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Original Article

Efficacy of continuous theta burst stimulation of the primary motor cortex in reducing migraine frequency: A preliminary open-label study

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Abstract

Background: Theta burst stimulation is a type of pattern-specific repetitive transcranial magnetic stimulation that requires less stimulation time and lower intensity to induce long-lasting effects comparable to those of other repetitive transcranial magnetic stimulation protocols. This pilot study investigated whether continuous theta burst stimulation (cTBS) on the primary motor cortex reduced headache frequency in patients with migraine.

Methods: Nine patients with migraine were recruited into our study. All patients received 20 cTBS sessions (bursts of 3 50-Hz TMS pulses at 200-ms intervals for 40 seconds), administered every weekday for 4 consecutive weeks. All patients kept headache diaries for 4 weeks before stimulation (baseline; T1), during stimulation (T2), and 4 weeks after stimulation (T3). The primary outcome measures were the changes of total headache and migraine days from baseline (Wilcoxon signed-rank test; T2 and T3 vs. T1).

Results: The number of total headache days was reduced at T2 and T3 compared with T1 [9.4 ± 6.2 days ($p = 0.024$) and 8.7 ± 10.1 days ($p = 0.012$) vs. 13.4 ± 10.1 days]. The number of migraine days was also reduced at T2 and T3 compared with T1 [2.9 ± 2.7 days ($p = 0.021$) and 1.0 ± 1.6 days ($p = 0.008$) vs. 8.6 ± 8.7 days].

Conclusion: Our results indicate that cTBS on the primary motor cortex might reduce the number of total headache and migraine days in patients with migraine. However, large-scale randomized controlled trials are necessary to further validate the findings.

Keywords: continuous theta burst stimulation; primary motor cortex; repetitive transcranial magnetic stimulation

1. Introduction

Migraine is one of the most common neurological disorders, and it causes severe disability. The World Health Organization ranked migraine among the 20 most disabling diseases,[1] and classified severe migraine as having the highest level of functional disability, compatible with major depression disorder, quadriplegia, and terminal malignancy, in its Global Burden of Disease report.[2]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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The global prevalence of migraine is about 8–15%.[3,4] In Taiwan, the estimated prevalence of migraine is 9.1% (~150 million people; 14.4% in women and 4.5% in men).[5] This disorder results in an estimated 3.7 million missed workdays, incurring an annual cost of approximately NT$4.6 billion.[6] Migraine thus imposes a heavy burden not only on individuals, but also on families and society. As prophylactic medications for migraine have adverse effects and cannot completely prevent migraine attacks, nonmedicinal alternatives are needed.

In recent years, hyper-excitability of the central nervous system (CNS) has been demonstrated in patients with migraine.[7] The modulation of CNS excitability (i.e., neuromodulation) provides an opportunity for nonpharmacological treatment of these patients. Since its introduction in 1985, repetitive transcranial magnetic stimulation (rTMS) has been shown to effectively modulate CNS excitability through the modification of synaptic plasticity.[8] Low-frequency rTMS ($\leq$ 1 Hz) can reduce cortical excitability, whereas high frequencies ($\geq$ 5 Hz) can correspondingly increase it. Additionally, rTMS has been previously used for several therapeutic purposes,[9] including the treatment of chronic pain[10,11] and migraine.[12,13]

Theta burst stimulation (TBS) is a pattern-specific type of rTMS. Compared with conventional rTMS protocols, TBS requires less stimulation time and lower intensity to induce comparably long-lasting effects in the human cerebral cortex.[14] The use of conventional rTMS paradigms to relieve provoked acute or experimental pain has been reported.[15] The continuous TBS (cTBS) had an inhibitory effect on the excitability of the cerebral cortex.[14] However, the use of cTBS as an antinociceptive approach has not been well studied. In this study, we explored whether the application of cTBS to the primary motor cortex (M1) in patients with migraine reduced migraine frequency.

2. Methods

2.1. Patients

Patients with migraine were recruited for this pilot study from the Headache Clinic of Taipei Veterans General Hospital, Taipei, Taiwan. No participant had prior rTMS experience, a cardiac or cerebral pacemaker, metal in the cranium, epilepsy, pregnancy, and any systemic or neurological disease. The diagnosis of migraine was based on the criteria of the International Classification of Headache Disorders, 2nd edition.[16] All participants completed a detailed headache intake form at the time of recruitment.

