Effect of adjunctive intermittent theta-burst repetitive transcranial magnetic stimulation as a prophylactic treatment in migraine patients: A double-blind sham-controlled study

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ABSTRACT

Background: The left dorsolateral prefrontal cortex (DLPFC) seems to exert a bilateral control of chronic pain states such as migraine. Repetitive transcranial magnetic stimulation (rTMS) is known to modulate brain excitability, neurotransmitters, and endogenous opioids involved in pathophysiology of migraine.

Aim: This study was designed to assess the efficacy of adjunctive intermittent theta-burst stimulation (iTBS) to the left DLPFC, as a prophylactic treatment in migraine.

Materials and Methods: The study was a double-blind, sham-controlled experiment. Patients with migraine were allotted to active (n = 20) or sham (n = 21) rTMS, respectively. Each patient received ten sessions of iTBS over the left DLPFC. Patients were rated at baseline and at 2, 4, 6, and 12 weeks after receiving the treatment. Scores were obtained from the headache diary and by applying the Migraine Disability Assessment Scale (MIDAS).

Results: There was a significant decrease in frequency, duration, and severity of migraine in the active group than the sham group over the study period. The effect was more pronounced during the initial 2 weeks. The MIDAS score reduced significantly in the active group than the sham group at 12 weeks. There were no significant adverse effects observed during the entire period of study.

Conclusion: Compared to sham stimulation, adjunctive active iTBS over the left DLPFC was safe and effective in reducing the frequency, duration, and severity of migraine headache and in reducing disability associated with the illness.

Key words: Dorsolateral prefrontal cortex, intermittent theta-burst stimulation, migraine, repetitive transcranial magnetic stimulation

INTRODUCTION

Migraine is a common disabling primary headache disorder. It is usually episodic with a wide range of clinical presentations. In adult population, its prevalence is more in females (18.2%) than in males (6.5%).[1] Individuals with a family history of migraine are almost 45%–50% more likely to experience migraine headache.[2] Due to its chronic disabling nature, preventive therapy is indicated in about a third of patients with migraine. Various prophylactic drugs such as beta-blockers, anticonvulsants, calcium channel blockers, and antidepressants are used with each drug having its own limitations.
The exact pathogenesis of migraine is still unclear. A neurovascular origin is widely considered where both neuronal and vascular components are relevant and most probably interrelated. The neuronal structures involved are the cerebral cortex, the brain stem, and components of the trigeminovascular system. Using electrophysiological techniques, an increase in cortical bioelectrical activity is seen in migraine patients compared to normal patients.

Results from previous works show dorsolateral prefrontal cortex (DLPFC) having a modulatory influence on cortico–cortical and cortico–subcortical connections of the descending pain modulatory system. Patients with chronic pain show a decrease in gray matter density in the DLPFC compared with healthy controls. This reflects the endogenous role of DLPFC in pain control mechanism. It is also seen that activations in the DLPFC produce placebo-induced analgesia. A subgroup of migraine patients with speech disturbances as a feature of the prodromal symptoms was also found to have relatively impaired language abilities on routine testing. This suggests a role of dominant hemisphere involvement in migraine pathophysiology. In one study on volunteers, repetitive transcranial magnetic stimulation (rTMS) was applied after application of capsaicin on both the dorsum of hands. The result showed that the left DLPFC stimulation resulted in pain relief in both the hands, whereas right-sided stimulation did not have any effect. This favors the role of the left DLPFC in bilateral pain control mechanism.

Studies on the effect of rTMS in migraine are few and show variable results. It is seen that rTMS treatment at high frequency is able to restore normal or quite normal levels of DLPFC activation. In some previous studies where high-frequency rTMS was used in chronic migraine prophylaxis showed improvement in symptoms whereas low-frequency rTMS showed a lack of effect.

