Original Article

High-Frequency Repetitive Magnetic Stimulation at the Sacrum Alleviates Chronic Constipation in Parkinson's Patients

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Abstract

Objective: This study was to investigate the therapeutic effect of high-frequency repetitive magnetic stimulation (HF-rMS) at the sacrum for chronic constipation in Parkinson's patients (PD). **Materials and Methods:** Eventually 48 PD patients were enrolled from July 2019 to October 2020, and randomly divided into the HF-rMS group (the intervention group, $n = 24$) and the sham HF-rMS group (the control group, $n = 24$). The intervention group received HF-rMS at the sacrum, whereas the control group received ineffective magnetic stimulation. We performed clinical evaluation before and after HF-rMS treatment, including constipation score scale (KESS questionnaire), Unified Parkinson's Disease Rating Scale (UPDRS-III exercise examination), Hoehn-Yahr (H-Y) stage of motor function; simple mental status scale (MMSE), anxiety/depression table (HAD-A/HAD-D), the activity of daily living (ADL), and quality of life scale for patients with constipation (PAC-QOL) to evaluate symptoms and satisfaction of PD patients with chronic constipation. **Results:** There was no significant difference in the clinical characteristics between the two groups. As compared to the control group, the HF-rMS group displayed a larger change (pre and posttreatment) in the KESS scores of PD patients with chronic constipation, suggesting a significant improvement. Moreover, HF-rMS significantly promoted the mood, activity of daily living, and quality of life of PD patients when comparing the alteration of HAD-A/HAD-D scores, ADL scores, and PAC-QOL scores between the two groups. Finally, there was no significant difference in the change of the UPDRS III score and the MMSE score between the two groups. **Conclusion:** HF-rMS at the sacrum can improve chronic constipation in PD patients.

Keywords: Constipation, high-frequency repetitive magnetic stimulation, Parkinson's disease

Introduction

Parkinson's disease (PD) is a degenerative disease in which α-synuclein is abnormally deposited in the inner and outer multi-nervous systems of the brain. It is common in middle-aged and elderly people, with insidious onset and slow progress. Clinically, it is characterized by static tremors, muscle rigidity, slow movement, and postural balance disorder as motor symptoms. In addition, recent studies have increasingly focused on non-motor symptoms in PD patients. Constipation is one of the most common non-motor features of PD, reported in 80% to 90% of patients.[1,2] Braak's Lewy pathodynamic model of PD involves the intestinal nervous system (ENS) and dorsal motor nucleus of the vagus nerve (DMV) in the early stage. The pathological progression of α-synuclein is centripetal from the ENS to the DMV via vagal pathways, and from DMV to more rostral areas of the central nervous system.[3-5] The prion-like spread of α synuclein pathology may be the main mode of transmission.[6] An autopsy survey published by the Arizona Parkinson's disease association showed that almost all patients with PD have Lewy's disease in the peripheral nervous system, especially in the intestinal nervous system.[7] These findings have aroused increasing interest in gastrointestinal symptoms as a premotor manifestation of PD. A prominent example is constipation leads to psychological and social distress, and eventually reduces the quality of life.[8] Disease severity, sex, age, and antiparkinsonian medication are the main risk factors for the non-motor symptoms (NMS) that have been discussed in a recent review.[9] PD-associated morbidity and mortality in the United States contribute $6 billion to healthcare costs annually.[10] Magnetic stimulation, as a kind of physical therapy, has a broad prospect in the treatment of neurological diseases due to good tolerance, painlessness, fewer side-effect, and convenience. In previous studies, repetitive transcranial magnetic stimulation has been widely used in stroke, epilepsy, depression, constipation, and so on. Recently, peripheral magnetic stimulation attracted the attention of investigators in the treatment of constipation. In 2014, Carrington *et al*.[11] reported that sacral nerve stimulation (SNS) may act on the pelvic afferent or central level, thus regulating constipation.

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In 2019, Young-Cheol Yun *et al*.[12] found that transabdominal functional magnetic stimulation improves constipation in brain-injured patients. However, there are few studies for high-frequency repetitive magnetic stimulation (HF-rMS) in the treatment of PD patients with chronic constipation. Using the intervention of HF-rMS, we explored the therapeutic effect of HF-rMS at the sacrum on the constipation of PD patients and provided a new strategy for the treatment of PD patients with constipation.

