Clinical Protocol

rTMS for the Treatment of Freezing of Gait in Parkinson's Disease

2018-06-28

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NCT number: NCT03219892

1. List of abbreviations

BOLD = blood-oxygen-level-dependent;

FOG = freezing of gait;

FOGQ = Freezing of Gait Questionnaire;

H-Y = Hoehn and Yahr;

LEDD = levodopa equivalent daily dose;

MDS-UPDRS III = Movement Disorder Society-Unified Parkinson's Disease Rating Scale motor scores;

MMSE = Mini-Mental State Examination;

MMRM = mixed effect model repeated measures;

MoCA = Montreal Cognitive Assessment;

NC = normal controls;

PD-FOG = Parkinson's disease patients with freezing of gait;

PD-noFOG: Parkinson's disease patients without freezing of gait;

rTMS = repetitive transcranial magnetic stimulation;

SMA = supplementary motor area.

2. Introduction

Freezing of gait (FOG) is a common and debilitating symptom in patients with Parkinson's disease (PD), characterized by sudden and brief episodes of inability to produce effective forward stepping [1]. FOG is a major risk factor for falls, and greatly contributes to reduced mobility and quality of daily life [2]. Treatment of FOG has been perceived as a very challenging task. Although various treatment approaches exist, including pharmacological and surgical options, evidence is inconclusive for many approaches and no clear treatment protocols are available until now [3].

Repetitive transcranial magnetic stimulation (rTMS), a noninvasive neural modulation technique, has been closely applied as a treatment for various neurologic and psychiatric disorders [4]. A recent meta-analysis demonstrated that rTMS could improve motor symptoms for PD patients with a moderate effect size [5]. To date, however, only few rTMS studies have focused on its efficacy on FOG in patients with parkinsonism, and most of them targeted the primary motor cortex or dorsolateral prefrontal cortex [6-10]. Even though some evidence indicates the involvement of the supplementary motor area (SMA) in the pathogenesis of FOG [11-13], no report has described the SMA rTMS in PD patients with FOG.

Moreover, few studies combined functional magnetic resonance imaging (fMRI) and rTMS to unravel the mechanism of its beneficial effects. To address these issues, the investigators conducted a randomized, double-blind, sham-controlled study to explore the efficiency of SMA-rTMS on FOG in PD patients.

3. Study objectives

To explore the efficacy and neural mechanisms of rTMS over the SMA on FOG in PD patients.

4. Trial design

We will perform this current clinical trial with nested two sub-studies. Specifically this will include:

1. A cross-sectional resting-state fMRI study to obtain the brain connectivity pattern that specific to FOG in PD patients;

2. A randomized, double-blind, sham-controlled rTMS trial to study the clinical efficiency of SMA-rTMS on FOG in PD patients, as well as to investigate the underlying neural mechanisms by comparing the changes of the specific FOG related brain pattern identified in the resting-state fMRI study.

5. Eligibility criteria

The overall study will recruit three groups, including PD patients with FOG (PD-FOG), PD patients without FOG (PD-noFOG) and normal controls (NC). The inclusion and exclusion criteria are listed as below.

For the resting-state fMRI study, we will recruit all the three groups' subjects. For the rTMS study, we will invite the PD-FOG subjects from the resting-state fMRI study to participate into the trial.

6.1 Inclusion criteria

1. PD-FOG subjects

(i) 40-80 years old;

(ii) Patients diagnosed with idiopathic PD according to the UK Brain Bank Clinical Criteria;

(iii) FOG positive: presenting with one or more of the following three criteria [11].

1) convincing subjective reports of FOG, based on consistent behavioral characteristics of the phenomenon (including a typical feeling of the feet being "glued" to the floor);

2) patients' recognition of a typical phenotype by showing them a short video (70s) demonstrating typical freezing episodes;

3) response to a standardized gait task that contained specific elements known to provoke FOG, including gait initiation, a narrow passage, dual tasking, and rapid 3600 axial turns in both directions [14].

(iv) Mini-mental state examination (MMSE) questionnaire score above 24 points.

2. PD-noFOG subjects:

(i) 40-80 years old;

(ii) Patients diagnosed with idiopathic PD according to the UK Brain Bank Clinical Criteria;

(iii) FOG negative.

(iv) Mini-mental state examination (MMSE) questionnaire score above 24 points.