Theta-burst stimulation (TBS) has emerged as a novel method of brain stimulation. It briefly alters cortical excitability in the human brain through repetitive transcranial magnetic stimulation (rTMS). Two major TBS paradigms were developed: continuous theta-burst stimulation (cTBS) and intermittent theta-burst stimulation (iTBS). cTBS induces a long-term depression-like effect, whereas iTBS induces a long-term potentiation-like effect. The stimulus intensity required for TBS is lower than that for other rTMS protocols, with a much shorter conditioning time. With the advent of noninvasive transcranial magnetic stimulation, currently, it is being studied extensively in the treatment of migraine. Single-pulse transcranial magnetic stimulation is approved by the Food and Drug Administration for use in acute treatment for migraine with aura. However, rTMS as a prophylactic treatment in migraine has not been well established. A study where cTBS over primary motor cortex was used for migraine prophylaxis showed improvement in symptoms.

There is a dearth of literature regarding the use of iTBS in the treatment of migraine. The objective of the current study is to assess whether stimulating left DLPFC using iTBS would act as an adjunctive treatment in migraine prophylaxis. Considering the central modulation of migraine pain, we chose to stimulate the left DLPFC.

MATERIALS AND METHODS

Subjects
Forty-one right-handed patients with a diagnosis of migraine with or without aura, according to the International Classification of Headache Disorders-II, were selected for the study. The age ranges of patients selected were between 18 and 60 years. Patients with at least two migraine attacks per month for the last 3 consecutive months were enrolled in the study. Patients taking prophylactic medication for migraine were advised to continue the same medication during the study period. Written informed consent for the study was obtained from the participants. Their sociodemographic profile was noted. Exclusion criteria included any other type of chronic or recurrent headache, other neurological or major psychiatric diseases, other debilitating physical conditions, other clinically relevant painful conditions, pregnancy, or having any cochlear implants, cardiac pacemaker, and metal body implanted in head-and-neck region. The study was approved by the Institute Ethics Committee.

Procedure
To ensure that patients selected were right handed, the Handedness Preference Schedule was applied. A detailed physical examination was done to rule out any neurological disease. The Hamilton Rating Scale for Depression and the Hamilton Rating Scale for Anxiety were applied to rule out comorbid depression and anxiety, respectively. Screening standard questionnaire for rTMS was applied before enrollment to rule out any major physical abnormalities. Baseline scores before the start of rTMS sessions were obtained by the Migraine Disability Assessment Scale (MIDAS) and records of previous 3 months headache diary maintained by the patients. Patients were advised to maintain the headache diary for at least the next 3 months.

By alternate allocation, patients were assigned to real (active) or sham treatment (every alternate patient to either real or sham group). Then, ten iTBS sessions, two sessions per day in adjunct to the prophylactic antimigraine treatment, were given for a period of 5 consecutive days. rTMS side effect checklist was applied after each session. Patients were rated at 2, 4, 6, and 12 weeks after receiving the treatment, from headache diary and by applying MIDAS. Patients were maintained on the same dose of prophylactic medications throughout the study period. Nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans were used as rescue medications. All patients were using NSAIDs,
whereas eight patients were using triptans as rescue medications during the study period.

**Stimulation procedure**

*Estimation of motor threshold*

The motor threshold (MT) for the abductor pollicis brevis (APB) muscle was determined using a figure-of-eight-shaped TMS coil at 1-Hz frequency. The left motor cortex for the contralateral APB was determined by the following methods. The center of the TMS coil was placed 5-cm lateral to the vertex in the left side, on interauricular line. The handle was angled 45° away from the sagittal plane. The coil was methodically moved across the left frontoparietal region of the cranium centered at the above-indicated point until stimulation of the right APB muscle. MT was defined as the lowest intensity, which produces five motor-evoked potential responses of at least 50 μV in ten trials.

* Determination of site for application of intermittent theta-burst stimulation to left dorsolateral prefrontal cortex*

The left DLPFC stimulation site was determined by measuring 5-cm anterior in a parasagittal line from the point of maximum stimulation of the right APB muscle.

Ten sessions of iTBS were administered over the left DLPFC at 80% of active MT. iTBS was applied through Magstim Rapid Square® device using a figure-of-eight-shaped coil. For active stimulation, the coil was held tangentially to the scalp with the handle pointing upward. iTBS was applied in a theta-burst pattern (bursts of three stimuli at 50 Hz repeated at 5-Hz frequency). Each train of stimulation lasted for 2 s, with an intertrain interval of 8 s. Twenty such trains comprising 600 pulses were applied in each session. In sham stimulation, the same coil and same parameters were applied like active stimulation except for the placement of coil perpendicular to the brain surface over the left DLPFC site.