Material and Methods

Subjects

A total of 48 eligible PD patients who were diagnosed for the first time were enrolled at the Integrated Hospital of Traditional Chinese Medicine, Southern Medical University from July 2019 to Oct 2020, including 26 males and 22 females, aged 66–70 years old. Each patient was diagnosed by an experienced deputy physician at the Department of Neurology. Subjects were included in this study based on the following inclusion and exclusion criteria. Inclusion criteria: met the clinical diagnostic criteria for primary PD established by the British Parkinson's Disease Association Brain Bank,[13] namely, motor retardation, resting tremor, muscle stiffness, and postural balance disorders (unrelated to primary vestibular, cerebellar, and proprioceptive dysfunction), Exclusion criteria: a history of recurrent stroke or brain injury; Parkinson's syndrome; psychiatric diseases; major primary diseases such as heart, liver, kidney, hematopoietic system, endocrine system, etc.; undergoing PD surgery; digestion tract diseases and secondary digestive tract injury. Rome III criteria were used to evaluate constipation in PD patients as previously reported.[14] For all questionnaires, the interview was conducted by a researcher who did not know the patients' previous medical history and the objective of this study. For each question, the recruited PD patients were requested to give the appropriate answer during the interview and avoid discussion with the researcher. This study conformed to the provisions of the Declaration of Helsinki and was approved by the institutional review board of Integrated Hospital of Traditional Chinese Medicine, Southern Medical University. Written consent forms were received from all subjects. This study was approved by the ethics Committee of Integrated Hospital of Traditional Chinese Medicine, SouthernMedical University on April 9th, 2019.

All patients took levodopa and dopamine receptor agonists (such as pramipexol hydrochloride or ropinirole). Besides these drugs, three patients took selegiline hydrochloride (one patient in the intervention group and two patients in the sham control group). All enrolled subjects did not use amantadine or anticholinergics.

The PD patients with chronic constipation took medications (such as lactulose and suppositories glycerol) or improved their dietary structure. But the symptoms of their constipation still existed. The subjects did not change the use of their constipation medications or their dietary structure during the HF-rMS treatment.

The Knowles-Eccersleye-Scott Symptom Questionnaire

The Knowles-Eccersleye-Scott Symptom (KESS) Questionnaire[15,16] is an optimized version based on CSS, which has been demonstrated that not only can evaluate the condition of constipation, but also classify the patients. The scale contains 11 items, which are expected to be completed within 5 minutes, with a maximum score of 39 points. We performed clinical evaluation before the rMS intervention and on the day the protocol ended. The higher the score was, the more serious the constipation was. The evaluation items included the course of constipation, the use of laxatives, the frequency of bowel movements, unsuccessful evacuation, the feeling of incomplete evacuation, abdominal pain, abdominal distension, enema/digitations, time taken (minutes at each evacuation/evacuation trial, difficult evacuation leading to the painful effort, stool consistency.

Other Questionnaires

Before and after treatment, we assessed the clinical conditions of PD patients using the following scales of motor symptoms and other NMS, the activity of daily living, and quality of life. The Motor function of PD was assessed by the H-Y stage and UPDRS-□ Scale.[17] Depression and anxiety have been found that increased the risk of constipation in PD patients. Cognitive impairment was also considered an important factor. Thus, we assessed cognitive function and mood by MMSE[18] and HAD-A/HAD-D.[19,20] Eventually, the activity of daily living and Quality of life of PD patients were assessed through the ADL scale[21] and PAC-QOL scale, respectively.[22]

Magnetic Stimulation

The HF-rMS group (intervention group, $n = 24$) was treated with percutaneous magnetic stimulation for sacral nerves, and the center of the "figure-eight-shaped" coil was aligned with the midpoint of the sacral bone [Figure 1]. The magnetic stimulator, CCV-IV type, and a "figure-eight-shaped" coil (manufactured by YIRUIDE, Wuhan, China) were used in the rMS treatment. HF-rMS was used for 20 minutes at a time (3-second stimulation followed by 27-second interval).

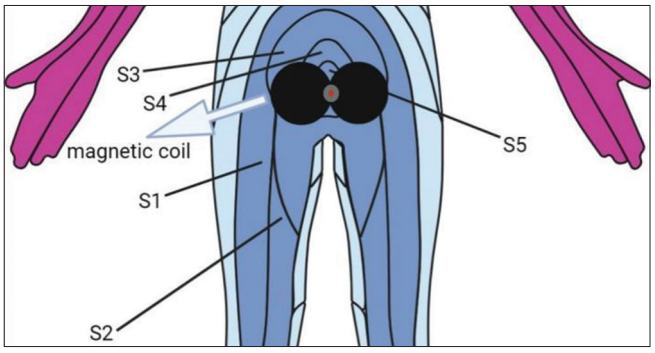

Figure 1: Stimulation location of high-frequency repetitive magnetic stimulation (HF-rMS). The center part of the figure-of-eight coils was placed at the center of the sacral bone

