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Short communication

Cerebellar repetitive transcranial magnetic stimulation for patients with essential tremor

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ABSTRACT

Introduction: The possibility of repetitive transcranial magnetic stimulation (rTMS) as an alternative therapy for essential tremor (ET) patients has emerged. However, its effect on medicated ET patients is lacking. The aim of this pilot study was to investigate the effect of cerebellar low-frequency rTMS as an "add-on" treatment.
Methods: In this single-blinded, randomized, sham-controlled pilot study, patients with ET were randomized into two groups, one receiving real-rTMS and the other sham-rTMS. For 5 days, 1200 stimulations per day were applied to the bilateral cerebellar hemispheres at an intensity of 90% of the resting motor threshold (RMT) with a frequency of 1-Hz. Motor evoked potentials (MEPs) and the Fahn-Tolosa-Marin tremor rating scales (TRS) were measured before, immediately, and 4 weeks after the completion of the rTMS procedures. All patients continued taking medications during all procedures.
Results: Among 22 patients, 12 and 10 patients were randomized into the real- and sham-rTMS groups, respectively. Repeated analysis of variance (ANOVA) measurements showed that the total TRS, TRS-A and B were changed both in real and sham-rTMS groups without interaction between time and group. TRS-C and MEPs, were not significantly changed at each follow-up point in either the real or sham-rTMS sessions.
Conclusion: We conclude that cerebellar low-frequency rTMS is safe, but has no significant effect as an "add-on" therapy in patients with ET.

1. Introduction

Essential tremor (ET) is a common movement disorder, which is characterized by a postural and kinetic tremor mainly affecting both arms [1]. Although this disorder is not life threatening, it can significantly impair patients' daily living activities. Beta-blockers and primidone have been used as the treatment of choice for patients with ET. However, up to 50% of ET patients report that they are not satisfied with the reduction of their tremor symptoms with these medications [2].

Various non-invasive brain stimulations (NIBS) including repetitive TMS (rTMS), theta burst stimulation, and transcranial alternating current stimulation have been tried as a non-pharmacological treatment in ET patients [3,4]. Based on the cerebello-thalamo-cortical (CTC) involvement in ET [5–7], cerebellar stimulation may be expected to have therapeutic effects in ET patients. Indeed, single and multiple sessions of rTMS on the cerebellum at a frequency of 1 Hz have shown transient effects on physiological and clinical tremor severity in ET patients [8,9]. If NIBS has an additive effect on improvement of tremor in addition to medications, it will help the quality of life in ET patients. However, no study has investigated whether rTMS has such an additive effect. Therefore, we investigated the effects of cerebellar low-frequency rTMS as an "add-on" treatment in patients with ET.

2. Methods

This was a single-center, single-blinded, randomized, sham-controlled pilot study. This study was approved by the Institutional Review Board of Chung-Ang University Hospital, and all participants provided written informed consent.

2.1. Participants

Patients diagnosed with ET according to the Movement Disorder Society diagnostic criteria were included in this study [1]. The patients had bilateral postural or kinetic tremor of the arms, no dystonia, and no

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possibility of drug-induced secondary tremor. In addition, we included subjects in this study only if they had significant residual tremor despite using beta-blockers or other drugs as symptomatic management. Patients who had a cardiac pacemaker, insulin pump, or any metallic devices inside the body were excluded.

2.2. rTMS procedure

Subjects were randomized into a group receiving real rTMS and another group receiving sham rTMS. Resting motor threshold (RMT) of the right abductor pollicis brevis muscle was measured. We measured RMT as the lowest stimulus intensity required to produce motor-evoked potentials (MEPs) of at least 50 μV in at least 5 of the 10 consecutive trials. Stimulation intensity for the rTMS procedure was set at 90% of the RMT. We employed rTMS with a Magstim rapid stimulator-2 (Magstim, Whitlan, UK) using a 7-mm figure-of-eight coil. The stimulation site for the cerebellum was 3 cm lateral and 1 cm inferior to the inion. The rTMS was applied over each side of the cerebellum in turn (Supplementary material 1). The order of the stimulation to each side was randomly assigned. For 5 days, 1200 stimulations per day were applied with an intensity of 90% of the RMT at a frequency of 1 Hz (600 stimulations to each side of the cerebellum). Each session of 1 Hz rTMS consisted of 20 trains with a duration of 30 s each, separated by 10 s. The sham rTMS consisted of the same procedure, but the coil was applied perpendicular to the scalp.