*Rating*

Patients were rated by a researcher who did not participate in the iTBS sessions and who was blind to the patient’s treatment group allocations. Rating was done at baseline and at 2, 4, 6, and 12 weeks after receiving the treatment, from the headache diary maintained by patients and by applying MIDAS.

*Statistical analysis*

Statistical analysis was done using IBM SPSS version 22.0 (IBM Corp©, Armonk, NY, USA). Different parametric and nonparametric measures were used, wherever applicable. Descriptive statistics such as percentage, mean, and standard deviation (SD) were used for the description of sample characteristics. Clinical variables were analyzed using Chi-square/Fisher’s exact test of categorical variables. Continuous variables were analyzed using independent samples t-test for comparing both the groups. Repeated measures ANOVA was done to compare within patients and between group effects. Time points were baseline and 2nd-, 4th-, 6th-, and 12th-week assessments, and the groups were active and sham. Significance was set at probability \( P < 0.05 \).

**RESULTS**

After all patients completed the study for a period of 3 months, statistical analysis was done. Sociodemographic and clinical profiles were compared between the active and sham groups. There were no significant differences between the two groups in terms of age, sex, marital status, and other sociodemographic profile. Furthermore, no significant differences were found between the two groups in terms of diagnosis, age of onset, duration of illness, and prophylactic treatment received [Table 1].

When the effect of treatment of iTBS over time (i.e., at baseline and at 2, 4, 6, and 12 weeks) in both the groups (active and sham) on the frequency, duration, and severity of headache was analyzed, change in scores over time was noted within patients. When compared between the groups over time, a significant difference (\( P < 0.001 \)) was found in frequency scores between the two groups. The scores decreased significantly in the active group compared to sham with respect to baseline. *Post hoc* analysis on frequency score showed a significant decrease in headache frequency from baseline across further assessments except between 4 and 6 weeks (\( a\geq e>c, d>b \)) [Table 2]. The decrease was more between baseline and 2 weeks of assessment. After 2 weeks, there was a gradual increase in score till 12 weeks, compared to assessment at 2 weeks. There was a decrease in 12-week score compared to baseline [Figure 1]. When the duration of headache hours was compared between the groups over time, a significant difference (\( P < 0.001 \)) was found between the two groups over time. The scores were more decreased in the active group compared to sham with respect to baseline. *Post hoc* analysis on duration...
score showed a significant decrease in headache hours from baseline across further assessment times except between 4 and 6 weeks (a > c, d > b). The decrease was more between baseline and 2 weeks. After 2 weeks, there was a gradual increase in score till 12 weeks, compared to assessment at 2 weeks, but there was a decrease in 12-week score compared to baseline [Figure 2]. When compared between the groups over time, a significant difference (P < 0.001) was found in headache severity score between the two groups. The scores were more

Table 1: Comparison of various sociodemographic and clinical variables across groups’ continuous and categorical variables (n=41)

