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Short Communication

Internal Medicine Section

Poor Tolerance of Motor Cortex rTMS in Chronic Migraine

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ABSTRACT

Background: Two small studies had evaluated the efficacy of rTMS in migraine. One tested high frequency rTMS over the dorsolateral prefrontal cortex while the other evaluated 1 Hz rTMS over the vertex.

Aim: To test the feasibility of 10 Hz rTMS of motor cortex as an adjunctive therapy in patients with chronic migraine.

Materials and Methods: We randomized (2:1 ratio) chronic migraine patients on medical preventive treatment to receive either rTMS or sham therapy for 10 sessions. rTMS (80% resting motor threshold, 10Hz, 20 trains, 5 secs/train, inter-train interval 1 min, total 1000 stimuli/session) was applied over the right motor cortex.

Result: Nine patients were randomized. Six received rTMS and three had sham therapy. Three patients in the rTMS arm withdrew from the study due to increased headache frequency and discomfort from the treatment. The remaining six cases (3 rTMS, 3 sham) completed the study. The study was prematurely stopped due to the significant worsening of headache from rTMS. No significant differences in outcome measures were found between real and sham rTMS.

Conclusion: Although the study was terminated prematurely, the high dropout rate (50%) due to worsening headaches suggested that rTMS over the motor cortex is poorly tolerated in chronic migraine.

Keywords: Adverse effect, Chronic migraine, Central sensitization, Cortical excitability, Headache, rTMS

INTRODUCTION

Chronic migraine (CM) significantly impairs activity of daily living in sufferers. Current medical therapies are inadequate in many patients, prompting the search for alternative treatment modalities. In recent years, repetitive transcranial magnetic stimulation (rTMS) has been evaluated as adjuvant therapy in reducing frequency and severity of attacks [1,2]. Two main rationales underlie this therapeutic approach; activation of descending pain modulatory pathways through cortical stimulation and the restoration of abnormal cortical excitability in migraineurs by rTMS [1,2].

Pain afferents from trigeminal and occipital innervations synapse onto second-order neurons in a trigemino-cervical complex located in the brainstem and upper cervical cord [3]. These connect with pain modulatory sites in the brainstem (such as the periaqueductal grey matter) and sensory thalamus. It has been postulated that stimulation of the motor cortex (M1) modulates pain by activating fibres that connect with pain modulatory sites in the thalamus and brainstem causing a top-down activation of descending pain control systems and also blunting of affective reactions to pain via interconnections with orbitofrontal-perigenual cingulated cortex [4].

There is evidence to suggest that abnormal cortical excitability of the brain predisposes a migraineur to migraine attacks [5]. Studies have also demonstrated that rTMS over the M1 region help restore defective intracortical inhibition and normalize excitability in brains of migraineurs [5].

We wanted to evaluate the feasibility of high-frequency 10 Hz rTMS of M1 region as an adjunctive therapy in patients with chronic migraine. However, the study was stopped prematurely when 3 subjects reported exacerbation of headaches from the treatment. We describe details of the study and discuss possible reasons for the adverse effects experienced in these patients.

MATERIALS AND METHODS

Subjects

Patients with CM and on headache preventive medication were recruited from the Neuroscience clinic of National University Hospital, Singapore between years 2009 and 2011. They were diagnosed in accordance to the International Headache Society [6] criteria; headaches occurring more than fifteen days per month over a three-month period of which more than eight are migrainous, in the absence of medication overuse. Patients were randomized into either real or sham rTMS (2:1 ratio respectively) as adjunct treatment and were blinded to the type of rTMS treatment they received. During this time, all patients continued their headache preventive medication with no change in dosages. Our institutional review board approved this study and all patients provided informed consent.

rTMS intervention: rTMS was delivered via a Magstim Rapid stimulator (Magstim Co., Whitland, Wales, UK) using a 7cm figure-of-eight coil. Resting motor threshold (RMT) was determined by finding the minimal intensity over the right M1 that elicited a 50μV MEP amplitude response in 5 out of 10 single-pulse TMS. In the rTMS group, each patient received 10 sessions. rTMS was applied over the right M1 consisting of 20 trains (5 secs/train, inter-train interval - 1 min, 1000 stimuli in total) using 80% RMT at 10 Hz. In the sham group, the frequency, duration, number of stimuli and inter-train interval was kept identical to the rTMS group but stimulation intensity was set at 10% of stimulator output and the coil was angled 30° away from the scalp.

