frequency ($P = 0.015$ and $P = 0.006$ at 1 and 3 months, respectively) and high-frequency ($P = 0.004$ and $P = 0.013$ at 1 and 3 months, respectively) groups [Table 3].

FIQR score

The FIQR score was significantly decreased in low-frequency, high-frequency, and sham groups immediately post-rTMS ($P < 0.001$). The change (percent change from baseline) in FIQR was significant at 1 and 3 months ($P < 0.001$) in both low- and high-frequency groups in comparison to the sham group [Table 3].

Adverse events

Two adverse events (dizziness and headache) were reported during the study. Dizziness was reported by two patients in the high-frequency rTMS group and one patient in the low-frequency rTMS group. Headache was reported by one patient each in the low- and high-frequency groups.

Discussion

The present study compares the effectiveness of low-frequency and high-frequency rTMS in relieving pain and associated symptoms among people with FMS. Studies found that rTMS could cause changes in brain activity and have aftereffects on the brain, such as LTP or LTD, and the aftereffects induced by rTMS depend on the frequency and duration of stimulation.[16] Low-frequency stimulation has an inhibitory effect on brain

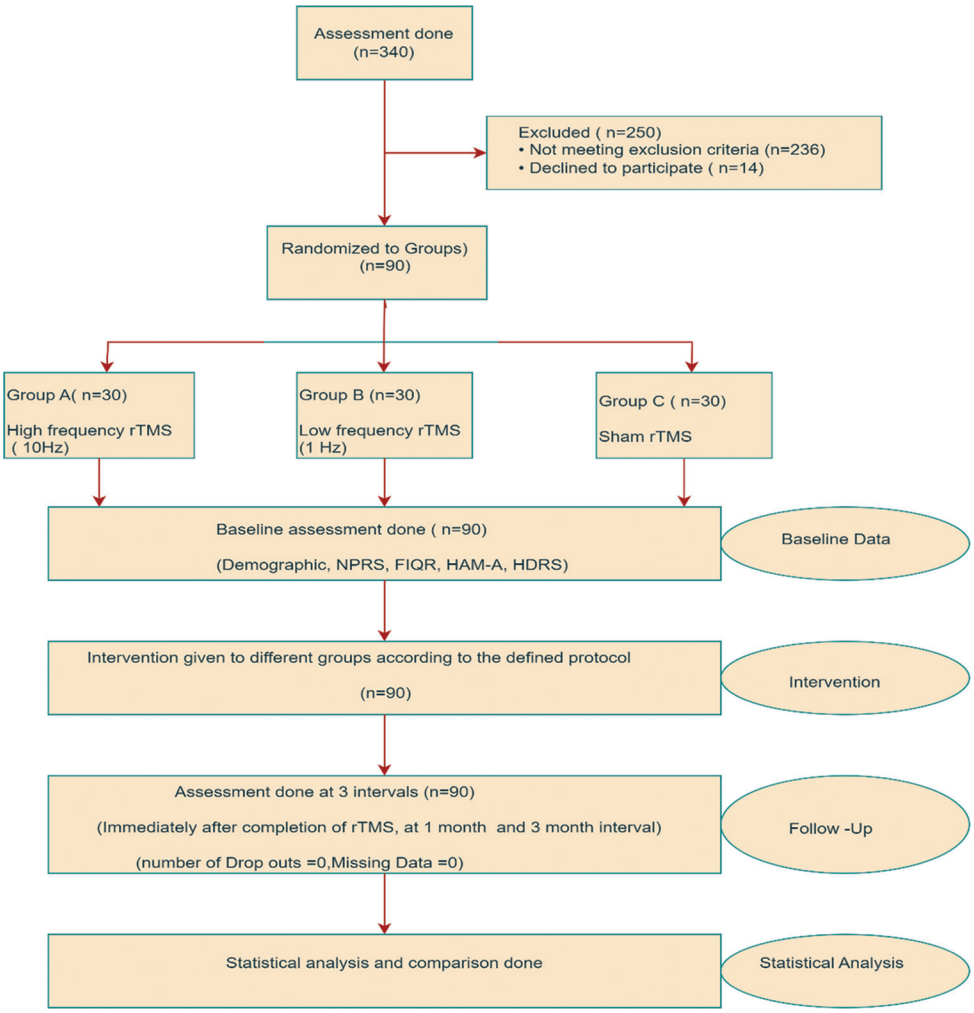

Figure 1: CONSORT flow chart of patients enrolled in the study. CONSORT = Consolidated Standards of Reporting Trials, FIQR = Revised Fibromyalgia Impact Questionnaire, HAM-A = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, NPRS = Numerical Pain Rating Scale, rTMS = repetitive transcranial magnetic stimulation

activity, whereas high-frequency stimulation increases cortical excitability.[23] The underlying mechanism of prefrontal rTMS might consist of the release of endogenous opioids and modulation of the frontolimbic network.[24] Researchers have reported that low-frequency stimulation of DLPFC could significantly reduce pain and related symptoms by targeting spinal pain circuits and top–down modulation,[6] whereas high-frequency stimulation might achieve direct antinociceptive effects by activating descending pain inhibitory controls.[25]

In this randomized, sham-controlled study, we found that both low- and high-frequency rTMS at DLPFC are effective and safe for the management of pain, depression, and anxiety, thereby improving the QoL in people with FMS. Immediately post-rTMS, the level of pain experienced by both low- and high-frequency groups was significantly reduced, which continued for 3-month follow-up period. Similarly, anxiety was reduced immediately post-rTMS in high-frequency group patients. In