3. NC

(i) 40-80 years old;

6.2 Exclusion criteria

(i) presence of contraindications for rs-fMRI or rTMS;

(ii) history of deep brain stimulation surgery;

(iii) marked rest tremor;

(iv) comorbidities of neurological disease other than PD;

(v) left-handedness.

7. Study procedures (resting-state fMRI study)

7.1 Ethics requirements and informed consent

The whole experiments will be performed according to the Declaration of Helsinki and approved by the Institutional Review Board of Xuanwu Hospital of Capital Medical University. All subjects will give informed consent. Informed consent must be obtained before any trial related procedures are undertaken.

7.2 Clinical assessments

For all the PD patients, clinical assessments will be evaluated during their practical "OFF" state(withdrawal of anti-Parkinson medications for at least 12 hours), including:

(i)Movement Disorder Society-Unified Parkinson's Disease Rating Scale motor scores (MDS-UPDRS III);

(ii)Hoehn and Yahr (H-Y) stage;

(iii)Freezing of Gait Questionnaire (FOGQ);

(iv)Mini-Mental State Examination (MMSE);

(v) Montreal Cognitive Assessment (MoCA).

7.3 Rs-fMRI acquisition

Imaging will be carried out in a SIEMENS Trio 3T scanner. Participants will be instructed to keep their head still and eyes closed during scanning, but not fall asleep. Earplugs and a head coil with foam pads will be used to minimize machine noise and head motion. For PD patients, rs-fMRI scans will be acquired following a 12-hour period of medication withdrawal. Structural images will be acquired using a sagittal magnetization prepared rapid gradient echo three-dimensional T1-weighted sequence (repetition time [TR] = 1970 ms, echo time [TE] = 3.9 ms, inversion time [TI] = 1100 ms, flip angle [FA] = 15°). BOLD images will be obtained using the following SE-EPI sequence: repetition time = 2000 ms, echo time = 30 ms, voxel size = 3.0 × 3.0 × 3.0 mm3, slice thickness / gap = 4.0/0 mm, axial slices = 33 layers, flip angle = 90°, FOV = 256 mm × 256 mm, matrix size = 64 × 64, and scanning time = 8 min.

7.4 Rs-fMRI data preprocessing

The acquired rs-fMRI data will be preprocessed using the AFNI software package [15]. Several pre-processing steps will be performed, including de-spiking, slice timing correction, and 3D isotropic reslicing.

7.5 Rs-fMRI data processing

We will compare the brain connectivity pattern of PD-FOG subjects with PD-noFOG and NC subjects respectively, thus getting the specific pattern for FOG and PD in PD-FOG subjects.

8. Study procedures (rTMS study)

8.1 Ethics requirements and informed consent

The whole experiments will be performed according to the Declaration of Helsinki and approved by the Institutional Review Board of Xuanwu Hospital of Capital Medical University. All subjects will give informed consent. Informed consent must be obtained before any trial related procedures are undertaken.

8.2 Randomization and mask procedure

Patients in the rTMS study will be randomly assigned (with a 2:1 ratio) by a computer-generated block allocation into two groups, to receive either a verum (N=20) or sham (N=10) rTMS over SMA. The randomization sequence will be revealed only to the unmasked clinician responsible for the rTMS stimulation. The investigators and patients will be masked to the randomization group.

8.3. Verum and sham treatment strategies

We will perform verum or sham rTMS in ten sessions over two successive weeks, one session per day for five consecutive days per week. The rTMS sessions will be conducted one week after the acquisition of pre-rTMS fMRI acquired in the rs-fMRI study. To apply focal rTMS over the SMA, the stimulation site is determined as 3 cm anterior to the leg motor area along with the sagittal midline [16-18]. The coil will be held so that the induced current is perpendicular to the midline. The stimulus intensity is set to 90% of the rest motor threshold for the first dorsal interosseous muscle when the primary motor hand area is stimulated. In each session, a 5-second burst of 10-Hz rTMS will be repeated 20 times every minute (in total, 1,000 pulses, 20 minutes' duration). For the sham rTMS, the same stimulation parameters will be used, but the coil will be placed in 90° angulation over the SMA so that no relevant current flow is induced in the cortical tissue [19].

