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Repetitive transcranial magnetic stimulation in chronic tension-type headache: A pilot study

Bhawna Mattoo[1], Suman Tanwar[1], Rohit Bhatia[2], Manjari Tripathi[2] & Renu Bhatia[1]

Departments of [1]Physiology & [2]Neurology, All India Institute of Medical Sciences, New Delhi, India

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***Background & objectives*: Tension-type headache (TTH) is the most common type of primary headache disorder. Its chronic form is often the most ignored and challenging to treat. Transcranial magnetic stimulation (TMS) is a novel technique in the treatment of chronic pain. The aim of this pilot study was to explore the effect of low-frequency repetitive TMS (rTMS) on pain status in chronic TTH (CTTH) by subjective and objective pain assessment.**

***Methods*: Patients (n=30) diagnosed with CTTH were randomized into rTMS (n=15) and placebo (n=15) groups in this study. Pre-intervention detailed history of patients was taken. Numerical Rating Scale (NRS) for Pain and questionnaires [Headache Impact Test-6 (HIT-6), McGill Pain Questionnaire, Pain Beliefs Questionnaire, Coping Strategies Questionnaire, State-Trait Anxiety Inventory Test, Hamilton Rating Scale for Depression and WHO-Quality of Life Questionnaire-Brief version] were filled, and objective assessments such as nociceptive flexion reflex (NFR) and conditioned pain modulation were done. The tests were repeated after 20 sessions (5 days/week). In the rTMS group, 1200 pulses in eight trains of 150 pulses each were given at 1Hz over the right dorsolateral prefrontal cortex (RDLPFC). In the placebo group, the rTMS coil was placed such that magnetic stimulation did not reach the cortex.**

***Results*: The NRS score decreased significantly ($P<0.001$) and NFR thresholds increased significantly ($P=0.011$) in the rTMS group when compared to placebo group.**

***Interpretation & conclusions*: Subjective improvements in the NRS, HIT-6, McGill Present Pain Intensity, trait of anxiety and psychological pain beliefs were observed. The increase in the thresholds of NFR served as an objective marker for improvement in pain status. Further studies need to be done to confirm our preliminary findings.**

Key words Brain stimulation - chronic pain - neuromodulation - nociceptive flexion reflex - pain assessment - prefrontal cortex

Repetitive transcranial magnetic stimulation (rTMS) is based on the principle of the generation of a magnetic field outside the head, which alters circuit activity inside the brain by producing an induced current, and can be used to target the cortical areas of pain modulation[1]. It has found application in the treatment of many chronic pain conditions such as fibromyalgia, neuropathic pain and migraine. High-frequency rTMS over the motor cortex and left dorsolateral prefrontal cortex (DLPFC) has shown

beneficial effects in headache disorders such as chronic migraine, cluster headache and trigeminal neuralgia[2], whereas low-frequency rTMS in the range of 1 Hz over right DLPFC (RDLPFC) has potential therapeutic applications in disorders such as depression and fibromyalgia[3].

Tension-type headache (TTH) is the most prevalent headache disorder, and its chronic form remains neglected as patients often fail to seek professional care and help. For most patients, a combination of pharmacological and non-pharmacological therapy is recommended. The chronicity of headache forces the chronic TTH (CTTH) patients to self-medicate, leading to long-term drug use/abuse and associated poor compliance, two of the characteristic features of chronic pain. Inadvertent drug use also predisposes these patients to several side effects such as gastritis and dependence. Hence, there is a need for a non-invasive and safe treatment modality which can provide long-term relief to such patients[4]. Chronic pain is known to be intimately linked to both anxiety and depression, where one may be the cause for the other[5]. By decreasing the activity of the DLPFC using cathodal transcranial direct current stimulation, a change in both anxiety/depression and pain levels has been noted[6]. Therefore, inhibition of the right prefrontal cortex could be a potential approach by transcranial magnetic stimulation (TMS) for the modulation of pain networks and help in pain relief[6]. The current study was a preliminary attempt to understand the effect of rTMS on CTTH, a stress-related debilitating type of headache. The primary outcome was defined at one month after the intervention as a reduction in the Numerical Rating Scale (NRS) for pain in rTMS group versus placebo group and an increase in nociceptive flexion thresholds in rTMS versus placebo group. The secondary outcome measure was improvement in the pain scores.