Prior to entering the study, all participants had to provide signed informed consent. The Institutional Review Board of Taipei Veterans General Hospital approved the study protocol (VGHIRB No.: 95-02-01).

2.2. rTMS

Each patient sat in a comfortable chair and was asked to relax. A recording electrode was placed on the left abductor pollicis brevis (APB) muscle, and a reference electrode was placed on the metacarpal–phalangeal joint. After that, motor-evoked potential signals were displayed on a conventional electromyographic machine (Neuropack M1; Nihon Kohden, Tokyo, Japan). We first determined the "hot spot" ($M1_{APB}$) for activation of the left APB muscle, where stimuli-evoked motor potentials had the maximal peak-to-peak amplitude. The coil was moved in 5-mm increments to determine the optimal scalp position. We then determined the resting motor threshold (RMT) at the hot spot, which was defined as the minimum stimulation intensity required to evoke a motor-evoked potential > 50 μV in at least five of 10 trials.

2.3. Stimulation protocol

After the stimulation site ($M1_{APB}$) and intensity (RMT) were determined, rTMS (cTBS) was delivered to the $M1_{APB}$ through a figure-eight coil connected to a Magstim Rapid magnetic stimulator (Magstim Co., Whitland, Dyfed, UK). cTBS consisted of bursts of three 50-Hz TMS pulses, repeated at 200-ms intervals for 40 seconds. The intensity was set at 80% of each patient's RMT. The coil was placed tangentially to the scalp, approximately 45° from the midline, and the handle of the coil was angled 45° posterolaterally. Treatment consisted of 20 rTMS (cTBS) sessions, delivered every weekday for 4 consecutive weeks. All patients received cTBS.

2.4. Outcome evaluation

All participants kept headache diaries for 4 weeks before stimulation (baseline; T1), during stimulation (T2), and 4 weeks after stimulation (T3); they submitted their diaries at the conclusion of each time period. The primary outcome measures were the changes of total headache and migraine headache days from baseline, i.e., T2 versus T1 and T3 versus T1. The secondary outcome measures were the frequency of migraine abortive medicine use, Beck Depression Inventory (BDI), and Hospital Anxiety and Depression Scale (HADS) total (T) scores in each time period, and changes from baseline (Fig. 1).

2.5. Safety and tolerability measures

We recorded spontaneously reported treatment-emergent adverse events during each visit. Patients' vital signs were

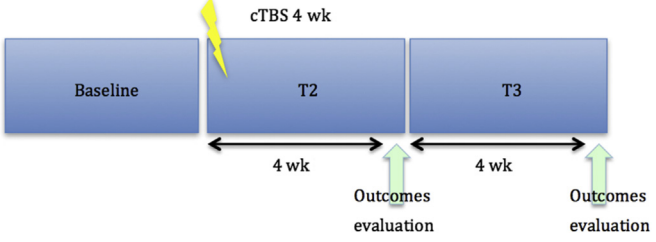

Fig. 1. Outcome evaluation. cTBS = continuous theta burst stimulation; T2 = during stimulation; T3 = 4 weeks after stimulation.

measured, and physical and focused neurological examinations were conducted during each visit.

2.6. Statistical analysis

All analyses were performed with SPSS version 21.0 software (IBM, Armonk, NY, USA). The Wilcoxon signed-rank test was used for analyzing the changes of primary and secondary outcomes at T2 and T3 compared with T1. Spearman's rank correlation coefficients (r_s) were used to determine the association between the change of total headache or migraine frequencies and BDI scores. Nonparametric tests were used due to the small number of observations and potential violation of the normality assumption. Statistical significance was defined as $p < 0.05$, and all tests were two-tailed.

3. Results

Nine patients (1 man, 8 women) with a mean age of 35.8 ± 10.5 (range, 32–51) years participated in the study. The mean duration of headache history was 12.8 ± 6.5 (range, 3–17) years. The patients used analgesics on an average of 4.3 ± 3.4 (range, 2–10) days per month. Three (33.3%) of the patients had chronic migraine and had been taking prophylactic medication (metoprolol, propanolol, or topiramate) for at least 3 months (Table 1).

3.1. Primary outcome measures

cTBS significantly reduced the mean number of total headache days per month, from 13.4 ± 10.1 days at T1 to 9.4 ± 6.2 days at T2 ($p = 0.024$) and 8.7 ± 10.1 days at T3 ($p = 0.012$). The mean number of migraine days per month was also reduced significantly, from 8.6 ± 8.7 days at T1 to 2.9 ± 2.7 days at T2 ($p = 0.021$) and 1.0 ± 1.6 days at T3 ($p = 0.008$; Fig. 2).