8.4. Study clinical assessments

8.4.1 Baseline clinical assessments

All clinical assessments for the rTMS study will be carried out in the "ON" state at the same time of the day, including:
(i) MDS-UPDRS III scores;
(ii) Gait analysis;
(iii) FOGQ.

8.4.2 Follow-up clinical assessments

Follow-up evaluations for each participant (except the FOGQ) will be performed before rTMS and after the 5th and 10th sessions, and then 2 weeks and 4 weeks after the last session, defined as T1, T2, T3 and T4 respectively. The FOGQ will be evaluated at T2 and T4.
(i) MDS-UPDRS III scores (T1, T2, T3 and T4);
(ii) Gait analysis (T1, T2, T3 and T4);
(iii) FOGQ (T2 and T4).

8.4.3 post-rTMS resting state-fMRI

Patients will undergo another resting-state fMRI scan, that is the post-rTMS fMRI acquisition, one or two days after the 10th session of rTMS. The acquisition paradigm, preprocessing and processing methods are same as used in the prior rs-fMRI study.

8.5 Outcomes

8.5.1 Primary clinical outcomes

We will use the improvement of FOGQ score, a self-assessment scale for evaluating FOG severity, as the primary clinical outcome.

8.5.2 Secondary clinical outcomes

The MDS-UPDRS III will be included as a secondary clinical outcome to evaluate the rTMS effect on motor symptoms. Additionally, as FOGQ is a subjective measure, we also adopted an additional objective evaluation tool, a Timed Up-and-Go (TUG) test, as another secondary outcome.

8.5.3 Secondary resting-state fMRI changes

The changes of the specific brain connectivity pattern identified in the resting-state fMRI study will be included as another secondary outcomes.

9. Recording Adverse Events

A record of any adverse events will be recorded and the relationship to rTMS treatment assessed and forwarded to the study co-ordinating centre.

10. Statistical analysis plan and sample size

10.1 Sample size calculations

As mentioned above, the primary clinical outcome for the rTMS study is the FOGQ score. Our sample size for the rTMS study will be calculated using the pooled estimate of within-group SDs of FOGQ obtained from a previous study [6]. The sample size will be determined by a priori using G*Power, assuming a moderate effect size of 0.48, α=0.05, power=0.8, number of groups=2, number of measurements (for the primary outcome / FOGQ) = 3 for a two-way repeated measures analysis of variance. The total sample size needed is 26. Considering a dropout rate of 20%, the sample size is 33.

10.2 Statistical analysis plan

Demographic data will be presented as mean ± SD for continuous variables. Independent two samples t-test will be performed for the comparison of continuous variables, and the $\chi 2$ test will be used to compare categorical variables. Paired t-test and McNemar's test will be used to test the biomarker changes before and after rTMS. In order to estimate the clinical effects of rTMS on the primary and secondary clinical outcomes, we applied a mixed effect model repeated measures (MMRM) model to evaluate within group and between group differences, and also their interaction difference. For respondents missing one or more interviews, MMRM allows data from completed interviews to be retained in analyses [20]. For each variable, we applied a separate model where the independent variables are the group (verum rTMS, sham rTMS) and the visit (T0, T1, T2, T3, and T4), and the group*visit condition interaction term. The fixed factors in these models are group and visit, while the random factor is the subject. The threshold for the level of significance is set at $\alpha = 0.05$. All statistical analyses will be performed using JMP Pro 12.0 software (SAS Institute Inc., NC). Graphics will be created using Prism 7.0.

11. Direct access to source data

The investigators will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial

participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

12. Monitoring plan for the trial

The trial will be monitored according to the monitoring plan agreed and written by the Sponsor.

13. Finance and funding

This work is supported by the grants from the Beijing Municipal government (PXM2017_026283_000002), Beijing Municipal Science & Technology Commission (Z161100000216140; Z171100000117013), Beijing Municipal Administration of Hospitals' Mission Plan (SML20150803), Scientific and Technological Innovation Capacity Developing-Scientific Research Base Building-Talent Development Fund of Beijing Institute for Brain Disorders, National Natural Science Foundation of China (61473196; 81601109), and Beijing Talents Foundation (2016000021223TD07; 2016000020124G107).

14. Publication policy

Results will be published in peer reviewed journals and presented at conferences. Publications policy will be decided by the steering committee.

15. References

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