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A Clinical Randomized Controlled Study of Low-Frequency rTMS Therapy on Lower Limb Motor Dysfunction after Stroke

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Abstract: *Objective:* To investigate the efficacy and safety of low-frequency repetitive transcranial magnetic stimulation (rTMS) for the treatment of lower limb motor dysfunction after stroke. *Methods:* A total of 96 patients with stroke and lower limb motor dysfunction were enrolled in this study, and were randomly divided into the experimental group and the sham stimulation group using the method of calculator-generated random numbers. Both groups received conventional medication and rehabilitation therapy. The experimental group received 4 weeks of 1 Hz rTMS treatment in the primary cortical motor area (M1) of the healthy side, with the treatment coil tangent to the skull surface; the sham stimulation group underwent the same procedures as the experimental group, but the treatment coil was perpendicular to the skull surface instead. Lower-extremity subscale of the Fugl-Meyer Assessment (FMA-LE), Berg Balance Scale (BBS), gait analysis, and lower-extremity surface electromyography (LESEM) were performed in both groups before and after rTMS treatment. Results: All 96 patients completed the test with no shedding and no adverse reactions. After treatment, the FMA-LE score and BBS score of the 2 groups of patients were significantly improved as compared with the pre-treatment ($P < 0.05$), and the TUG test time was reduced as compared with the pre-treatment ($P < 0.05$). The true stimulation group had greater improvement in all assessment indexes than that of the sham stimulation group ($P < 0.05$). After treatment, the electromyographic activity of the tibialis anterior and rectus femoris muscles in the true simulation group improved significantly. The step length, step speed, and step frequency were also significantly improved in both groups after treatment, and the symmetrical ratio of step length and support time was reduced ($P < 0.05$). Comparison between the groups revealed that the true simulation group significantly improved after rTMS treatment as compared to the sham stimulation group ($P < 0.05$). *Conclusion:* 1Hz rTMS treatment safely and effectively improved motor and balance function in patients with post-stroke lower limb motor dysfunction.

Keywords: Repetitive transcranial magnetic stimulation; Three-dimensional gait analysis; Electromyography stroke lower limb dysfunction rehabilitation

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1. Introduction

The function of the lower limbs is impaired in more than 80% of patients after stroke, contributing to poor gait stability, increased energy consumption, and asymmetry walking, thus adversely affecting the patient's quality of life [1]. Repetitive transcranial magnetic stimulation (rTMS) has been widely used in the treatment and research of a variety of neurological and psychiatric disorders in recent years as it is painless, noninvasive, simple, safely and effectively regulates neural activity, and promotes neuroplasticity [2]. Due to the proximity of the lower limb corticomotor area to the longitudinal fissure of the brain and its deep location in the body, this region cannot be easily stimulated by rTMS. Hence, studies of rTMS on the treatment of post-stroke motor dysfunction are mainly focused on the upper limbs, and its application to the rehabilitation of the lower limbs after stroke lacks sufficient research either as a separate treatment or as an adjunctive treatment [3–5]. Therefore, this study combined three-dimensional gait analysis technology to investigate the clinical efficacy and safety of using low-frequency rTMS on the healthy M1 region for the treatment of post-stroke lower limb motor dysfunction.

2. Materials and methods

2.1. Participants

96 patients with post-stroke lower limb dysfunction who were treated in the Department of Rehabilitation Medicine of the Affiliated Hospital of Guangdong Medical University during the period from January 2019 to January 2022 and met the inclusion criteria were selected as study subjects. All enrolled patients signed a written informed consent.

2.1.1. Inclusion criteria

(1) Meet the diagnostic criteria set by the Fourth National Cerebrovascular Academic Conference in 1995, and the diagnosis of cerebral infarction (CI) or cerebral hemorrhage was confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI); (2) The duration of the disease was more than 3 months and less than 1 year; (3) Unilateral hemiparesis was caused by the first stroke and aged 18–80 years old; (4) Stable condition, can perform three-step commands and have good treatment compliance; (5) Can walk independently or with the aid of assistive devices; (6) consented.

2.1.2. Exclusion criteria

(1) Significant cognitive impairment and inability to cooperate with the training; (2) serious bone and joint or trauma, and other diseases that affect walking; (3) vestibular lesions, cerebellar or brainstem infarction; (4) previous history of epilepsy or taking antiepileptic drugs; (5) contraindications to the treatment of rTMS, wearing a pacemaker, has a metallic implant in the skull, and other metallic implants in the body.

2.1.3. Shedding criteria

(1) Subjects with poor compliance; (2) subjects who do not wish to continue with the clinical trial; (3) those that were selected due to the occurrence of serious adverse reactions.