Material & Methods

This was a single-centre, randomized, placebo-controlled patient blinded, pilot study evaluating the role of low frequency rTMS in CTTH prophylaxis. The study was approved by the Institutional Ethics Committee (IESC/T-113/25.02.2015) and registered in the Clinical Trials Registry of India (CTRI/2016/10/007344). Informed written consent was obtained from all participants before randomization.

Patient selection: Consecutive CTTH patients from the Neurology outpatient service of All India Institute of Medical Sciences, New Delhi, India, between July 2015 and September 2016 who volunteered and underwent therapy and testing at the Pain Research and TMS laboratory, department of Physiology were included in the study. The diagnosis of CTTH was based on the International Classification of Headache Disorders-3[7]. The patient drug history was noted, and standard of care was continued. Probable medicine-overuse headache was excluded. All patients were asked to maintain a headache diary. There were no dropouts during the study.

Inclusion criteria: Right-handed CTTH patients, of age 18-55 yr, with a history of headache >15 days in a month for three months or more, were included in the study. The duration, frequency, severity, functional disability and associated symptoms were recorded. Rescue medication intake for the headache was also recorded (Table I).

Exclusion criteria: Patients using opioid drugs or muscle relaxants or those with a history of drug abuse, hormonal therapy, endocrinopathy or neuropathy were excluded from the study. Patients on other pain-relieving measures such as yoga, acupuncture and acupressure were also excluded. Patients with contraindications to TMS such as ferromagnetic implants in head-and-neck regions, cardiac pacemakers, history of seizures and pregnant or lactating females were all excluded.

Randomization: Thirty patients were randomized to rTMS (n=15) and placebo (n=15) groups using computer-generated random numbers in blocks of 10 and sealed in opaque envelopes. The randomization (ST), evaluation (BM) and assignment (ReB) were done by different investigators. The nature of treatment was blinded to the patients.

Outcomes were defined at four weeks after the completion of 20 sessions. Primary outcomes after the intervention were a decrease in the NRS in rTMS group versus placebo group and an increase in nociceptive flexion thresholds in rTMS versus placebo group. The secondary outcomes were defined as a change in pain scores measured using the McGill Pain Questionnaire (MPQ)[8], Pain Belief Questionnaire (PBQ)[9], Coping Strategies Questionnaire (CSQ)[10] and Headache Impact Test-6 (HIT-6)[11].

For subjective pain assessment, questionnaires such as NRS where patient had to rate his/her pain on a scale of 0 'no pain' to 10 'worst imaginable pain', MPQ, PBQ, CSQ, State-Trait Anxiety