Table 1
Baseline demographic characteristics and headache profiles of participants ($n = 9$).

Parameter	Mean ± SD (range) or *n* (%)
Age (y)	35.8 ± 10.5 (24–51)
Sex	
Male	1 (11.1)
Female	8 (88.9)
BMI (kg/m^2)	21.9 ± 2.7 (19.1–25.7)
Duration of headache history (y)	12.8 ± 6.5 (3–17)
Migraine diagnosis	
Episodic migraine	6 (66.7)
Chronic migraine	3 (33.3)
Total headache frequency (d/mo)[a]	7.78 ± 6.2 (3–20)
Analgesic use (d/mo)[a]	4.3 ± 3.4 (2–10)
BDI score	9.2 ± 8.4 (3–30)
HADS-T score	34.7 ± 2.7 (31–38)
Total headache (d)	13.4 ± 10.1 (3–29)
Migraine (d)	8.6 ± 8.7 (1–28)

BDI = Beck Depression Inventory; BMI = body mass index; HADS-T = Hospital Anxiety and Depression Scale total scores; SD = standard deviation.

[a] Average of past 3 months.

3.2. Secondary outcome measures

The frequency of abortive medication use per month was reduced significantly compared with baseline (3.8 ± 3.0 days) at T3 (2.4 ± 3.3 days, $p = 0.042$), but not at T2 (2.8 ± 2.7 days, $p = 0.084$). The mean BDI score was also significantly lower than baseline (9.2 ± 8.4) at T3 (4.8 ± 6.0, $p = 0.012$), but not at T2 (7.2 ± 11.3, $p = 0.16$). By contrast, no change in mean HADS-T score from baseline (34.7 ± 2.7) was observed (T2: 36.0 ± 1.5, $p = 0.776$; T3: 34.6 ± 4.3, $p = 0.888$). According to the Spearman's rank correlation analyses, the changes of total headache or migraine days were not associated with the change of the BDI scores, where total headache days T2: $r_s = 0.021$, $p = 0.957$; T3: $r_s = -0{,}017$, $p = 0.965$; migraine days: T2: $r_s = -0.193$, $p = 0.618$; T3: $r_s = -0.266$, $p = 0.489$.

3.3. Adverse events

No significant adverse events were reported during the experimental period.

4. Discussion

In this study, we demonstrated that the application of cTBS over the M1 area effectively reduced headache frequency. The 4-week cTBS treatment significantly reduced the number of total headache and migraine days, and this effect persisted 4 weeks after treatment. The effect on sizes of the reduction in the mean frequency of all headaches and migraines were 4.7 days and 7.6 days per month, respectively, exceeding those reported previously for pharmacological treatment (average 0.5–2 days per month).[17–20] Our results are similar to those of a previous study, in which acupuncture reduced the mean number of headache days per month from 20.2 ± 1.5 days to 9.8 ± 2.8 days. cTBS and acupuncture thus appear to have more substantial effects than prophylactic migraine medication.[21] However, these effects were not associated with improvement of depression or anxiety in the present study, as BDI and HADS-T scores were not correlated with improvement in total headache or migraine frequency.

However, there have been some studies applying rTMS to modulate the cortical excitability in patients with migraine, which resulted in clinical improvement.

Brighina et al[22] in 2004 first demonstrated the positive effects of high-frequency rTMS application over the left dorsolateral prefrontal cortex (DLPFC) in patients with chronic migraine, in terms of decreased frequencies of migraine attack and analgesic use, as well as reduced headache impact. However, no such effect was observed in a subsequent large-scale randomized double-blind study, in which a similar high-frequency rTMS protocol was utilized for 18 patients with chronic migraine.[23] This discrepancy in findings may result from differences in patient selection and stimulation protocols. However, one