2.2. Main instruments and equipment

The rTMS therapeutic instrument OSF-6 (Wuhan OSF Medical Company) was used, with an output pulse frequency of 0 Hz–100 Hz ± 5%, a maximum magnetic induction strength of 2.0–3.7 T ± 5%, and a circular coil beat (model Y125) with a direct coil of 12.5 cm.

2.3. Research process

2.3.1. Grouping methodology

This study was a single-blind, sham-stimulation controlled experiment. The patients were divided into a sham stimulation group and an experimental group using the random number table method, each group with 48 cases. The grouping order was generated by the random number table method and was kept in sealed envelopes which were opened only at the time of registration of patients for treatment. All patients were unaware of the enrollment. Each clinical assessment was evaluated by the same investigator who unaware of the grouping of subjects. rTMS was performed by a trained therapist who was not involved in the clinical assessment, patient follow-up, or data analysis.

2.3.2. Research methodology

Patients in the experimental group and sham stimulation group were given both conventional rehabilitation therapy and rTMS therapy. Conventional rehabilitation therapy was formulated according to the specific conditions of the patients, and the drugs administered provided nutrition to the nerves, improved cerebral circulation, anti-platelet aggregation, and so on. Rehabilitation training was carried out by experienced therapists on a one-to-one basis for 50 minutes each time, once a day. This was carried out as a single course of treatment for 5 days, followed by 2 consecutive courses for a total of 10 sessions.

The rTMS treatment program was provided for patients in the sham stimulation group. 6 parameters were included: a frequency of 1 Hz was used, 90% intensity for motor threshold (MT) inhibitory stimulation, a 10-second interval, treatment time of 2 seconds for 20 minutes, with 1000 total stimulations. This program was carried out as a single course of 1 treatment per day for 5 days, followed by 2 consecutive courses.

The stimulation site was determined by the localization cap developed according to the international electroencephalogram (EEG) 10–20 system. The stimulation coil was placed tangent to the patient's skull surface, and the middle position of the circular coil was placed on the healthy side (M1). The stimulation intensity was set to 90% of the threshold to stimulate movement in the evoked bunion-spreading muscle.

For the sham stimulation group, the magnetic head was placed perpendicular to the scalp, and the rest of the parameters were the same as those of the experimental group. During the treatment process, patients were closely observed for any discomfort, and any adverse reactions such as headache, dizziness, tinnitus, scalp allergy, etc. before and after treatment were recorded and treated.

2.3.3. Clinical assessment

The Berg Balance Scale (BBS) was used to assess the patient's balancing ability, which consisted of 14 items, including standing up, sitting down, standing independently, standing with eyes closed, reaching forward with the upper arm, turning around for a week, stepping on steps alternately with both feet and standing on one leg, etc. The lowest score for each item is 0, and the highest score is 4, with a total score of 56 points. The BBS scores were divided into three groups: 0–20, 21–40, and 41–56. The balancing abilities represented by these scores corresponded to the three activity states of "wheelchair-bound," "assisted walking," and "independent walking." A total BBS score of less than 40 indicated a risk of falling when walking.

The lower-extremity subscale of the Fugl-Meyer Assessment (FMA-LE) was used to assess the motor function of the lower extremities, and the FMA was considered the gold standard for the recovery of motor function after stroke [7]. The FMA-LE consisted of 34 items, including reflexes, synergy patterns, and coordination. Each item was scored in a sequence of 3, with a score of 2 for "fully achievable," 1 for "partially achievable," and 0 for "completely inaccessible."

2.3.4. Gait analysis

Measurement of gait parameters, spatial asymmetry, and temporal asymmetry was performed using the motion 3D gait analysis system, which consisted of an infrared capture system (Motion Analysis raptor-44-megapixel camera 6 and Motion capture software), a linear walkway with pressure sensitive sensors (AMTI- BP600600-2K), surface electromyography (EMG) tester, and an analysis software (Motion Analysis Orthotrak; IBN-SPSS18.0; Microsoft EXCEL2010). The motion analysis infrared capture system was used to capture the walking movement, force situation, and other movements of the patients. The point coordinate values during the movement of the patients were obtained through the motion system, and the kinematic and kinetic parameters of the joints were calculated using the Helen Hayes model.