| Variables                            | Mean±SD/ (n/%) Active (n=20) | Mean±SD/ (n/%) Sham (n=21) | t/ F² | df | P  |
|--------------------------------------|-----------------------------|----------------------------|------|----|----|
| Age (years)                          | 31.35±7.51                  | 30.23±9.02                 | 0.428| 39 | 0.673|
| Age of onset (years)                 | 25.72±7.84                  | 25.09±8.85                 | 0.24 | 39 | 0.807|
| Duration of illness (years)          | 5.64±5.33                   | 5.14±4.24                  | 0.33 | 39 | 0.742|
| Sex                                  |                             |                            |      |    |    |
| Male                                 | 3 (15.0)                    | 7 (33.3)                   | 1.867| 1  | 0.172|
| Female                               | 17 (85.0)                   | 14 (66.7)                  |      |    |    |
| Marital status                       |                             |                            |      |    |    |
| Single                               | 8 (40.0)                    | 9 (42.9)                   | 0.034| 1  | 0.853|
| Married                              | 12 (60.0)                   | 12 (57.1)                  |      |    |    |
| Family income per month (Rs.)        |                             |                            |      |    |    |
| <5000                                | 8 (40.0)                    | 5 (23.8)                   | 2.29 | 3  | 0.653|
| 5000-10,000                          | 4 (20.0)                    | 8 (38.1)                   |      |    |    |
| 10,000-30,000                        | 5 (25.0)                    | 6 (28.5)                   |      |    |    |
| >30,000                              | 3 (15.0)                    | 2 (9.5)                    |      |    |    |
| Occupation                           |                             |                            |      |    |    |
| Employed                             | 7 (35)                      | 5 (23.8)                   | 0.620| 1  | 0.431|
| Un employed                          | 13 (65)                     | 16 (76.2)                  |      |    |    |
| Past history of medical illness      |                             |                            |      |    |    |
| Present                              | 4 (20.0)                    | 4 (19.0)                   | 0.006| 1  | 0.939|
| Absent                               | 16 (80.0)                   | 17 (81.0)                  |      |    |    |
| Diagnosis                            |                             |                            |      |    |    |
| Migraine without aura                | 17 (85)                     | 21 (100)                   | 3.399| 1  | 0.065|
| Migraine with aura                   | 3 (15)                      | 0 (0)                      |      |    |    |
| Drug status (prophylactic)           |                             |                            |      |    |    |
| TCA                                  | 8 (40)                      | 7 (33.3)                   | 2.32 | 4  | 0.675|
| Beta-blocker                         | 4 (20.0)                    | 9 (42.8)                   |      |    |    |
| Anticonvulsant                       | 1 (5)                       | 2 (9.5)                    |      |    |    |
| Combinations/others                  | 5 (25)                      | 5 (23.8)                   |      |    |    |
| Nil                                  | 2 (10)                      | 5 (23.8)                   |      |    |    |

P=NS, TCA – Tricyclic antidepressant; SD – Standard deviation

Table 2: Effect of treatment of repetitive transcranial magnetic stimulation over time (i.e., at baseline and at 2, 4, 6, and 12 weeks) between groups (active and sham) on frequency, duration, and severity of migraine headache (n=41)

| Variable       | Time     | Mean±SD | Greenhouse-Geisser interaction | F   | df | Partial η² | Observed power | P     | Post hoc     |
|----------------|----------|---------|--------------------------------|-----|----|------------|----------------|-------|-------------|
| Frequency      | Baseline | 1.00±0.26| 0.84±0.17                      | With time | 23.34 | 4 | 0.722 | 1 | 0.000* | a>e>c, d>b |
|                | 2 weeks  | 0.32±0.37| 0.78±0.29                      |          |     |           |                |       |             |
|                | 4 weeks  | 0.51±0.24| 0.82±0.23                      |          |     |           |                |       |             |
|                | 6 weeks  | 0.60±0.18| 0.80±0.23                      | Time*group | 33.89 | 1.98 | 0.465 | 1 | 0.000* | a>e>c, d>b |
|                | 12 weeks | 0.67±0.24| 0.84±0.17                      |          |     |           |                |       |             |
| Duration       | Baseline | 9.77±4.68| 5.50±1.93                      | With time | 28.65 | 4 | 0.761 | 1 | 0.000* | a>e>c, d>b |
|                | 2 weeks  | 2.80±4.99| 4.47±1.88                      |          |     |           |                |       |             |
|                | 4 weeks  | 4.05±4.04| 4.97±1.96                      |          |     |           |                |       |             |
|                | 6 weeks  | 5.01±3.74| 5.01±1.88                      | Time*group | 36.00 | 2.36 | 0.480 | 1 | 0.000* | a>e>d>c> b |
|                | 12 weeks | 6.10±3.84| 5.50±1.82                      |          |     |           |                |       |             |
| Severity       | Baseline | 7.15±0.77| 6.58±0.90                      | With time | 30.45 | 4 | 0.772 | 1 | 0.000* | a>e>d>c<b |
|                | 2 weeks  | 2.90±2.78| 6.02±1.07                      |          |     |           |                |       |             |
|                | 4 weeks  | 5.40±1.10| 6.27±0.88                      |          |     |           |                |       |             |
|                | 6 weeks  | 5.79±0.80| 6.34±0.83                      | Time*group | 23.87 | 1.33 | 0.380 | 1 | 0.000* |             |
|                | 12 weeks | 6.36±0.82| 6.47±0.94                      |          |     |           |                |       |             |