subsequent 1 and 3 months, this improvement was observed in both low- and high-frequency groups in comparison to the sham group. Depression was reduced at 1 month in the low-frequency group and at 3 months in both groups. QoL was significantly improved in both low- and high-frequency groups immediately post-rTMS, which further continued for 3-month follow-up period. FMS manifests with chronic pain associated with anxiety and depression, leading to poor QoL.[26] Studies have demonstrated the effectiveness of rTMS in the management of pain along with anxiety and depression associated with FMS. A significant improvement is reported in pain and depression with high-frequency (10 Hz) rTMS in the left DLPFC.[27] Also, a low-frequency (1 Hz) rTMS in the right DLPFC is reported to be effective in reducing pain and associated symptoms of FMS.[6] Studies have demonstrated that the brain matrix involved in the modulation and processing of pain includes DLPFC, anterior cingulate, primary somatosensory and motor cortex, insula, striatum, thalamus, amygdala, and hippocampus.[6] Modulation of these cortical areas by both low- and high-frequency rTMS leads to relief of pain and associated symptoms of FMS.[16] We

Table 2: Demographic and baseline characteristics of study participants

Parameters	Group			*P*
	A (*n*=30)	B (*n*=30)	C (*n*=30)	
Age in years, mean (SD)	43.23 (14.71)	38.13 (7.33)	42.77 (10.43)	0.158
Age, *n* (%)				0.194
18–30 years	6 (20.0)	5 (16.7)	3 (10.0)	
31–40 years	8 (26.7)	13 (43.3)	11 (36.7)	
41–50 years	5 (16.7)	10 (33.3)	7 (23.3)	
51–60 years	7 (23.3)	2 (6.7)	8 (26.7)	
61–70 years	3 (10.0)	0 (0.0)	1 (3.3)	
71–80 years	1 (3.3)	0 (0.0)	0 (0.0)	
Marital status, *n* (%)				0.318
Married	27 (90.0)	30 (100.0)	29 (96.7)	
Unmarried	3 (10.0)	0 (0.0)	1 (3.3)	
Duration of illness in months, mean (SD)	14.73 (7.47)	13.27 (6.25)	13.13 (8.28)	0.397
BMI (kg/m^2), mean (SD)	24.78 (2.84)	24.96 (2.82)	25.56 (2.82)	0.541
Systolic BP (mmHg), mean (SD)	118.80 (11.06)	118.40 (10.67)	118.47 (11.30)	0.989
Diastolic BP (mmHg), mean (SD)	71.93 (8.35)	70.93 (9.09)	72.33 (8.57)	0.813
Pulse rate (beats per minute), mean (SD)	79.27 (13.30)	74.83 (11.23)	78.60 (11.54)	0.271
Baseline scales, mean (SD)				
NPRS	5.94 (1.09)	6.15 (0.73)	5.49 (0.90)	0.022
FIQR	66.87 (7.79)	61.60 (10.27)	57.50 (14.01)	0.006
HAM-A	19.40 (7.15)	19.87 (7.11)	19.17 (8.49)	0.749
HDRS	20.30 (5.42)	21.33 (7.88)	18.10 (5.30)	0.179
Medication before trial, *n* (%)				
Analgesics	26 (86.7)	30 (100.0)	26 (86.7)	0.119
Antidepressants	12 (40.0)	8 (26.7)	8 (26.7)	0.436
Anticonvulsants	14 (46.7)	16 (53.3)	14 (46.7)	0.837

