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High-Frequency Repetitive Transcranial Magnetic Stimulation at 20 Hz: A Case Series Evaluating Efficacy in Treatment-Resistant Migraine After 10 Hz Repetitive Transcranial Magnetic Stimulation Failure

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Background: High-frequency transcranial magnetic stimulation (TMS) interventions were approved for migraine headache by the US Food and Drug Administration since 2013; however, it is unclear if 10 Hz frequency repetitive TMS (rTMS) patient relapses, should frequency of TMS be enhanced to 20 Hz protocol? This case series addresses the effectiveness of 20 Hz frequency rTMS in treatment-refractory migraine patients.

Case Report: Five voluntary treatment-refractory migraine patients, referred from Medicine, Neurology, and Neurosurgery departments with mean duration of 11.8 years of migraine, not responding to any medications and failed to respond to 10 Hz frequency standard international guidelines, were subjected to 20 Hz, 5 sessions in the first week followed by weekly sessions for additional 4 weeks.

Conclusions: Compared to initial 10 Hz treatment, 20 Hz rTMS significantly reduced both frequency and severity of migraine. Over a follow-up period of 3-6 months, patients exhibited lasting improvements, indicating that 20 Hz rTMS is an effective neuromodulation intervention for individuals with refractory migraines.

Key words: rTMS neuromodulation, effectiveness, acceptability, treatment-refractory migraine

BACKGROUND

Migraine headache is a prevalent and disabling neurological disorder affecting approximately 12% of the global population, with a notable female preponderance (1). A subset of individuals with migraine experience treatment resistance characterized by persistent, debilitating headaches occurring on > 8 days per month despite the use of ≥ 3 preventive medication classes (2). Treatment-resistant migraine presents a significant clinical challenge due to its complex and not fully understood mechanisms. As conventional pharmacological approaches often prove inadequate, there is a pressing need for alternative therapeutic strategies. Recent advancements in neuromodulation technologies have introduced single-pulse transcranial magnetic stimulation (sTMS) as a promising intervention for refractory migraines (3). TMS intervention was approved for migraine since 2013, and particularly high-frequency (> 5 Hz) neurostimulation has shown a modest effect on the intensity and frequency of migraine headache. The goal of optimizing patient outcomes in neuromodulation therapy lies in tailoring TMS parameters to achieve better clinical responses. However, it is uncertain whether patients experiencing relapse or diminished effects at

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10 Hz frequency of repetitive TMS (rTMS) could benefit from enhanced TMS frequency. Whether increasing the frequency improves the treatment efficacy of migraine patients and prevents them from relapse remains ignored in treatment protocols. Further, the evidence from South Asian countries remains sparse in exploring the effectiveness of TMS in treating refractory migraine cases, leaving a gap in our understanding of its applicability in this region.

This case series presents findings from 5 patients with treatment-resistant migraine from South Asia who initially underwent 10 Hz TMS but failed to achieve sustained improvement. Notably, when the frequency was increased to 20 Hz, all patients demonstrated marked clinical improvement and a stable course of symptom relief. Authors suggest that higher-frequency TMS may offer a more effective approach for refractory migraine headaches, offering promise for enhanced long-term management.

CASE PRESENTATION

Case vignettes are shown in Table 1.

DISCUSSION

Treating migraine, especially resistant or refractory cases, has always been challenging with traditional medications. However, over the past 30-40 years, advancements in our understanding of neurobiology have led to the development of new drugs that are now commonly used to manage migraine more effectively. One such emerging treatment modality in management of resistant migraine that has shown promising prospects is neuromodulation through TMS, which works through stimulating areas of the brain or its neural networks, changes in blood flow and metabolic changes, and improvement in synaptic plasticity (4). The rationale of this modality is to improve the head pain and associated symptoms by altering the neural tissue activity of pathophysiologically relevant targets in a noninvasive fashion. TMS over the occipital cortex has been shown to interfere with mechanically and chemically induced cortical spreading depression, which is considered the pathophysiological substrate of migraine aura. Additionally, TMS may modulate spontaneous and C-fiber-evoked trigeminovascular activity of third-order thalamic neurons, suggesting a potential mechanism for migraine pain modulation (5). Thus, TMS has come out as a potential treatment option and has been US Food and Drug Administration approved for treatment of migraine since December 2013. This approval was based on an efficacy study of TMS in 201 patients of moderate-to-severe migraine with aura; 38% showed significant reduction immediately after 2 hours of TMS, and another 34% reported freedom from pain after 24 hours (6).

