STUDY PROTOCOL AND STATISTICAL ANALYSIS

Official Title: Effectiveness of Transcranial Magnetic Stimulation on Dysphagia in Patients with Parkinson's Disease: A Randomized Double-Blind Study

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Our study included patients aged 40-75 years with a diagnosis of Parkinson's disease who were followed up at the Physical Medicine and Rehabilitation and Neurology outpatient clinics and who experienced dysphagia symptoms. Inclusion criteria included being followed up with a diagnosis of Parkinson's disease, moderate to severe Parkinson's disease (Hoehn-Yahr 2-4), patients describing dysphagia symptoms, and being able to give informed consent. Exclusion criteria included intracranial metallic devices, cardiac pacemakers, history of seizures, antipsychotic use, diagnosis of depression, diagnosis of dementia, findings of additional neurological disease (intracranial lesion on imaging, hydrocephalus, positive Babinski sign, cerebellar signs), and normal FEES evaluation.

A total of 129 patients followed up with a diagnosis of Parkinson's disease from the Physical Medicine and Rehabilitation and Neurology outpatient clinics were screened based on their files. Forty-one patients who met the inclusion criteria were interviewed. Six patients declined to participate in the study. Six patients experiencing dysphagia symptoms had normal FEES results. The remaining 29 patients were included in the study. After randomization, there were 14 participants in the 5 Hz group and 15 participants in the 10 Hz group. During the treatment process, one patient from the 5 Hz group and two patients from the 10 Hz group withdrew from the study for personal reasons. Thirteen patients from each group participated in the post-treatment and 9-month follow-up evaluations. The relevant study flow chart is shown in Figure 1.

Patient files were scanned through the hospital system, and patients who met the inclusion criteria for the study were contacted by telephone. During this conversation, patients were informed about the content, purpose, duration, and possible complications of the study. Patients who agreed to participate in the study were invited for an examination. During this examination, patients were assessed for the presence of exclusion criteria. For patients deemed suitable for participation, the swallowing assessment form, FOIS, FSS, and EAT-10 test were completed. This was followed by a flexible endoscopic swallowing evaluation (FEES). During this evaluation, the YALE-2016 valeric residue scale, YALE-2016 piriform sinus residue scale, and penetration aspiration scale were scored. Participants were then assigned to one of two treatment groups.

Randomization was performed using a computer program. Treatments were administered at 5 Hz to one group and 10 Hz to the other group. Treatments consisted of a total of 10 sessions over two weeks, applied bilaterally to the pharyngeal and mylohyoid cortex by another researcher. Neither the researchers performing the assessments nor the patients were aware of

the treatment group. The TMS device used in our clinic was the Magstim Rapid 2 (Magstim Co Ltd, Spring Gardens, Whitland, UK), and a butterfly coil (D70) was used for stimulation. All treatment parameters except frequency were kept the same in both treatment groups. rTMS treatment was administered with a pulse duration of 10 seconds, an interval of 25 seconds, a total of 2000 pulses, and a stimulation intensity of 90% of the RMT of the first dorsal interosseous muscle of the hand. The current literature was reviewed when determining the treatment stimulation point. Studies conducted with stroke patients showed that 4-6 cm lateral and 2-4 cm anterior to the vertex were used for mylohyoid cortex stimulation. (17–20) The study referenced by all these studies is the one conducted by Khedr et al., in which the cortical topography of the swallowing muscles was mapped. (21) In our study, the vertex point was determined according to the international 10–20 method. Subsequently, based on the existing literature, 6 cm lateral and 3 cm anterior to the vertex point was determined as the mylohyoid and pharyngeal cortex stimulation point. Both groups were given cervical strengthening, shaker, massako exercises, and triflo breathing exercises as home exercises. After 10 sessions of rTMS treatment, the patients underwent a second evaluation, and the scores from the first evaluation were used.

After rTMS treatment, patients were asked to continue swallowing exercises. They were called for a follow-up evaluation at 9 months. The same evaluations performed at the first and second visits were also performed at the third visit.

G-Power software was used to calculate the sample size. According to the ANOVA analysis, the significance value was $p<0.05$; the effect size was 0.30, and the minimum sample size was calculated as 26 at a 95% confidence interval.

The statistical analysis of the study was performed using IBM SPSS Statistics version 27.0 and R analysis version 4.5.0. Descriptive statistical methods were used to examine demographic data. The normality of data distribution was assessed using the Shapiro-Wilk test. Since the data were found to be non-normally distributed, non-parametric tests were used.

The “Cochran test” and “Brunner Langer test” were used to evaluate the time-dependent distribution of categorical data within groups, and the “Dunn Bonferroni test” was used for pairwise comparisons of significant data. The “Chi-square test” was used for the intergroup evaluation of categorical data. The Friedman test was used to evaluate the time-dependent change in numerical data within groups, and the Mann-Whitney U test was used for the intergroup evaluation. The correlation of pre-treatment parameters was evaluated using Spearman correlation analysis.

The statistical significance level was set at $p<0.05$.