Group A: high-frequency rTMS, Group B: low-frequency rTMS, group C: sham rTMS. BMI=Body mass index, BP=Blood pressure, FIQR=Revised Fibromyalgia Impact Questionnaire, HAM-A=Hamilton Anxiety Rating Scale, HDRS=Hamilton Depression Rating Scale, NPRS=Numerical Pain Rating Scale, rTMS=Repetitive transcranial magnetic stimulation, SD=Standard deviation

Table 3: Different scales and their change from baseline to immediately posttreatment and 1 and 3 months after treatment

Measured scale	Time of assessment	Group			χ^2	*P*
		A (*n*=30)	B (*n*=30)	C (*n*=30)		
NPRS	Baseline	5.94 (1.09)	6.15 (0.73)	5.49 (0.90)	7.676	0.022
	Post-rTMS	2.15 (0.87)	2.12 (0.15)	3.47 (0.89)	37.059	<0.001
	1 month	2.51 (0.87)	2.47 (0.62)	4.09 (0.96)	41.489	<0.001
	3 months	2.68 (1.08)	2.45 (0.62)	4.34 (0.70)	42.364	<0.001
FIQR	Baseline	66.87 (7.79)	61.60 (10.27)	57.50 (14.01)	5.474	0.006
	Post-rTMS	29.14 (12.30)	23.03 (4.58)	43.90 (11.36)	40.381	<0.001
	1 month	29.71 (13.66)	25.05 (5.81)	49.61 (9.14)	43.853	<0.001
	3 months	31.55 (15.28)	25.35 (6.75)	49.59 (6.81)	40.381	<0.001
HAM-A	Baseline	19.40 (7.15)	19.87 (7.11)	19.17 (8.49)	0.577	0.749
	Post-rTMS	12.83 (3.72)	13.67 (4.26)	16.40 (5.68)	7.115	0.029
	1 month	12.83 (4.65)	12.93 (3.74)	16.87 (5.34)	12.230	0.002
	3 months	13.00 (5.53)	12.47 (3.77)	16.93 (5.42)	11.749	0.003
HDRS	Baseline	20.30 (5.42)	21.33 (7.88)	18.10 (5.30)	3.440	0.179
	Post-rTMS	13.13 (4.45)	14.00 (4.40)	15.73 (3.81)	5.390	0.068
	1 month	14.27 (5.73)	13.07 (4.58)	16.87 (4.04)	11.035	0.004
	3 months	13.77 (6.47)	11.27 (3.34)	17.27 (3.81)	22.816	<0.001