2.3. Clinical evaluation

Patients were evaluated using the Fahn-Tolosa-Marin tremor rating scale (TRS) before rTMS, after the rTMS session on day 5, and 4 weeks after the completion of rTMS sessions. The TRS score ranges from 0 to 84 because it consists of 21 items that can be scored from 0 to 4 [10]. It consists part A and B, in which the clinical severity of tremor is included, and C, which reflects the activities of daily lives in patients. Additionally, the Glass scale was retrospectively measured as a baseline clinical parameter.

2.4. Statistical analysis

The clinical and physiological characteristics of patients with real and sham-rTMS were compared using the Mann-Whitney *U* test. Mean TRS and MEPs at the different times were compared between real and sham-rTMS groups using repeated measures ANOVA. Multiple comparisons with Bonferroni correction were used to compare the variables at the different time points. All data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY), with a significance level of $p < 0.05$.

3. Results

Twelve and ten patients were randomized into the groups of real and sham-rTMS, respectively. One patient, who was randomized to the sham-rTMS group, dropped out because the use of propranolol was stopped during the follow-up period owing to bradycardia. Therefore, 12 and 9 patients were included in the final analysis in the real- and sham-rTMS groups, respectively. In total, 8 and 6 patients were taking only propranolol, and 4 and 3 patients were taking propranolol and clonazepam in the real- and sham-rTMS groups, respectively. The median age, symptom duration, daily dosage of propranolol, and clonazepam, baseline TRS scores, the Glass Scale, RMT, and mean MEP amplitude were comparable between the groups (Table 1). The mean total TRS was reduced by 33% in patients receiving real stimulation and by 20% in those receiving sham stimulation immediately following completion of rTMS; and was reduced by 31% in patients receiving real stimulation and 17% in those receiving sham stimulation 4 weeks after completion of rTMS, compared to the scores at baseline. For the TRS-A and TRS-B, and total TRS repeated ANOVA indicated a significant effect of 'time' ($df = 2$, $F = 14.786$, $p < 0.001$; $df = 2$, $F = 18.446$, $p < 0.0001$; $df = 2$, $F = 26.623$, $p < 0.001$, respectively) but no significant effect of 'group' ($df = 1$, $F = 1.976$, $p = 0.176$; $df = 1$, $F = 2.175$, $p = 0.157$; $df. = 1$, $F = 2.367$, $p = 0.140$, respectively) nor interaction. Multiple comparisons with Bonferroni correction showed that the TRS-A, B and total TRS were significantly reduced immediately and 4 weeks after rTMS compared to the scores at baseline. There was no difference in the TRS-C at any of the time points in both groups (Fig. 1). Repeated measures ANOVA showed that neither 'time' nor 'group' had a significant effect on MEP amplitude. Mean MEP amplitudes at the three time points (before rTMS, after the rTMS session on day 5 and 4 weeks after the completion of rTMS) were 080 ± 0.42 mV, 0.95 ± 0.64 mV, and 0.95 ± 0.51 mV, respectively, in the real-rTMS group and 00.90 ± 0.68 mV, 0.98 ± 0.81 mV, and 0.96 ± 0.80 mV, respectively, in the sham-rTMS group. None of the participants showed any adverse events such as headache, dizziness, syncope, or seizure.

Table 1
Characteristics of participants in real and sham-stimulation.

	Real-stimulation (n = 12)	Sham-stimulation (n = 9)
Number of female	4	6
Age (years)	68.8 (61–79)	65.2 (25–81)
Duration of symptoms (years)	8.8 ± 6.4	10.6 ± 11.9
Duration of treatment (years)	5.1 ± 3.9	4.8 ± 4.9
Clinical tremor rating scale-A	7.6 ± 4.0	8.2 ± 2.7
Clinical tremor rating scale-B	12.3 ± 6.9	16.1 ± 8.4
Clinical tremor rating scale-C	8.3 ± 5.7	10.1 ± 3.9
Glass scale	2.0 ± 0.9	2.0 ± 0.9
Dosage of propranolol (mg/day)	86.7 ± 37.5	84.4 ± 32.7
Resting motor threshold (%)	71.3 ± 9.8	65.6 ± 6.5
Motor evoked potentials (mV)	0.80 ± 0.42	0.90 ± 0.68