*P<0.001. Frequency – Number of days per week having migraine headache; Duration – Number of hours of headache per week, Severity – Average severity of headache pain on a scale of 0-10, with 10 being most painful; SD – Standard deviation
decreased in the active group compared to sham. *Post hoc* analysis on severity score showed a significant decrease in headache severity from baseline across further assessment times till 12 weeks \((a>e>d>c>b)\). The decrease was more between baseline and 2 weeks [Figure 3 and Table 2].

When the effect of treatment of iTBS over time (i.e., at baseline and at 3 months) in both the groups (active and sham) on MIDAS score was compared, a significant difference \((P < 0.001)\) was found between the two groups. The MIDAS scores decreased significantly in the active group compared to sham with respect to baseline. The improvement in migraine disability, headache days, and severity of headache all were decreased at 3 months with respect to baseline [Table 3].

From the above results, it was seen that in both the active and sham groups, there was a decrease in scores of frequency (number of days per week having migraine headache), duration (number of hours of headache per week), severity of headache (average severity of headache pain on a scale of 0–10), and migraine disability over a period of 3 months. However, in the active group, there was more decrease in scores in comparison to the sham group which was statistically significant both over the period of time and between the two groups.

**DISCUSSION**

This was a prospective, hospital-based, double-blind, sham-controlled iTBS study. In this study, 52 patients were allotted, out of which 11 patients had to be dropped out of the study. The current study had a large patient sample size \((n = 41)\) compared to previous studies, where rTMS was used to treat migraine.\(^{[11,14]}\) The mean age of patients in the active group was 31.35 (SD 7.51) years and in the sham group was 30.23 (SD 9.02) years. This was similar to a recent study determining the effect of rTMS in migraine, where the median age was 32 years.\(^{[13]}\) Among the total 41 patients, majority were female (17 – active group and 14 – sham group) which was similar to previous studies.\(^{[11,13,14]}\) In our study, 2 (10%) out of 20 in the active group and 5 (23.8%) out of 21 in the sham group were not taking any prophylactic medication. All others were on prophylactic treatment either by a tricyclic antidepressant, anticonvulsant, beta-blocker, or other medications by at least 3 months prior to the study. In previous studies determining effect of rTMS in migraine, similar prophylactic medications were used by the patients.\(^{[11,13,14]}\)

There were no major side effects during iTBS stimulation of the brain. The most common complaint of the patients receiving active treatment was mild scalp discomfort during iTBS stimulations which resolved spontaneously after stimulation.

### Table 3: Effect of treatment of repetitive transcranial magnetic stimulation over time (i.e., at baseline and 3 months) between groups (active and sham) on Migraine Disability Assessment Scale score \((n=41)\)

| Variable | Time | Mean±SD | Greenhouse-Geisser Interaction | F | Df | Partial \(\eta^2\) | Observed power | P |
|----------|------|---------|--------------------------------|---|----|------------------|----------------|---|
| MIDAS    | Baseline | 13.10±4.36 | 10.38±2.24 | With time | 114.46 | 1 | 0.746 | 1 | 0.000* |
|          | 3 months | 8.25±3.44 | 10.14±2.12 | Time*group | 94.04 | 1 | 0.746 | 1 | 0.000* |
| MIDAS-A  | Baseline | 12.00±3.22 | 10.14±2.12 | With time | 90.55 | 1 | 0.699 | 1 | 0.000* |
|          | 3 months | 8.10±2.88 | 10.05±2.07 | Time*group | 86.23 | 1 | 0.689 | 1 | 0.000* |
| MIDAS-B  | Baseline | 7.15±0.77 | 6.58±0.90 | With time | 65.06 | 1 | 0.625 | 1 | 0.000* |
|          | 3 months | 6.36±0.82 | 6.47±0.94 | Time*group | 37.85 | 1 | 0.493 | 1 | 0.000* |