Table I. Patient-wise pain characteristics

Serial number	Patient group	Age (yr)	Sex	Pain at maximum intensity (NRS)	Duration of headache (yr)	Medications	Mild nausea	Photophobia/ Phonophobia	Rescue analgesics/month
1	rTMS	37	Female	5	12.0	-	-	-	5
2	rTMS	35	Female	5	8.5	-	-	-	7
3	rTMS	34	Female	7	22.0	-	-	-	9
4	Placebo	30	Female	6	7.0	Amitriptyline	+	-	11
5	Placebo	21	Male	5	7.0	-	-	-	10
6	rTMS	21	Male	5	2.0	-	-	-	4
7	Placebo	33	Female	6	3.0	-	-	-/+	2
8	rTMS	31	Female	9	2.5	-	-	-/+	2
9	Placebo	31	Female	4	2.5	-	-	-/+	3
10	Placebo	40	Male	5	6.0	-	-	-	6
11	Placebo	33	Female	8	25.0	Amitriptyline	+	-	1
12	rTMS	32	Male	5	3.0	-	-	+/-	5
13	Placebo	45	Female	4.5	18	Amitriptyline, escitalopram	-	-	7
14	Placebo	45	Female	7	6.0	Amitriptyline, alprazolam	-	-	6
15	rTMS	45	Female	6	25.0	Amitriptyline	+	-	4
16	Placebo	45	Female	5	13.0	-	-	-	7
17	rTMS	36	Female	8	4.0	Amitriptyline	-	-	4
18	rTMS	30	Female	7	7.5	-	-	-/+	5
19	Placebo	40	Female	4	17.0	Amitriptyline	-	-	2
20	Placebo	50	Female	8	23.0	-	-	-	6
21	rTMS	38	Female	5	15.0	Amitriptyline, escitalopram	-	-/+	3
22	Placebo	36	Female	5	14.0	-	-	-	5
23	rTMS	35	Female	4	10.0	Amitriptyline, buspirone	-	-	6
24	Placebo	35	Female	9	10.0	Amitriptyline, escitalopram	-	-/+	12
25	Placebo	29	Female	5	4.0	Amitriptyline	-	-	2
26	rTMS	40	Female	7	21.0	Amitriptyline	-	-/+	3
27	Placebo	38	Female	5	8.0	Amitriptyline	-	-/+	7
28	rTMS	33	Female	5	3.5	-	-	-	8
29	rTMS	35	Female	8	3.0	Amitriptyline	-	-	1
30	rTMS	38	Female	10	5.0	Amitriptyline, escitalopram	+	-	11

NRS, numerical rating scale; rTMS, repetitive transcranial magnetic stimulation

Inventory (STAI)[12] Questionnaire, WHO Quality-of-Life Questionnaire[13], Hamilton Rating Scale for Depression[14] and HIT-6 were used.

For objective pain assessment, NFR threshold was recorded, an objective and highly reliable tool for pain evaluation. The patients reported to the laboratory with empty stomach between 0900 and 1000 h to minimize the effect of circadian rhythms and glycaemic levels. Electrodes were placed according to a study by Willer[15], and electrical stimuli to the sural nerve were delivered in trains of five rectangular wave pulses of

one millisecond duration at a frequency of 200 Hz[15]. The NFR threshold was defined as the average of the voltage, which produces reflex during the ascending sequence and below which the reflex could no longer be generated during the descending sequence. Furthermore, conditioned pain modulation (CPM) was done for which the patients were allowed 20 min of rest after which their left hand was dipped in cold water between 4 and 6°C for 90 sec and NFR was recorded. After the removal of hand, the NFR was recorded every minute up to five minutes[16].

Intervention: rTMS was given to the patients using NeuroMS/D® stimulator (Neurosoft, Russia) with a figure-of-eight coil. The protocol of rTMS by Brighina *et al*[17] was followed with some modification. Hotspot for left abductor pollicis brevis was identified using surface landmarks, the midpoint of an imaginary line joining the vertex to the tragus was used to target the motor cortex and TMS pulses were given to identify visible twitch in the left thumb[18]. Once this 'hotspot' was located, the resting motor threshold (RMT) was recorded as the minimum stimulator output which can cause a visible twitch in at least half of the 10 trials. After the calculation of RMT, the stimulation was fixed at a strength of 110 per cent of it. The stimulation was given 5 cm anterior to the previously identified hotspot for left thumb[3] over the RDLPFC. rTMS was given in 8 trains of 150 pulses with an inter-train interval of one minute. Each session lasted 26 min and 52 sec. A total of 1200 biphasic pulses were given during each session. There were five sessions each week from Monday to Friday for four weeks (20 sessions). For placebo stimulation, RMT measurement was not done. To achieve placebo stimulation, the coil was placed perpendicularly to RDLPFC at the least stimulation strength. Thus, the magnetic field did not penetrate the scalp although the patient heard the sound produced by the apparatus[19]. Patients' experience during TMS or after therapy was also noted. Any discomfort during rTMS or adverse events during stimulation and follow up were also noted.

