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Clinical Study

Low-frequency repetitive transcranial magnetic stimulation for dyskinesia and motor performance in Parkinson's disease

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ABSTRACT

Dyskinesias are one of the most frequent and disabling complications of the long-term treatment of Parkinson's disease (PD). Although the cause is not completely understood, it appears that an imbalance between excitatory and inhibitory inputs from the basal ganglia to the motor cortex leads to overactivation of motor and premotor areas. Overactivation of the supplementary motor area (SMA) has been observed in neuroimaging studies in dyskinetic PD patients. We investigated the effects of low-frequency repetitive transcranial magnetic stimulation (rTMS) of the SMA on levodopa-induced dyskinesias (LID) and motor performance in PD. We tested whether longer duration (10 days) and higher number of total pulses (1800 pulses) would enhance the beneficial effect. Seventeen dyskinetic PD patients were randomly assigned to real rTMS or sham (placebo) rTMS, and 1 Hz rTMS or sham rTMS was applied over the SMA for 10 consecutive days. Patients were assessed at baseline and 1 day after the last rTMS with a levodopa challenge test, and video recordings were taken. Dyskinesias and motor performance were rated off-line by two blinded raters using video recordings. After 10 days of treatment with rTMS, we observed that 1 Hz rTMS delivered over the SMA had decreased LID lasting for 24 hours without a change in motor performance, whereas sham rTMS induced no significant change in dyskinesia scores. These results support a possible therapeutic effect of low-frequency rTMS in LID. However, in order to suggest rTMS as an effective treatment, long-term observations and further investigations with a larger patient population are essential.

1. Introduction

Levodopa (L-dopa) is still the most effective drug for the symptomatic treatment of Parkinson's disease (PD). However, severe motor complications usually occur in conjunction with its chronic use. One of the most frequent and disabling complications of long-term treatment of PD is levodopa-induced dyskinesias (LID) [1–4]. Although the exact neural mechanisms underlying LID remain unknown, it is considered to be the result of reduced inhibition of thalamocortical neurons and overactivation of cortical motor and premotor areas, caused by the imbalance between excitatory and inhibitory inputs from the basal ganglia to the motor cortex [5–8]. Functional neuroimaging studies have demonstrated overactivation of primary cortical motor areas and the supplementary motor area (SMA) in dyskinetic PD patients [9,10].

The effects of repetitive transcranial magnetic stimulation (rTMS) over these cortical areas have been tested in a series of studies in dyskinetic PD patients. In these studies, 1 Hz rTMS applied either over the SMA or the motor cortex improved LID. However, the beneficial effects were not permanent and not potentiated by repeated sessions of stimulation [8,11–13].

Based on recent literature, we aimed to investigate the effects of low-frequency rTMS over the SMA on LID and on motor performance in patients with PD. Furthermore, we tested whether or not a longer duration (10 days) and higher number of total pulses (1800 pulses) of 1 Hz rTMS applied over the SMA would alleviate LID and prolong the beneficial effect without causing undesired side effects.

2. Method

Seventeen advanced PD patients (10 women, seven men) who had disabling peak-dose dyskinesias under dopaminergic treatment were enrolled in the study. Patients were diagnosed by a

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neurologist (R.C.) who specialises in movement disorders. The diagnosis of PD was made according to the United Kingdom Brain Bank Criteria [14]. Exclusion criteria were previous PD surgery and contraindications for rTMS. Antiparkinsonian medications producing the best control of PD symptoms were fixed for at least 1 month before enrollment until the end of the study except on the days of the L-dopa challenge test. The local Ethics Committee approved the study protocol, and informed consent was obtained from each patient.

The mean age of the patients was 61.88 ± standard deviation (SD) 9.06 years, and the mean disease duration was 11.41 ± SD 4.6 years. The patients were randomly assigned to the real rTMS (Group 1) or sham (placebo) rTMS (Group 2) treatment. The average equivalent dose of L-dopa in Group 1 was 1258 ± SD 238 mg/day and 1189 ± SD 200 mg/day in Group 2. Patient characteristics are presented in Table 1.

The MagPRO X100 magnetic stimulator and Keypoint 8-channeled Evoked Potential and EMG Recording System (Medtronic Sofamor Danek, Memphis, TN, USA) were used. A MCF-B65 figure-of-eight coil with 5 cm outer diameter was used for the real rTMS application, and a MC-P-B70 placebo coil (both Medtronic Sofamor Danek) with 7 cm outer diameter for the sham rTMS application. The figure-of-eight coil was placed over the scalp, 3 cm anterior to the Cz electrode of the 10–20 electroencephalography system in the sagittal midline with the coil handle pointing posteriorly [8,11]. In this way, a posteroanterior-directed current was created, and the SMA of both hemispheres were stimulated simultaneously.