The parameters of rMS were 20Hz, 40%–60% of maximal intensity with a total number of 2400 impulses. In the sham-rMS group (control group), a 5-cm board was placed at the stimulation site to block the magnetic stimulation with the same stimulation parameters as in the HF-rMS group. The magnetic stimulation was delivered to subjects once a day, for four weeks with the interval of weekend days. Although the subjects heard the sound produced by the magnetic stimulator, the magnetic field could not produce an effective stimulation due to the block. Magnetic stimulation and clinical evaluations were performed by different researchers, who did not know the objective of this study.

Statistical Analysis

Because the data did not meet the normal distribution, Wilcoxon signed rank sum test was used to compare the differences between the two groups before and after treatment. SPSS was used for statistical analysis. $P < 0.05$ was considered to be statistically significant.

Results

General Characteristics of PD Patients with Chronic Constipation

A total of 65 PD patients with chronic constipation diagnosed according to the UK Brain Bank criteria for PD and Rome III diagnostic criteria for functional constipation were enrolled in this trial. Seventeen of these patients did not satisfy our inclusion and exclusion criteria (two subjects with an unspecified diagnosis of PD, four subjects with drug-related Parking's syndrome, five subjects with a secondary stroke, two subjects with heart failure, one subject with chronic kidney insufficiency and three subjects with gastrointestinal diseases). Eventually, a total of 48 eligible patients were randomly assigned to the intervention group (n = 24) and the control group (n = 24) based on a computer-generated randomization table. Five patients (three in the intervention group and two in the control group, respectively) withdrew from this study before completion and were not included in the final analysis [Figure 2]. There was no statistically significant difference in the clinical characteristics between the intervention group and the control group [Table 1]. Also, no significant adverse effects were observed.

Change of KESS Scores Between Two Groups

After 4 weeks of treatment, we used the KESS questionnaire to evaluate the changes before and after HF-rMS treatment in the subjects. There were significant differences in the change of KESS between the HF-rMS group and the sham control group [$P < 0.05$, Table 2]. The constipation-related symptoms in the HF-rMS showed significant improvements as compared to the sham control group, including frequency of bowel movement ($P = 0.034$), unsuccessful evacuation ($P = 0.028$), enema/digitations ($P = 0.003$), time taken (minutes at each evacuation/evacuation trial) ($P = 0.041$), difficult evacuation leading to painful effort and stool consistency ($P = 0.038$) and stool consistency ($P = 0.033$) [Figure 3].

Table 1: Clinical characteristics of PD patients

	HF-rMS	Sham-rMS	*P*
Sex, M/F	14/8	12/9	0.9
Age (y, mean±SD)	66.7±9.6	69.6±8.2	0.28
Age onset (y, mean±SD)	57.2±7.6	59.5±8.4	0.31
Duration PD (y, Mean±SD)	8.8±5.9	9.3±6.7	0.65
Constipation duration (y, Mean±SE)	2.3±2.4	3.2±2.1	0.12
HY stage, *n* (%)			0.68
□-□	9	7	
□	10	9	
□-□	3	5	
L-dopa eq (mg/day)	676±326	629±345	0.18
KESS score (Mean±SE)	31.6±6.7	27.8±5.8	0.36
UPDRS III (Mean±SE)	29.4±3.5	26.8±3.1	0.43
PAC-QOL (Mean±SE)	45.7±4.1	47.4±3.8	0.19
MMSE (Mean±SE)	26.1±2.4	28.3±2.6	0.33
ADL (Mean±SE)	17.8±2.1	16.4±1.9	0.59
HADA (Mean±SE)	11.2±1.8	10.8±2.1	0.82
HADD (Mean±SE)	18.2±2.2	20.1±2.5	0.67

H-Y=Hoehn and Yahr; UPDRS III=Unified Parkinson's Disease Rating Scale, Part III; PAC-QOL Scoring=patient assessment of constipation quality of life scoring; MMSE=mini-mental state examination; ADL Scoring=activities of daily living Scoring; HAD-D=Hamilton Depression Scale; HAD-A=Hamilton Anxiety Scale; KESS=Knowles-Eccersleye-Scott Symptom. Clinical characteristics of PD patients

Table 2: Comparisons of the score from all scales before and after magnetic stimulation between two groups