\(*P<0.001\). MIDAS – Migraine Disability Assessment Scale; MIDAS-A – Number of headache days in the last 3 months; MIDAS-B – Severity of headache pain on a scale of 0–10, with 10 being most painful; Baseline – Before starting the treatment; SD – Standard deviation
In our study, when the mean frequency, duration of headache per week, and mean severity of each episode of headache were compared to baseline (before starting iTBS), and over a period of 12 weeks after starting iTBS, there was a significant difference ($P = 0.000$) found between the two groups. In both the groups, improvement in frequency, duration, and severity of headache over time was noted. There was more decrease in frequency, duration, and severity of headache in the active group than the sham group over the period of time. The decrease in scores was more pronounced during the 1st assessment at 2 weeks although the effect persisted till 12 weeks. Previously, similar results were found in migraine patients using high-frequency rTMS,[11,13] but in those previous studies, headache pain was rated with 0–3-point Likert scale, and the study period was 1 month only. In our study, 0–10-point Likert scale was used to measure the severity of pain more precisely. Furthermore, extending the study period to 3 months, we determined the effect of iTBS till 3 months.

When the score of MIDAS was compared between the two groups before starting iTBS and after 12 weeks (3 months), a significant difference ($P = 0.000$) was found. In the active group, the score reduced more than that of the sham group. Furthermore, when the migraine days/3 months and mean severity of headache were compared between the two groups, there was more decrease in migraine days and headache severity in the active group compared to the sham group. We have not found any previous study determining the effect of rTMS in migraine disability using MIDAS scale.

The laterality and site of stimulation in our study were important predictors of pain relief. This supports the earlier findings that suggest a role of dominant hemisphere involvement in migraine pathophysiology.[10] It also supports a crucial role of DLPFC in the descending pain modulatory system.[15]

Further, from earlier researches, it is evident that electrical stimulation activates the axons of the corticospinal neurons in the white matter, whereas magnetic stimulation activates the neurons trans-synaptically resulting in a greater spread.[22] On 20-Hz frontal stimulation, there is an increased dopamine in the hippocampus, suggesting change in dopamine transmission.[29] Earlier report suggested that when high-frequency rTMS was applied to the left DLPFC in healthy controls, there was an increase in glutamate/glutamine level not only at the site of stimulation but also in remote brain regions.[20] Endogenous opioids have also been reported to have a role in reducing migraine attacks following rTMS.[31] Studies on experimental animals showed that rTMS can modulate serotonergic transmission modifying the sensitivity of 5-HT2 receptors or desensitizing 5-HT1 autoreceptors.[32] From the above evidence and findings from our study, we can conclude that application of iTBS on the left DLPFC causes trans-synaptic activation of the DLPFC and adjacent cortical areas as well as remote areas. This neuronal activation through various bilaterally interconnected descending pain modulatory systems modulates the neurotransmitters involved such as dopamine, serotonin, and glutamine/glutamate to decrease the frequency and severity of pain in migraine. Hence, iTBS may prevent migraine by sustained change in the excitability of neurons and/or by modulating the neurotransmitters.

**CONCLUSION**

Adjunctive ten sessions of active iTBS over the left DLPFC was safe and effective in prophylactic treatment of migraine. It reduces the frequency, duration, and severity of migraine pain and also reduces the migraine disability whose effect persists at least for 3 months after the treatment.

**Limitations and future direction**

In this study, allocation of patients to the active and sham groups was not properly randomized. The DLPFC site was determined by measuring 5-cm anterior in a parasagittal line from the point of maximum stimulation of contralateral APB muscle. For exact site determination, neuronavigated rTMS would have been better choice. The same figure-of-eight-shaped coil was used for both active and sham stimulations as separate sham coil was not available. Most of the patients in our study were on prophylactic medications which are confounding factors, and the number of rTMS sessions was less.

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**Conflicts of interest**

There are no conflicts of interest.

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