The rTMS at 1 Hz frequency with duration of 30 minutes (total 1800 pulses, 90% of resting motor excitability threshold) was applied over the SMA for 10 consecutive days, at the same time each day for each Group 1 patient. For the sham application the same procedure was performed using the placebo coil instead.

The patients were assessed before the first rTMS application and 1 day after the last rTMS session using the L-dopa challenge test. In this test, patients received 1.5 times the equivalent dose of their morning medication with a single oral dose of L-dopa and benserazide after 12 hours of overnight withdrawal from L-dopa. After the completion of 10 days of rTMS procedure, each patient was evaluated at the same time and at the same dosage of L-dopa as in the previous baseline test. Motor performance and dyskinesias were evaluated and videotaped three times: at the "off period" (t0), and at 90 (t90) and 120 (t120) minutes after L-dopa administration. Dyskinesias were assessed during the following activation tasks: (1) sitting in a chair with hands on knees and sitting with hands hanging unsupported; (2) opening the mouth, with the tongue at rest within the mouth; (3) protruding the tongue; (4) tapping the thumb with each finger for 10–15 seconds with the right hand and then with the left hand; (5) standing up; (6) extending both arms, outstretched in front with palms down; and (7) walking a few paces, turning and walking back to the chair. The videos before and after rTMS applications were recorded to compact discs for evaluation by blinded raters. Two blinded neurologists specialising in the field of movement disorders (G.G.Y., E.Y.) then scored dyskinesias and motor performances off-line with video recordings. The means of the raters' scores were used for the statistical analyses. The motor performances were scored according to the Unified Parkinson Disease Rating Scale (UPDRS) Motor Section (Part 3) [15], and the dyskinesias were rated using the Abnormal Involuntary Movement Scale (AIMS) [16]. According to the AIMS, visible dyskinesias in each of the seven body parts (face, neck, trunk and each limb) were scored from 0 (absence of dyskinesia) to 4 (severe dyskinesia). Scores were lowered by one point if dyskinesias were provoked by action.

Subjective evaluation of the treatment by each patient was done using a visual analogue scale (VAS) on each day during the entire rTMS procedure. Items 32 and 33 of UPDRS Part 4, which evaluate motor complications of dopaminergic treatment, were also obtained before rTMS treatment (baseline) and on the first and tenth day (after the last rTMS session).

2.1. Statistical analysis

The Mann-Whitney U test was used for comparison of scores of the two groups before and after the rTMS procedure, and Wilcoxon signed rank test was used for the comparison of scores before and after the rTMS procedure within the same group. The collected analysis of the VAS scores was evaluated by Friedman analysis of variance. For all statistical analyses, a p value under 0.05 was considered significant.

3. Results

Nine patients received real rTMS (Group 1) and eight patients received sham rTMS (Group 2). No adverse effects were reported during the study. At the beginning of the study, there were no statistically significant differences between the two groups regarding sex, age, Hoehn–Yahr stage, and disease duration ($p > 0.5$, Mann-Whitney U test, Table 1).

At the baseline assessment, there was no significant difference between the groups in mean "off period" UPDRS motor scores ($p = 0.2$). Before rTMS treatment, analysis of AIMS scores at t90 and t120 showed that the mean AIMS score of Group 1 was significantly higher than of Group 2 ($p = 0.005$ and $p = 0.012$, respectively). Considering that the effect of medication could differ among patients, with some responding earlier and some later, we calculated the mean AIMS scores of t90 and t120 (t-mean), and found that the t-mean was also higher in Group 1 ($p = 0.007$, Table 2, Fig. 1).

Table 1
Baseline clinical characteristics of Parkinson's disease patients

	Group 1 (n = 9)	Group 2 (n = 8)	p value
Sex (Female/Male)	7/2	3/5	0.09[a]
Age, years (range)	64.78 ± 9.82 (50–79)	58.63 ± 7.39 (46–70)	0.22[b]
Hoehn–Yahr stage (range)	2.94 ± 0.53 (2–4)	2.81 ± 0.259 (2.5–3)	0.46[b]
Disease duration, years (range)	10.78 ± 5.87 (5–21)	12.13 ± 2.85 (9–17)	0.24[b]
UPDRS Part 3	28.83 ± 12.83	35.47 ± 6.02	0.21[b]
Average LED, mg/day	1251 ± 238	1189 ± 200	0.36[b]

Data are presented as mean ± standard deviation unless otherwise stated.
LED, levodopa equivalent dose; UPDRS, Unified Parkinson Disease Rating Scale.
[a] Pearson chi-square test.
[b] Mann–Whitney U test.

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