The EMG values of the tibialis anterior (TA) and rectus femoris (RF) muscles of the affected limbs during walking were measured using silver chloride (AgCl) surface electrodes. The cathodic electrode of the TA was placed at the upper 1/3 of the line from the tibial tuberosity to the ankle. The anodic electrode of the RF was placed at the midpoint between the anterior superior iliac spine and patella. The reference electrode was placed on the ulnar node and the anterior superior iliac spine. To determine the period of the gait, two foot switch sensors were placed under the heel and the first metatarsal head. The sampling rate was 3000 Hz with a bandpass filter of 40–400 Hz and a low-pass filter of 60 Hz. The EMG signals for the TA were recorded during the swing phase of gait and the EMG signals for the RF were recorded during the stance phase of gait.

2.3.5. Statistical methods

SPSS 19.0 statistical software was used for data analysis. Measured data were expressed as mean ± standard deviation and compared using paired *t*-test and chi-square (χ^2) test; qualitative data were described by relative numbers. Results were considered statistically significant at $P < 0.05$.

3. Results

3.1. Comparison of the general data of the two groups of patients

A total of 96 patients were included in this trial and no adverse reactions were reported. As shown in **Table 1**, there were no significant differences between the two groups in terms of demographics and stroke type ($P > 0.05$).

Table 1. Comparison of general information of the two groups of patients

Specificities	Experimental group	Sham stimulation group	*P*
Sex (m/f)	62/34	60/36	0.93
Age (years)	57.73 ± 14.57	56.93 ± 10.10	0.86
Duration of illness (months)	4.53 ± 2.05	4.74 ± 2.17	0.51
Type of stroke (ischemic/hemorrhagic)	57/39	65/31	1.0
Site of brain lesion (left/right)	45/51	39/57	1.0

Note: *Indicates the use of Fisher's exact probability method.

3.2. Changes in FMA-LE scores and BBS scores

Before treatment, the FMA-LE score and BBS score of the 2 groups of patients obeyed normal distribution, had uniform variance, and the difference between the groups was not statistically significant based on the *t*-test ($P < 0.05$). As shown in **Table 2**, all the assessment indicators were significantly better after the treatment ($P < 0.05$),

and the two groups were significantly correlated before and after the treatment ($P < 0.05$). The *t*-test of two independent samples showed that the difference between the two groups was statistically significant, and the improvement was more significant in the experimental group as compared to that of the sham stimulation group after treatment ($P < 0.05$).

Table 2. FMA-LE score and BBS score before and after treatment in the two groups of patients

Groups	Number of examples, *n*	FMA-LE (points)	BBS (points)
Experimental	48		
Pre-treatment	48	18.27 ± 3.39	39.67 ± 4.73
Post-treatment	48	25.8 ± 4.16[ab]	45.80 ± 3.68[ab]
Sham stimulation	48		
Pre-treatment	48	20.67 ± 3.52	38.67 ± 4.20
Post-treatment	48	22.67 ± 3.66[a]	42.67 ± 2.96[a]

[a]$P < 0.05$ Comparison within the group during pre-treatment; [b]$P < 0.05$ Comparison with sham-stimulated group at a same time point after treatment

3.3. Myoelectric signal changes

As shown in **Table 3**, RF EMG activity in the experimental group increased significantly ($P < 0.05$) during the standing phase after treatment, and TA EMG activity also increased significantly during the swing phase, while RF was significantly altered as compared to TA; there were no significant changes between TA and RF EMG activity in the sham stimulation group after treatment. Comparison between both groups showed that post-treatment assessment exhibited significant improvement in both TA and RF activity in the experimental group as compared to the sham stimulation group ($P < 0.05$).

Table 3. Comparison of EMG signals of the two groups

	Experimental group		Sham stimulation group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
TA on the affected side (μV)	15.18 ± 2.87	18.22 ± 4.50	17.99 ± 2.98	17.13 ± 6.88
Statistics (%)		19.2 ± 11.0		-6.8 ± 25.2
RF of the affected side (μV)	5.82 ± 2.54	7.68 ± 3.20	9.35 ± 2.38	9.36 ± 3.17
Statistics (%)		35.9 ± 36.4		-0.8 ± 14.0**

TA: Tibialis anterior; RF: Rectus femoris; statistics = (post-treatment -pre-treatment)/pre-treatment; *$P < 0.05$ vs. pre-treatment, **$P < 0.05$ vs. experimental group.

3.4. Changes in gait parameters

As shown in **Table 4**, before treatment, the differences in pacemaker, pace, step frequency, step symmetry ratio, and support time symmetry ratio of the two groups of patients were not statistically significant; after 4 weeks of treatment, the pacemaker, pace, and step frequency of the two groups all significantly improved after treatment ($P < 0.05$). The outcome of the experimental group was significantly better than the sham stimulation group ($P < 0.05$).