Group A: High-frequency rTMS, Group B: Low-frequency rTMS, Group C: Sham rTMS. Values are expressed as mean (SD). FIQR=Revised Fibromyalgia Impact Questionnaire, HAM-A=Hamilton Anxiety Rating Scale, HDRS=Hamilton Depression Rating Scale, NPRS=Numerical Pain Rating Scale, rTMS=repetitive transcranial magnetic stimulation, SD=Standard deviation

planned this study in the Indian population to compare the effectiveness of low- and high-frequency rTMS over sham intervention in FMS and found significant pain reduction immediately post-rTMS and up to 3 months of follow-up in

both low and high frequencies. Our findings are consistent with other Asian studies which also reported the efficacy of low- and high-frequency rTMS over sham control up to 1-month follow-up.[28] rTMS is US FDA approved for the treatment of pharmacotherapy-resistant depression, with five treatment sessions of high frequency (10 Hz) over the left DLPFC for 4–6 weeks.[13,29] According to a meta-analysis, high-frequency rTMS stimulation at the left DLPFC significantly improved the treatment of depression.[30] In our study, HDRS and HAM-A scores were significantly reduced at 1 and 3 months in both low- and high-frequency rTMS in comparison to the sham group. LTP of neuronal activity plays a key role in the therapeutic effects of rTMS, although the complete mechanism behind this remains unexplored.[23,31] rTMS is also reported to improve QoL in fibromyalgia when applied through left M1 or DLPFC (10 Hz)[16,32] and right DLPFC (1 Hz).[6] The results of our study also support this evidence and found that QoL is significantly improved following rTMS treatment at both low and high frequencies in comparison to the sham group.

Although the sample size of our study is small, the findings are similar to previous reports. Studies with a larger sample size including both genders with long-term follow-up shall be warranted.