	HF-rMS		Sham-rMS	
	Pre-rMS	Post- rMS	Pre-rMS	Post-rMS
KESS score	31.6±6.7	17.2±5.1*	27.8±5.8	24.3±4.4
UPDRS-□ score	29.4±3.5	27.6±3.7	26.8±3.1	25.6±3.3
PAC-QOL score	45.7±4.1	25±4.9*,#	47.4±3.8	41.2±4.5
MMSE score	26.1±2.4	23.7±3.1	28.3±2.6	24.6±3.2
ADL score	17.8±2.1	10.4±1.5*,#	16.4±1.9	15.6±1.7
HADA score	11.2±1.8	5.2±1.6*,#	10.8±2.1	9.5±1.7
HADD score	18.2±2.2	8.9±2.1*,#	20.1±2.5	19.1±1.9

Comparisons of the score from all scales before and after magnetic stimulation between two groups. UPDRS III: Unified Parkinson's Disease Rating Scale, Part III; PAC-QOL Scoring: Patient Assessment of Constipation Quality of Life Scoring; MMSE=mini-mental state examination; ADL Scoring=activities of daily living Scoring; HAD-D=Hamilton Depression Scale; HAD-A=Hamilton Anxiety Scale; KESS=Knowlese-Eccersleye-Scott Symptom. All score values express mean *P<0.05, compared to post-rMS; #P<0.05, compared to the sham control group. Wilcoxon signed-rank test suggested significant differences (P<0.05)

Changes in the Score of Motor Symptoms and NMS Between Two Groups

Motor symptoms of the HF-rMS group and sham HF-rMS group were assessed by UPDRS III score before and after the intervention. As in Table 2, the UPDRS III score in the HF-rMS group was remarkably reduced when compared with the sham control group ($P = 0.25$). For NMS, we assessed cognition and emotion by MMSE and HAD-A/HAD-D scales. In comparison to the sham control group, the HF-rMS group found a

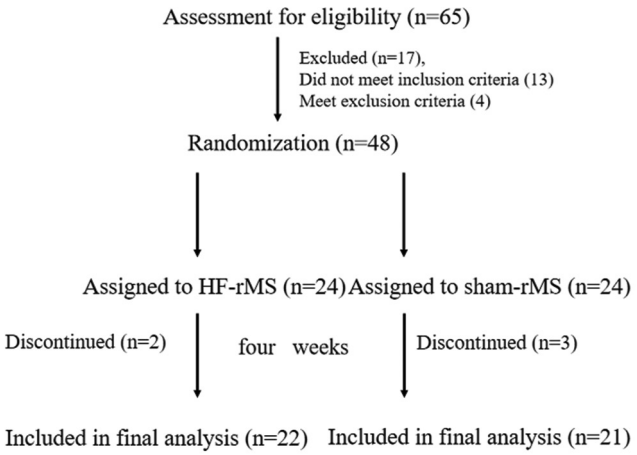

Figure 2: Study flow diagram illustrating the passage of participants through the entire trial

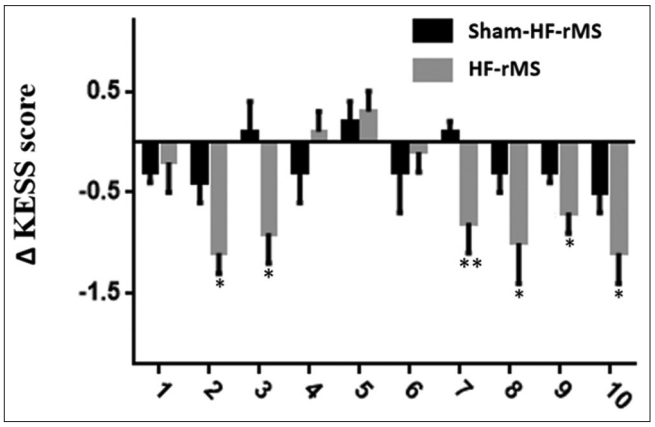

Figure 3: Change of KESS scores before and after magnetic stimulation in two groups. 1, Laxative use; 2, frequency of bowel movement; 3, unsuccessful evacuation; 4, the feeling of incomplete evacuation; 5, abdominal pain; 6, bloating; 7, enema/digitations; 8, time taken (minutes at each evacuation/evacuation trial; 9, difficult evacuation leading to painful effort; 10, stool consistency. △KESS = the score of KESS after magnetic stimulation-the score of KESS before magnetic stimulation. *Compared to the sham control group, the Wilcoxon signed-rank test suggested significant differences ($P < 0.05$)

significantly larger change in the HAD-A score ($P = 0.015$) and HAD-D score ($P = 0.028$) after the intervention, implying that HF-rMS markedly improved mood. But there was no significant difference in the change of MMSE score before and after intervention between the two groups ($P > 0.05$).