Indeed, many systematic reviews and meta-analyseshave been conducted to assess the effectiveness and safety of TMS for migraine management. However, there is no clear consensus or consistent evidence for a specific protocol working precisely for migraine headaches. Most researchers have used high-frequency TMS protocols hovering around 10 Hz frequency, especially over the left motor cortex compared to the left dorsolateral prefrontal cortex (7). So far, 9 randomized controlled trials, 2 systematic reviews, and 3 meta-analyses have been conducted for safety and efficacy of TMS for migraine. However, it is not clear if 10 Hz frequency is better than 20 Hz or if 10 Hz does not work, should we go for a 20 Hz TMS protocol? In the present case series of treatment-resistant migraine, we tried to escalate TMS frequency modules from 10 Hz to 20 Hz specifically when we observed diminishing effect with 10 Hz and given 5 sessions in week one and weekly once for next 4 weeks, unlike other regimes, which showed remarkable improvement in all treatment-refractory migraine headache patients. Over the course of 3-6 months following the intervention, these patients exhibited a significant reduction in both the frequency and severity of their migraine attacks. We explored 2 main associations of technical parameters on TMS efficacy. First, we found the higher stimulation intensity was associated with significant improvements, and secondly, 5 sessions in the first week are more efficacious than previously given 3 sessions in a week or alternate day TMS. Mean age of our patients was 36.8 years, with mean duration of migraine being 11.8 years (Table 1), which reflects chronic persistence of migraine despite on medications whose improvement began as early as second session of 20 Hz TMS. However, the evidence generated is only preliminary and in a very small sample who were keen to seek this innovative treatment modality, which can potentially mislead clinical decision-making until we evaluate the extrapolation of observations in large scale. The overall effectiveness of TMS response varies from 40% to 90.2% in various clinical trials as shown in Table 2 (8-20), which suggests that men usually respond poorly compared to their counterparts and the reasons could be because of selective bias, performance bias, detection

Table 1. Clinical and treatment profile of our treatment-resistant migraine headache patients.

Case	Age/ Gender	Duration of Migraine (y)	Migraine Frequency	Migraine Duration (min)	Aura With Migraine	Treatment Received in Past Before 20 Hz Frequency rTMS (90% MT Over Left DLPFC [F3], 400 Pulses/ Session)
Case 1	48/M	34	2-3 per wk	30-40	Present	Propranolol 40 mg/d, Flunarizine 10 mg/d, Sumatriptan 50 mg, Amitriptyline 25 mg/d, Gabapentin 300 mg/d, Valproate 500 mg bid, 10 Hz frequency rTMS, 600 pulses, 9 sessions therapy
Case 2	37/W	11	4-5 per d	30-40	Absent	Propranolol 40 mg/d, Amitriptyline 25 mg/d, Gabapentin 300 mg/d, Sumatriptan 50 mg, Flunarizine 10 mg/d, 10 Hz frequency rTMS, 600 pulses, 9 sessions therapy
Case 3	34/M	5	Twice Weekly	40-60	Present	Propranolol 40 mg/d, Valproate 500 mg bid, Amitriptyline 25 mg/d, Duloxetine 60 mg/d, Clonazepam 0.5 mg/d, 10 Hz frequency rTMS, 600 pulses, 5 sessions therapy
Case 4	36/W	5	Weekly	60	Present	Amitriptyline 25 mg/d, Flunarizine 10 mg/d, Naproxen 500 mg for acute relief, 10 Hz frequency rTMS, 600 pulses, 5 sessions therapy
Case 5	29/W	7-8	Twice Weekly	20-30	Present	Ibuprofen 400 mg/d, Tramadol 100 mg/d, Selegiline 10 mg/d, 10 Hz frequency rTMS, 600 pulses, 5 sessions therapy

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; MT, motor threshold; DLPFC, dorsolateral prefrontal cortex; M, man; W, woman; d, day; wk, week; y, year; min, minute.

bias, attrition bias, or reporting bias. The predominant variables that were found to improve after high-frequency rTMS included migraine duration, migraine index, functional disability, headache disability, reduced medication use, presence of concomitant depression, plasma β-endorphin levels, and overall quality of life. A future, stringent, randomized controlled multicenter trial is being planned by the investigators for exploring the effectiveness of the 20 Hz extended protocol in refractory migraine, which can potentially transform its course and outcome.