Table 4. Changes in gait parameters before and after treatment of the two groups

	Experimental group		Sham stimulation group	
	Pre-treatment	**Post-treatment**	**Pre-treatment**	**Post-treatment**
Pacemaker	29.85 ± 8.55	37.6 ± 7.22[ab]	28.45 ± 7.56	32.40 ± 6.00[a]
Pace	29.10 ± 8.55	45.45 ± 10.79[ab]	27.35 ± 7.16	32.40 ± 5.87[a]
Step frequency	39.45 ± 4.84	50.75 ± 5.65[ab]	38.95 ± 3.47	44.05 ± 3.44[a]
Step-symmetry ratio	1.29 ± 0.04	1.14 ± 0.03[ab]	1.31 ± 0.10	1.24 ± 0.8[a]
Support time symmetry ratio	1.32 ± 0.05	1.17 ± 0.04[ab]	1.34 ± 0.07	1.25 ± 0.05[a]

Note: [a]$P < 0.05$ Comparison within the group during pre-treatment; [b]$P < 0.05$ Comparison with the sham-stimulated group at a same time point after treatment

4. Discussion

After a stroke event, the limb motor system loses its regulatory effect of the higher central nervous system of the brain, causing the previously inhibited and primitive subcortical central motor reflexes to be released, resulting in motor dysfunction due to weakening or paralysis of limb muscles, dysfunction of intermuscular motor coordination, and abnormal tension [8]. Studies have reported that even though 70%– 80% of stroke survivors were able to walk during the chronic phase, their walking speed and coordination were continuously impaired [9].

In this study, we used three-dimensional gait analysis technology combined with EMG and clinical assessment to analyze the effect of 1 Hz rTMS on lower limb motor function after stroke. The results of this experiment suggested that 4 weeks of rTMS treatment significantly improved the pacemaker, pace, and step frequency, suggesting that 1 Hz rTMS treatment improved walking speed, gait asymmetry, and balance of the lower limb after stroke. Gait symmetry is another important parameter of energy expenditure and joint loading in the lower limbs. It has been shown that gait asymmetry is associated with poor motor control of the affected limbs and slower walking speeds [10], which, combined with the improved FMA-LE and BBS scores in this experimental group, suggested that motor control of the affected limbs and overall balance was improved, which may partially explain the improved gait asymmetry in this study.

Rastgoo et al. [11] showed that 1 Hz rTMS improved lower limb spasticity and motor function in chronic stroke patients; Forogh et al. [12] suggested that 1 Hz rTMS improved static balance and lower limb muscle strength in patients with lower limb motor dysfunction after stroke. Hence, the results of this study were consistent with previous studies. By using surface EMG combined with three-dimensional gait analysis technology, dynamic real-time selective recording and analysis of EMG activity reflecting the quadriceps muscle in the support phase and the TA muscle in the swing phase were used to assess the current involvement of said muscles. This study showed that the TA EMG activity during the swing phase and the RF EMG activity during the support phase in the experimental group increased, suggesting that rTMS may improve gait symmetry by improving the muscle strength of the affected limbs and, consequently, the gait symmetry. The insignificant improvement in ankle joint activation in this trial may be related to the significant decrease in dorsiflexor muscle strength of the affected limb after the stroke, and was not followed up in this trial.

The mechanism of action of rTMS treatment is based on the application of low-frequency rTMS on the healthy motor cortex to alters the excitation or inhibition between the cerebral hemispheres, which promotes the recovery of motor function in hemiplegic patients after stroke. In addition, it has been shown that rTMS can also improve the motor function of the lower limbs by regulating the functional activity of other parts connected

to the neurons at the stimulated site [10]. However, the circular coil used in this experiment may have produced an insufficiently focused magnetic field on the cranial surface, and its functional changes could also be caused by larger networks or cortical areas [13] in different patients. Further combined neurophysiological studies are needed to confirm this.

5. Safety of rTMS treatment

Numerous studies have demonstrated that it is essentially safe to operate within the range of therapeutic parameters recommended by rTMS safety guidelines. In this study, rTMS treatment with low frequency (1 Hz) and an intensity of 90% MT was used. There were no reports of adverse effects, which confirmed that the rTMS parameters applied in this experiment are relatively safe, but due to the small sample size, further studies are still needed for clarification.

6. Conclusion

1 Hz rTMS treatment safely and effectively improved the motor and balance abilities of patients with lower limb dysfunction after stroke. However, a larger sample size and longer follow-up periods are needed in the future to study its effect on the functional recovery of the lower limbs after stroke. The relationship with cortical excitability changes should also be investigated with the help of functional imaging.

Disclosure statement

The authors declare no conflict of interest.

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