Statistical analysis: All data were checked for normality using D'Agostino and Pearson's omnibus normality test. The baseline characteristics among the rTMS and placebo stimulation groups were compared using Mann–Whitney U-test/unpaired *t* test if the data were non-parametric or parametric, respectively. Statistical significance of the change in the scores of NRS and nociceptive flexon reflex (NFR) between groups and difference in pre-readings from post in placebo versus rTMS group were compared using Mann-Whitney U-test. Graphpad Prism version 5.01 for Windows, (GraphPad Software, San Diego, California, USA), was used for the statistical analysis.

Results

The baseline characteristics of rTMS and placebo groups were compared after randomization and no significant differences were found as shown in Table II.

Subjective assessment: The NRS score of headache reduced from 5 (4,5) to 3.5 (2,5) in placebo group and from 5 (4,7) to 1 (0,2) in rTMS group [median (interquartile range)]. The change was significant in rTMS group versus placebo ($P<0.001$). There was also a significant change in rTMS group in HIT-6 score ($P<0.001$), Present Pain Intensity ($P<0.001$), Pain Beliefs Questionnaire (PBQ): psychological beliefs ($P\leq0.001$) and trait of anxiety ($P=0.01$) in rTMS group. The change in the McGill domains of pain, WHO Quality-of-Life, Coping Strategies Questionnaire, organic pain beliefs and State of anxiety is depicted in Table III.

Objective assessment: The thresholds (volts) for NFR in the placebo group changed from 30 (20,37) to 29 (22,37) and in the rTMS group from 22 (18,29) to 29 (23,43). The change in NFR was compared in both groups and was significant in rTMS group ($P=0.011$). For CPM during cold pressor test, four placebo and two rTMS patients were excluded from the analysis of latency, amplitude and duration as their thresholds had changed during CPM. The comparison was made between the change in the NFR parameters by the cold pressor test and the magnitude of the difference was compared between placebo and rTMS groups. Changes were not significant as shown in Table IV.

Table II. General characteristics of placebo/repetitive transcranial magnetic stimulation (rTMS) groups (n=15)

Characteristics	Placebo group	rTMS group
Age (yr)	36.7±7.6	34.7±5.32
Weight (kg)	59.2±9.9	61.2±12.32
Height (cm)	157 (152,158)	158 (154,164)
Average pain (NRS)	5.03±1.75	5.6±2.13
Duration of headache (yr)	7 (4,22)	6 (2,9)

Data are expressed as mean±SD for parametric and median (quartiles) for non-parametric data. NRS, numerical rating scale; SD, standard deviation

Table III. Questionnaire scores in placebo/repetitive transcranial magnetic stimulation (rTMS) group before and after intervention