4. Discussion

In this study, we showed that low-frequency cerebellar rTMS was safe, but we failed to show the superiority of real-rTMS compared to sham-rTMS as an "add-on" treatment for ET patients who are taking medications. Both real and sham-rTMS groups showed improvement in TRS-A, B and total TRS after intervention, but TRS-C did not change in either groups. Part A and B of TRS reflect the severity of tremor measured by neurological examination, whereas part C is measured as how much the tremor affected the daily life of the patient by the interview. Those findings indicated that the reduction of tremor severity did not lead to an improvement in function of patients' daily lives. Note can be made that the sham group was slightly worse at baseline, and that the percent improvement was numerically better in the real-rTMS group, and these differences might have been significant in a larger study. Unlike the results of TRS-A and B, TRS-C did not change in either group. Parts A and B of TRS reflect the severity of tremor measured during neurological examination, whereas part C reflects the effects of tremor on the daily life of the patient, as determined by interview. The discrepancy in response of sub-scores to the rTMS intervention indicated that the reduction of tremor severity, as assessed on neurological examination, was not sufficient to improve patients' daily functioning.

The efficacy of inhibitory cerebellar stimulation on patients with ET is unclear. Multiple sessions of inhibitory cerebellar stimulation had short- and long-lasting effects, reducing tremor severity both clinically and physiologically [9]. However, a placebo effect could not be excluded because the study did not include a control group undergoing sham stimulation. A sham-controlled, crossover study evaluating the efficacy of inhibitory transcranial direct current stimulation (tDCS) on the cerebellum in patients with ET failed to show any change in tremor severity, as assessed both by a clinical rating scale and physiological