Primary outcome measures: A headache diary was kept by all patients to record primary outcome measures starting from one month before the study till 2 months after. These outcome measures included: 1) Total headache days; 2) Overall headache index (number of headaches within 28 days × average severity of each headache day × duration in hours of headache each day) ÷ 28 days; 3) Headache severity (0 to 3 scale; 0- no headache, 1- easily ignored, 2- affects daily function but can carry on, 3- unable or difficult to carry on daily function); 4) Headache duration in hours; and 5) Name and dose of analgesic medication used. Outcome measures at baseline, one month and two months after the start of the study was compared between sham and real groups.

RESULTS

The study aimed to recruit 30 subjects but was stopped prematurely due to adverse effects. Fifteen patients (aged 21-65) were recruited. Six did not complete their headache diaries properly and were

dropped from the study during the leading first month. Eventually nine were randomized to receive either real (n=6) or sham (n=3) rTMS as adjunct treatment. Three patients given real rTMS withdrew due to increased headaches or discomfort related to the treatment. One patient was not able to tolerate the cutaneous pain over the scalp and withdrew on the first day of treatment. The pain persisted for the rest of that day. Another patient withdrew after experiencing a major exacerbation of migraine attack after three days of treatment. The migraine attack lasted three days. A third patient felt scalp discomfort during treatment and withdrew after five days of treatment. He felt that the treatment exacerbated the intensity of his daily headaches. The remaining three patients given real rTMS and all patients given sham treatment completed all 10 sessions. No significant differences in outcome measures were found between real and sham rTMS.

DISCUSSION

Our study suggests that 10Hz rTMS over M1 is poorly tolerated by chronic migraine patients. Scalp discomfort and headaches have commonly been reported in rTMS studies, occurring in up to 40% of cases [7]. However, they were usually mild to moderate in severity and responded promptly to simple analgesics. The exact causes are unclear but may be related to the induced muscular contraction and trigeminal stimulation. In previous clinical trials, only a small percentage (<2%) of subjects discontinued treatment due to pain [7].

Two previous small studies had evaluated the efficacy of rTMS in migraine. Brighina et al., [1] postulated that excitatory effects of high frequency rTMS over the dorsolateral prefrontal cortex modulate pain through its connectivity with pain processing centers in the brainstem and thalamus. In a study involving 11 subjects, they found a significant reduction in attack frequency, headache index and number of abortive measures in the active treatment group compared to the sham stimulation group during and a month after the treatment. Teepker et al., [2] postulated instead that the inhibitory effect of low frequency rTMS may decrease the brain hyperexcitability in migraineurs and decrease migraine attacks. In a placebo-controlled study involving 27 patients, they evaluated 1 Hz rTMS over the vertex and found no significant differences in number of migraine attacks and days between placebo and active treatment groups. No increase in headache was reported in these two studies.

The reason for the increased headache adverse effects in our patients is unclear. Stimulation intensities used on our subjects during the study (range: 44-52% of machine output) were not higher than that in other studies involving the M1. Teepker et al., [2] stimulated over the vertex, Brighina et al., [1] stimulated the left frontal cortex while we stimulated the right M1. We cannot be certain if the increased headache adverse effect is related to the site of stimulation but to our knowledge, headaches were not more frequent with M1 stimulation in other subject populations [7].

The condition of chronic migraine in our subject population is a likely contributing factor. Chronic migraine patients with frequent attacks are known to have more abnormal cortical excitability and more susceptible to migraine triggers [5]. The mechanisms involve central sensitization of neurons in trigemino-cervical complex and thalamus with increased sensitivity to peripheral stimuli [8]. Persistent use of pain-relief medications has also been reported to lower pain thresholds and amplify responses to migraine triggers [9]. The usage of pain-relief medications in our patients ranged from 8 to 14 days a month and may have contributed to a lowered pain threshold.

Cutaneous allodynia is frequent in chronic migraine patients, related to the presence of central sensitization [10]. Although, we did not screen for its presence, cutaneous allodynia is a likely explanation for one patient finding pain over the scalp intolerable during the therapy.

Certain limitations of our feasibility study needs acknowledgement. The number of subjects was too small for any conclusion about the efficacy of the treatment. We did not systematically examine the degree of any headaches or allodynia in the subjects at the onset of the rTMS procedure. Examining these in future study may determine better the relation of any headache exacerbation with the rTMS. Nevertheless, the high dropout rate (50%) from headache adverse effect suggested that high frequency rTMS over the M1 region should be used with caution in patients with chronic migraine. Should it be required, we suggest that patients should be headache free for at least 24h after the most recent attack and free of cutaneous allodynia before undergoing therapy.

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