Questionnaire	Placebo group (n=15)		rTMS group (n=15)		*P* value Δ placebo vs. Δ rTMS
	Pre	Post	Pre	Post	
Headache Impact Test-6	68 (64,70)	62 (59,70)	67 (60,70)	40 (36,46)	<0.001
WHOQOL-BREF					
Physical	38 (31,50)	44 (31,63)	44 (31,56)	56 (50,63)	0.64
Psychological	44 (44,50)	56 (50,75)	56 (44,63)	63 (44,75)	0.4
Social	56 (56,81)	69 (44,81)	56 (44,75)	69 (50,81)	0.6
Environmental	56 (31,63)	44 (31,63)	38 (31,44)	44 (31,56)	0.47
MPQ					
Sensory	8 (7,13)	6 (2,10)	15 (8,19)	8 (1,12)	0.13
Affective	4 (2,7)	1 (0,3)	3 (2,5)	1 (0,2)	0.5
Evaluative	1 (0,3)	0 (0,1)	0 (0,2)	0 (0,2)	0.3
Miscellaneous	5 (4,6)	3 (0,5)	4 (1,6)	1 (0,3)	0.39
Pain-rating index	19 (14,27)	10 (3,22)	22 (18,25)	10 (3,22)	0.7
Present pain intensity	2 (2,3)	0 (0,1)	3 (2,4)	0 (0,1)	<0.001
CSQ					
Diverting attention	18 (15,26)	11 (0,27)	23 (15,30)	10 (5,20)	0.08
Re-interpreting pain sensation	6 (0,12)	4 (0,12)	6 (3,12)	6 (3,12)	0.05
Coping self-statements	12 (8,20)	6 (0,16)	12 (9,17)	12 (10,12)	0.4
Ignoring pain sensations	7 (2,10)	5 (2,20)	7 (3,10)	6 (0,10)	0.8
Praying or hoping	7 (2,19)	3 (0,12)	2 (0,6)	0 (0,6)	0.3
Increased activity level	12 (7,16)	9 (7,16)	10 (7,12)	11 (6,12)	0.7
Increasing pain behaviour	16 (12,18)	16 (15,17)	18 (16,18)	15 (11,18)	0.1
Catastrophizing	9 (0,12)	10 (2,15)	7 (4,10)	8 (5,13)	0.3
PBQ					
Organic	8 (5,12)	6 (4,12)	11 (4,15)	7 (3,12)	0.45
Psychological	14 (10,18)	15 (7,21)	21 (13,22)	11 (9,16)	<0.001
HAM-D	7 (3,13)	5 (2,7)	6 (5,13)	4 (0,7)	0.22
STAI					
State	51 (45,56)	46 (34,52)	49 (42,58)	40 (29,50)	0.68
Trait of anxiety	48 (36,53)	42 (32,47)	47 (44,53)	34 (26,48)	0.01

Δ, Difference between pre and post values in rTMS group was compared with difference in placebo group. Data are expressed as median (interquartile range). WHOQOL, World Health Organization Quality of Life; MPQ, McGill Pain Questionnaire: CSQ, Coping Strategies Questionnaire; PBQ, Pain Beliefs Questionnaire; HAM-D, Hamilton Depression Rating Scale, STAI; State-Trait Anxiety Inventory

Discussion

Our results reflect a beneficial effect of TMS on the pain status of CTTH patients by both subjective and objective methods. The study participants in rTMS group reported improvement in the subjective pain rating scale: NRS and HIT-6 scores, suggesting an analgesic effect of the low-frequency rTMS on the RDLPFC[20]. A similar effect was seen in temporomandibular joint disorders where transcranial direct current stimulation was used on the RDLPFC[21]. As chronic pain is a multifaceted problem, multidimensional pain questionnaires (McGill, Pain Coping Strategies and PBQs) were utilized to evaluate the sensory, affective, motivational and evaluative components of pain. This is to evaluate low-frequency rTMS as an intervention and identify its target in pain circuitry. In the present study, a significant improvement was observed in the Present Pain Intensity (McGill Questionnaire) in the rTMS group.

Table IV. Change in conditioned pain modulation after intervention

Per cent change (during cold pressor test)	Placebo group		rTMS group	
	Pre	Post	Pre	Post
Threshold	0.49 (0,4.5)	0.79 (0,4.5)	0.35 (0,5.2)	0.44 (−4,3.8)
Latency	−1.44 (−9,46)	6.68 (−43,41)	4.66 (88,90)	−4.49 (−40,18)
Amplitude	10 (−12,70)	9.12 (−4,7)	−12 (−88,15)	−4.49 (−40,18)
Duration	−6.9 (−57,17)	2.49 (−8,37.5)	0.81 (−9,14)	0.29 (−22,33)

The change in the various parameters of NFR (threshold, latency, amplitude and duration) expressed as a median and interquartile range of per cent change from baseline during cold pressor test is depicted. The thresholds are compared for all individuals (rTMS n=15, placebo n=15). Four placebo and two rTMS group patients were excluded from the analysis of latency, amplitude and duration as their thresholds had changed during cold pressor test. The changes were non-significant between the placebo and rTMS groups. NFR, nociceptive flexion reflex; rTMS, repetitive transcranial magnetic stimulation