CONCLUSIONS

In this case series, we evaluated the effectiveness and acceptability of 20 Hz high-frequency rTMS in patients with treatment-resistant migraine who did not respond to the initial 10 Hz protocol. Following the international federation of clinical neurophysiology guidelines for protocol and stimulus determination, all of the 5 patients demonstrated that 20 Hz rTMS significantly reduced both frequency and intensity of migraine attacks compared to initial 10 Hz treatment with good tolerability. Our protocol is another variant where 5 sessions in the first week, followed by weekly sessions for 4 additional weeks, were delivered compared to alternate day sessions followed by previous experts. These findings underscore the potential of high-frequency escalation of rTMS as a promising alternative treatment option in refractory migraine. This further reflects the heterogeneity of more possible protocols and intervention parameters, and the evidence for 20 Hz frequency is still limited, which will require further large-scale extrapolation to inform clinical decision-making and guideline development for standardized use of TMS, particularly in countries like India.

Ethics Statement

Ethical review and approval were not required for the study on human patients in accordance with the local legislation and institutional requirements. The patients provided their written informed consent to participate in this study.

Table 2. Summary of previous studies of rTMS treatment in migraine.

Study	Sample Size	TMS Protocol	Outcome	Session Details
Khairkar et al 2025*	5	20 Hz, 800 pulses, 90% RMT (left DLPFC, C3)	Marked reduction in frequency and intensity of migraine headache	Five sessions in week 1 followed by weekly sessions for 5 wk
Leahu et al 2021(8)	65 (52 women)	67 Hz, 140 pulses, 60% RMT (multifocal stimulation)	Reduction in headache frequency and severity in real group	Multiple sessions
Kalita et al 2021 (9)	83 (72 women)	10 Hz, 600 pulses, 70% RMT, left M1 + Amitriptyline	Reduced headache frequency and conversion of chronic to episodic migraine in 67%	Three sessions per wk for 3 mo
Kumar et al 2021 (10)	20 (11 women)	10 Hz, 600 pulses, 70% RMT, left M1	Reduced migraine severity, improved VAS and MIDAS scores for one mo	Five sessions per wk
Amin et al 2020 (11)	33 (22 women)	5 Hz, 900 pulses, 100% RMT, left DLPFC	Decreased headache frequency compared to sham	One session per wk
Sahu et al 2019 (12)	41 (31 women)	iTBS (bursts of 3 stimuli at 50 Hz repeated at 5 Hz frequency). Each train of stimulation lasted for 2 s, with an intertrain interval of 8 s, 600 pulses, 80% AMT, left DLPFC	Significant reduction in migraine severity up to 12 wk	Each patient received 10 sessions of iTBS over the left DLPFC
Robblee et al 2019 (13)	263 (not reported)	sTMS, preventive and acute protocols	Reduced headache frequency and intensity during episodes	Four pulses every 15 min for prevention and treatment
Shehata et al 2016 (14)	29 (19 women)	10 Hz, 2,000 pulses, 80% RMT, left M1	Reduced severity, lasting effects only in rTMS + Botox group	Three sessions per wk for 1 mo
Conforto et al 2014 (15)	18 (9 active, 9 sham)	10 Hz, 1,600 pulses, 110% RMT, left DLPFC	Decreased headache frequency in both groups	Three to four sessions per wk, 8 wk
Misra et al 2012 (16)	51 (45 women)	10 Hz, 600 pulses, 70% RMT, left M1	Reduced headache frequency and migraine severity	Three sessions of alternate day 10 Hz rTMS comprising 600 pulses in 10 trains were delivered to left frontal cortex
Lipton et al 2010 (17)	164 (65 women)	sTMS (inion, real v sham)	Reduced migraine frequency and severity for 48 h compared to sham	One session after aura onset, targeting inion
Teepker et al 2010 (18)	27 (22 women)	1 Hz, 500 pulses, 100% RMT, vertex	Migraine frequency reduction in both real and sham groups	One session per wk
Clarke et al 2006 (19)	42 (36 women)	sTMS (2 pulses, 5 s apart)	Immediate pain relief lasting 24 h in 32% of patients	One session, applied over painful area or occipital cortex
Brighina et al 2004 (20)	11 (7 women)	20 Hz, 400 pulses, 90% AMT, left DLPFC	Reduction in headache frequency and severity in the real group	Three sessions per wk for 1 mo

*Present study

Abbreviations: TMS, transcranial magnetic stimulation; RMT, resting motor threshold; DLPFC, dorsolateral prefrontal cortex; VAS, Visual Analog Scale; MIDAS, Migraine Disability Assessment; iTBS, intermittent theta burst stimulation; AMT, active motor threshold; sTMS, single-pulse transcranial magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation; s, second; min, minute; h, hour; wk, week; mo, month.

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