Change in the ADL Score and the PAC-QOL Score Between Two Groups

We conducted comparisons in the change of activity of daily living and quality of life before and after intervention between the two groups [Table 2]. Compared to the sham control group, the scores of the ADL scale and PAC-QOL scale in the HF-rMS group were significantly reduced ($P < 0.05$), suggesting that HF-rMS promoted the activity of daily living and quality of life.

Discussion

In this study, we evaluated the effect of HF-rMS at the sacrum on constipation in PD patients by KEGG scale and other scales. Compared with the sham-rMS group, the intervention group showed a significant improvement in constipation, including frequency of bowel movement, unsuccessful evacuation, enema/digitations, time taken (minutes at each evacuation/evacuation trial), difficult evacuation leading to painful effort and stool consistency, suggesting that HF-rMS improves constipation probably by stimulating nervous plexus around the rectum, as a result, promoting blood circulation and movement of the rectum, other muscle movements associated with defecation. Additionally, HF-rMS at the sacrum significantly promoted the mood and life quality of PD patients. Finally, tolerance and compliance of HF-rMS were good, without obvious adverse effects observed.

As electrical stimulation exerts its effects, magnetic stimulation can generate electric fields and currents to stimulate neuromuscular tissues. Thus, magnetic stimulation has a similar effect to electrical stimulation. However, compared with electrical stimulation, there was no obvious attenuation for a magnetic pulse that passes through tissues with high resistance, such as bone, fat, and skin, without affecting the pain-conducting myelinated fibers.[23] Magnetic stimulation of the sacral nerve root can induce the motor potential of the pelvic sphincter, eventually contributing to the contraction of the pelvic floor muscle.[24] Additionally, magnetic stimulation, especially HF-rMS, produces a broader effect, such as improving blood circulation in the stimulated tissues.

In PD patients, constipation can be caused by a variety of reasons, usually resulting in slow colonic transport or outlet dysfunction.[25] In 2006, Kwang Jae Lee *et al*.[24] evaluated the potential clinical value of sacral dermatome stimulation for PD patients with constipation and showed its beneficial effects on the frequency of spontaneous bowel movements, straining on defecation, and rectal sensation in a subset of the patients. Moreover, magnetic stimulation to sacral nerves significantly increased pancolonic antegrade propagating sequence frequency in patients with slow-transit constipation and coordinated rectal and anal sphincter activities through the different lengths of relaxation periods between visceral and striated muscle contractions after being co-activated to facilitate stool evacuation in PD patients.[26] By releasing appropriate neuro-transmitters,[27-29] magnetic stimulation may modulate the myenteric plexus, ganglia, and interneuron connections to facilitate colon motility. In this study, HF-rMS might have similar mechanisms for the improvement of constipation in PD patients. Furthermore, the improvement of constipation symptoms of PD patients by HF-rMS might be related to plasticity and release of acetylcholine and 5-HT. loss of cholinergic neurons in PD patients may be also the reason for the slow colonic transmission.[30]

However, currently, there are no effective neuroprotective or disease-modifying therapies that would prevent the progression of the disease.[31] Thus constipation treatment is also symptomatic treatment, including diet intervention, physical exercise, the use of light laxatives, local use of botulinum toxin and deep brain stimulation of the hypothalamic nucleus. Diet intervention and physical exercise are mainly for patients with mild constipation but do not work well for patients with severe constipation. HF-rMS provided a new strategy for the treatment of constipation in PD patients, due to safety, good tolerance, convenience, and painlessness.

This study has several limitations. First, this is a single-center and small-scale exploratory study; double-blinding might be not complete. Thus, the conclusion might be limited. Second, the constipation symptoms of PD patients had been only investigated by the KESS questionnaire, and we failed to perform some objective measures such as colonic transit time and defecography. Thus, there was a limited corresponding relationship between subjective symptoms and objective gastrointestinal dysfunctions. Third, the use of questionnaires often underestimated the degree of dysfunction. Finally, the treatment time of this study was only 4 weeks, thus the effect of longer-term treatment needed to be further investigated.

In conclusion, our results suggested that HF-rMS at the sacrum alleviates chronic constipation in PD patients. It was worth mentioning that HF-rMS was safe and well tolerated, convenient and painless in the treatment of PD constipation. Therefore, HF-rMS might be a potential therapeutic strategy for PD constipation.

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Conflicts of interest

There are no conflicts of interest.

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