A previous study also reported improvement in MPQ scores by rTMS in various disorders[22]. The present study showed a significant improvement in the STAI on anxiety trait and in the PBQ on psychological pain beliefs. Considering the importance of the DLPFC in mood regulation and emotional processing[23], these findings substantiate what has been reported previously regarding low-frequency rTMS of RDLPFC[24,25], which has been widely used for substance abuse withdrawal-related anxiety[26,27].

A significant increase in the NFR threshold, an objective pain assessment tool, after therapy in the rTMS group reflects the role of top-down modulation of pain processing mediated at midbrain and spinal cord level[28,29]. Therefore, the targeted DLPFC area may have a top-down mode of inhibition of neuronal connections along the ascending midbrain–thalamic–cingulate pathway through descending fibres from the prefrontal cortex[30].

Diffuse noxious inhibitory control is the phenomenon of pain inhibiting pain and is also known as counterirritation; it involves a spinal–medullary–spinal pathway, with ascending information projecting from the ventrolateral quadrant of the spinal cord towards supraspinal centres and descending projections from supraspinal centres through the dorsolateral funiculi of the spinal cord to neurons in the dorsal horn[31]. However, there was no change in CPM after rTMS, suggesting that the diffuse noxious inhibitory controls were not activated enough by the therapy or might not contribute to the analgesic effects. Similar findings were reported for the high-frequency motor cortex stimulation[32].

There is evidence that rTMS may be used in managing chronic pain conditions[32-35]. The areas primarily targeted for pain relief by TMS are the DLPFC and the motor cortex. Pain has both sensory and affective components, and the prefrontal and limbic circuits are believed to be involved in mood regulation. Several investigators have explored the benefits of prefrontal rTMS in pain management[6,28,36]. The DLPFC is a functional area associated with executive functions such as attention, mood regulation, stimulus appraisal and expectation[37]. As DLPFC is an accessible site through rTMS, it has emerged as a target for adjunctive pain therapy. The RDLPFC was chosen for the study as a non-invasive brain stimulation study suggested that interhemispheric DLPFC connectivity affected pain tolerance by altering interhemispheric inhibition[6]. Low-frequency right hemisphere suppression probably results in the elimination of transcallosal inhibition, thereby allowing increased descending inhibition from the left hemisphere. Significant increase in thermal and mechanical pain thresholds and improvement in patient-rated pain intensity in chronic, acute and post-operative pain have been reported with low-frequency rTMS of the RDLPFC[37].

Our study had the following limitations: for placebo stimulation the position and strength of the coil were changed, but studies should be done using a placebo coil to exactly mimic the real coil. Furthermore, this made it impossible to blind the investigator. Surface landmarks were used to target DLPFC in our study. This does not account for heterogenous head morphology; therefore, a neural navigator [magnetic resonance imaging (MRI)-based targeting] can be used to target the exact site. Finally, the possibility of greater placebo effect in the rTMS group cannot be ruled out as this a preliminary study with a restricted sample size.

Our preliminary result show that low-frequency rTMS of the RDLPFC may have an analgesic effect in CTTH patients. There was a reduction in the impact of headache on their daily lives, which

was reflected by reduction in the anxiety trait and psychological pain beliefs. Larger trials using rTMS as an adjuvant/independent therapy need to be done in CTTH patients. Further studies are warranted using quantitative electroencephalography or functional MRI and by correlating the findings with the levels of neurotransmitters such as serotonin, dopamine and opioids to understand the exact mechanism of action of rTMS therapy.

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***Conflicts of Interest*:** None.

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For correspondence: Dr Renu Bhatia, Room No. 6007, Convergence Block, Department of Physiology, All India Institute of Medical Sciences, New Delhi 110 029, India
e-mail: renuaiims28@gmail.com