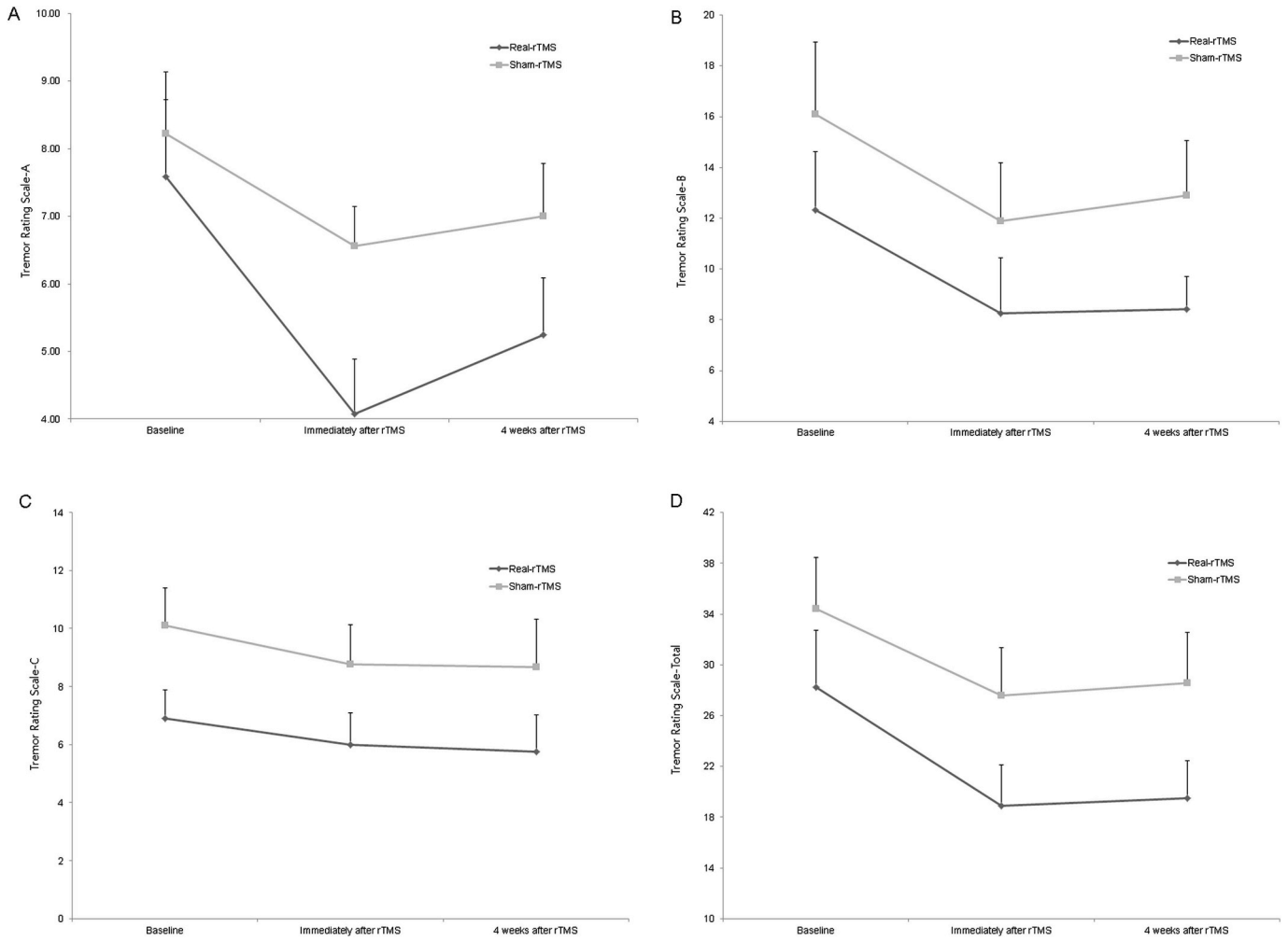

Fig. 1. Comparison of Fahn-Tolosa-Marin tremor rating scale (TRS)-A (A), B (B), C, (C), and total TRS (D) before and after rTMS interventions. TRS-A, B, and total TRS were changed significantly after rTMS sessions both groups. TRS-C was not changed at any of time points.

parameters, during both real and sham stimulation periods [11]. Both studies suggested that neural substrates other than the cerebellum are involved in the development of ET. In addition, differences in tools, sites and paradigms for brain stimulation in NIBS studies may lead to differences in results.

All participants continued taking medications at their usual dosage during all rTMS sessions and clinical evaluations. Therefore, we could not compare magnitude of the effect of medications between real and sham-rTMS groups. Irrespective of the effect of the medications on the tremor, low-frequency of rTMS over cerebellum may not be effective as an augmenting treatment strategy in partial responders to medications. In this study, the quantitative analysis of the severity of tremor was not evaluated using accelerometers, but only clinical scales were used. Because the rating scale of the TRS is roughly divided into 4 points from 0 to 4 it is unlikely to represent the exact changes in actual tremor amplitude. Accelerometric measurement might well have been better for this type of study.

Various types of NIBS have been investigated to ameliorate the symptoms of ET based on the fact that NIBS can either promote or inhibit cortical excitability in the human brain [3,4]. The exact mechanism by which low-frequency cerebellar rTMS might affect tremor in ET patients is still unknown. The CTC circuit has been proposed as a target to be modulated by rTMS because it has been believed to be the potential network causing tremor in ET patients [5,7]. Accordingly, the cerebellum has been the most popular subject of investigation as a potential target based on the knowledge that the cerebellum is associated with ET. We selected low-frequency rTMS on both sides of the cerebellar hemisphere and set the stimulus locations at both sides of the cerebellum, 3 cm lateral and 1 cm inferior from the inion. Although we did not designate the location of stimulation using an MRI-navigated system, the stimulation site might be close to the posterolateral cerebellum [12]. In addition, multiple sessions were selected based on previous results that showed only an immediate effect on tremor from a single session and a longer effect from multiple sessions of rTMS [8,9]. We believe that the protocol we used should have maximized the effect of rTMS on ET patients, Although the result of our study was negative, it is meaningful in that this was the first study to investigate the additional effect of cerebellar rTMS along with medications. Moreover, the design of the study was randomized and sham-controlled. Our results highlight the importance of a sham-controlled study design to confirm the effects of rTMS in open-label non-controlled studies.

There are limitations in our study in addition to its small size. We did not evaluate the responsiveness of tremor to medications, so we could not compare the difference of efficacy between rTMS and medications. In addition, tremor severity was assessed only by clinical rating scales without measuring physiological parameters. The physiological measure might have detected minor anti-tremor effects. Finally, a crossover design could compensate for the low statistical power resulting from the low number of patients, but this would have been problematic with the possibility of a carryover effect.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.03.019.

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