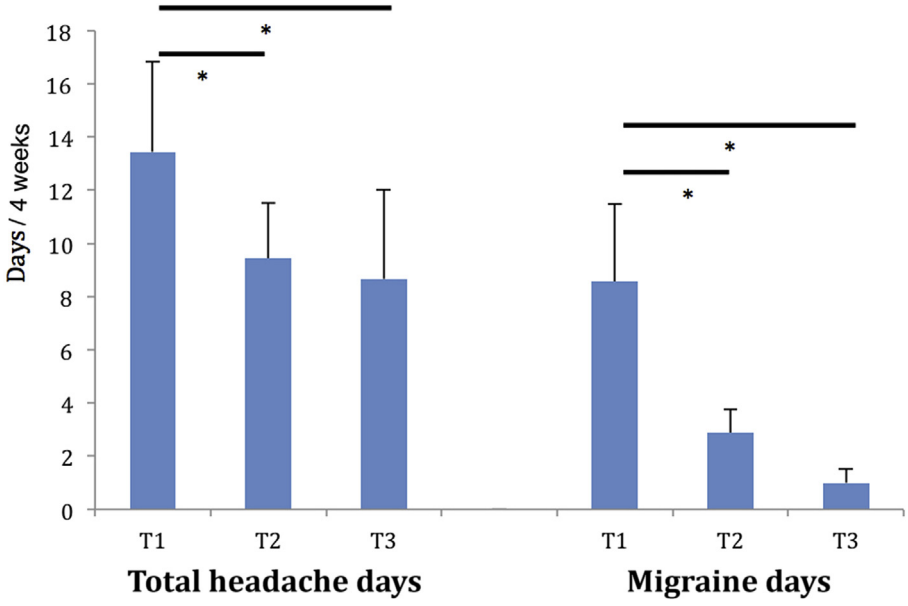

Fig. 2. Total headache and migraine days at baseline, during stimulation, and 4 weeks after stimulation. T1 = baseline; T2 = during stimulation; T3 = 4 weeks after stimulation.

should bear in mind that high-frequency rTMS over the DLPFC may modify the attentive and emotional aspects of pain, rather than the perception of pain itself. This modality is also likely to be beneficial in reducing the symptoms of depression.[24] Thus, the discrepancy between these two studies may derive from baseline differences in the participants' psychiatric comorbidities. The effect of high-frequency rTMS over the DLPFC on migraine prophylaxis may therefore require further evaluation.

The M1 is another target of choice. Histological[25] and neurophysiological[26] studies have clearly demonstrated the intimate connection between M1 and the primary somatosensory cortex (S1). Furthermore, it has also been demonstrated that M1 stimulation exerts its modulation effect on S1 more pronouncedly than direct S1 stimulation[27] or stimulation on the other cortices,[28] providing the basis for M1 modulation in reducing pain perception.[9–11] As S1 is also responsible for pain perception in migraine headache,[29] modulation of S1 excitability through M1–S1 connection is a reasonable approach.

Misra et al[12] demonstrated that high-frequency rTMS over the M1 reduced headache frequency and severity, analgesic usage, and functional impairment in patients with migraine. It may conflict with the concept that one should reduce cortical excitability by low-frequency rTMS through its inhibitory effect in treating patients with migraine. However, it was recently proposed that repeated pain perception may alter the responses to rTMS in patients with migraine, throughout the metaplasticity effect.[30] The effect of high-frequency rTMS in patient with migraine are therefore more likely inhibitory than excitatory as observed in normal individuals. As cTBS also exerts its modulation through an inhibitory effect, our results are consistent with those of Misra et al's[12] study. Our results suggest that cTBS over the M1 has a migraine prophylactic effect similar to that of high-frequency rTMS over the same region. As cTBS can be delivered within 1 minute, which is only one-fifteenth to one-tenth the duration of high-frequency rTMS treatment, it may provide better patient compliance with noninvasive brain stimulation in a clinical setting.

The exact mechanisms by which cTBS over the M1 area ameliorates headache frequency remains unknown. The effect of rTMS (including TBS) is known to be due to long-term potentiation/depression-like modification of synaptic transmission,[31] and later to a genetic modification effect (gene transcription and protein synthesis) in perisynaptic cells.[32,33] The modulation of cortical hyper-excitability may have therapeutic effects in patients with migraine.

This study had several limitations. It was exploratory and involved a small number of patients and a single active treatment component. However, the significant effects observed despite these limitations suggest that the study results were not likely false positive. Nevertheless, further large-scale studies with a sham control group are warranted.

In conclusion, the results of this study suggest the potential of rTMS using a cTBS paradigm over the M1 as an alternative migraine treatment strategy. This treatment was well tolerated and may be effective as a migraine prophylaxis. However, large-scale randomized controlled trials are required to validate our findings.

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