Conclusion

In conclusion, rTMS is a safe and effective therapeutic option for treating people with fibromyalgia. Both low- and high-frequency rTMS over DLPFC are equally effective in improving pain and associated symptoms (depression and anxiety) along with QoL. It can be employed as an alternative option or a supplementary treatment in cases where standard medical treatment is not producing adequate or desired results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Galvez-Sánchez CM, Reyes Del Paso GA. Diagnostic criteria for fibromyalgia: Critical review and future perspectives. J Clin Med 2020;9:1219.
2. Galvez-Sánchez CM, Montoro CI, Duschek S, Reyes del Paso GA. Depression and trait-anxiety mediate the influence of clinical pain on health-related quality of life in fibromyalgia. J Affect Disord 2020;265:486–95.
3. Hazra S, Venkataraman S, Handa G, Yadav SL, Wadhwa S, Singh U, *et al*. A cross-sectional study on central sensitization and autonomic changes in fibromyalgia. Front Neurosci 2020;14:788.
4. Richard JY, Hurley RA, Taber KH. Fibromyalgia: Centralized pain processing and neuroimaging. J Neuropsychiatry Clin Neurosci 2019;31:A6-187.
5. Eller-Smith OC, Nicol AL, Christianson JA. Potential mechanisms underlying centralized pain and emerging therapeutic interventions. Front Cell Neurosci 2018;12:35.
6. Tanwar S, Mattoo B, Kumar U, Bhatia R. Repetitive transcranial magnetic stimulation of the prefrontal cortex for fibromyalgia syndrome: A randomised controlled trial with 6-months follow up. Adv Rheumatol 2020;60:34.
7. Amris K, Jespersen A, Bliddal H. Self-reported somatosensory symptoms of neuropathic pain in fibromyalgia and chronic widespread pain correlate with tender point count and pressure-pain thresholds. Pain 2010;151:664–9.
8. Gracely RH, Grant MAB, Giesecke T. Evoked pain measures in fibromyalgia. Best Pract Res Clin Rheumatol 2003;17:593–609.
9. Su YC, Guo YH, Hsieh PC, Lin YC. Efficacy of repetitive transcranial magnetic stimulation in fibromyalgia: A systematic review and meta-analysis of randomized controlled trials. J Clin Med 2021;10:4669.
10. Thomas AW, Graham K, Prato FS, McKay J, Forster PM, Moulin DE, *et al*. A randomized, double-blind, placebo-controlled clinical trial using a low-frequency magnetic field in the treatment of musculoskeletal chronic pain. Pain Res Manag 2007;12:249–58.
11. Brakemeier EL, Wilbertz G, Rodax S, Danker-Hopfe H, Zinka B, Zwanzger P, *et al*. Patterns of response to repetitive transcranial magnetic stimulation (rTMS) in major depression: Replication study in drug-free patients. J Affect Disord 2008;108:59–70.
12. Ansari AH, Pal A, Ramamurthy A, Kabat M, Jain S, Kumar S. Fibromyalgia pain and depression: An update on the role of repetitive transcranial magnetic stimulation. ACS Chem Neurosci 2021;12:256–70.
13. Cotovio G, Ventura F, Rodrigues da Silva D, Pereira P, Oliveira-Maia AJ. Regulatory clearance and approval of therapeutic protocols of transcranial magnetic stimulation for psychiatric disorders. Brain Sci 2023;13:1029.
14. Altas EU, Askin A, Beşiroğlu L, Tosun A. Is high-frequency repetitive transcranial magnetic stimulation of the left primary motor cortex superior to the stimulation of the left dorsolateral prefrontal cortex in fibromyalgia syndrome? Somatosens Mot Res 2019;36:56–62.
15. Martin L, Borckardt JJ, Reeves ST, Frohman H, Beam W, Nahas Z, *et al*. A pilot functional MRI study of the effects of prefrontal rTMS on pain perception. Pain Med 2013;14:999–1009.
16. Zhu PA, Xie JY, Liu H, Wen Y, Shao YJ, Bao X. Efficacy of high-frequency repetitive transcranial magnetic stimulation at 10 Hz in fibromyalgia: A systematic review and meta-analysis. Arch Phys Med Rehabil 2023;104:151–9.
17. Cheng CM, Wang SJ, Su TP, Chen MH, Hsieh JC, Ho ST, *et al*. Analgesic effects of repetitive transcranial magnetic stimulation on modified 2010 criteria diagnosed fibromyalgia: Pilot study. Psychiatry Clin Neurosci 2019;73:187-93.
18. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;292:2388-95.
19. Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. Pain 1993;55:195–203.
20. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
21. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–5.
22. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The revised fibromyalgia impact questionnaire (FIQR): Validation and psychometric properties. Arthritis Res Ther 2009;11:R120.
23. Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med 2015;58:208–13.
24. Li CT, Su TP, Hsieh JC, Ho ST. Efficacy and practical issues of repetitive transcranial stimulation on chronic medically unexplained symptoms of pain. Acta Anesthesiol Taiwan 2013;51:81-7.
25. Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, *et al*. Effects of unilateral repetitive transcranial magnetic stimulation of motor cortex on chronic widespread pain in fibromyalgia. Brain 2007;130:2661-70.
26. Yepez D, Grandes XA, Talanki Manjunatha R, Habib S, Sangaraju SL. Fibromyalgia and depression: A literature review of their shared aspects. Cureus 2022;14:e24909.
27. Short BE, Borckardt JJ, Anderson BS, Frohman H, Beam W, Reeves ST, *et al*. Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: A randomized, controlled pilot study. Pain 2011;152:2477–84.

28. Lee SJ, Kim DY, Chun MH, Kim YG. The effect of repetitive transcranial magnetic stimulation on fibromyalgia. Am J Phys Med Rehabil 2012;91:1077–85.
29. Cohen SL, Bikson M, Badran BW, George MS. A visual and narrative timeline of US FDA milestones for transcranial magnetic stimulation (TMS) devices. Brain Stimul 2022;15:73–5.
30. Hou WH, Wang TY, Kang JH. The effects of add-on non-invasive brain stimulation in fibromyalgia: A meta-analysis and meta-regression of randomized controlled trials. Rheumatology 2016;55:1507–1.
31. Chervyakov AV, Chernyavsky AY, Sinitsyn DO, Piradov MA. Possible mechanisms underlying the therapeutic effects of transcranial magnetic stimulation. Front Hum Neurosci 2015;9:303.
32. Tekin A, Özdil E, Güleken MD, İlişer R, Bakım B, Öncü J, *et al*. Efficacy of high frequency [10 Hz] repetitive transcranial magnetic stimulation of the primary motor cortex in patients with fibromyalgia syndrome: A randomized, double blind, sham-controlled trial. J Musculoskelet Pain 2014;22:20–6.