Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(2) 662–672

DOI: 10.1177/0300060518807340
journals.sagepub.com/home/imr
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Repetitive transcranial magnetic stimulation in combination with neuromuscular electrical stimulation for treatment of post-stroke dysphagia

Chengliang Zhang[1,*], Xiuqin Zheng[2,*], Rulan Lu[1], Wenwei Yun[1], Huifang Yun[3] and Xianju Zhou[1]

Abstract

Objective: This study was performed to determine whether repetitive transcranial magnetic stimulation (rTMS) combined with neuromuscular electrical stimulation (NMES) effectively ameliorates dysphagia and how rTMS protocols (bilateral vs. unilateral) combined with NMES can be optimized.

Methods: Sixty-four patients were randomly divided into four groups using a random distribution table: the sham rTMS plus NMES (Sham-rTMS/NMES), ipsilesional 10-Hz rTMS plus NMES (Ipsi-rTMS/NMES), contralesional 1-Hz rTMS plus NMES (Contra-rTMS/NMES), and bilateral rTMS plus NMES (Bi-rTMS/NMES) groups. Cortical excitability as measured by the amplitude of the motor evoked potential at the mylohyoid muscle cortical representative area, swallowing function as measured by the Standardized Swallowing Assessment, and the degree of dysphagia were evaluated at baseline, after the stimulation course, and at the 1-month follow-up.

Results: Bi-rTMS/NMES produced higher cortical excitability and better swallowing function recovery. Compared with NMES alone, unilateral rTMS plus NMES had additional effects on

[1]Laboratory of Neurological Diseases, Department of Neurology, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, Jiangsu, China
[2]Department of Neurology, Changzhou Peace Hospital, 102nd Hospital of PLA, Changzhou, Jiangsu, China
[3]Department of Anesthesiology, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, Jiangsu, China

*These authors contributed equally to this work.

Corresponding author:
Xianju Zhou, Laboratory of Neurological Diseases, Department of Neurology, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, 29 Xinglong Alley, Changzhou, Jiangsu 213003, China.
Email: xianju_zhou@yahoo.com

cortical excitability and rehabilitation of dysphagia, but there were no differences between the Contra-rTMS/NMES and Ipsi-rTMS/NMES groups. No adverse events occurred.

Conclusion: The combination of rTMS with NMES was superior to NMES alone in improving the recovery of post-stroke dysphagia, and the combination of bilateral rTMS with NMES was more effective than unilateral rTMS combined with NMES.

Keywords

Post-stroke dysphagia, repetitive transcranial magnetic stimulation, neuromuscular electrical stimulation, motor evoked potential, swallowing function, rehabilitation

Date received: 25 June 2018; accepted: 25 September 2018

Introduction

Post-stroke dysphagia, which is a type of neurogenic dysphagia, is the most common and well-studied swallowing disorder in clinical practice.[1] Dysphagia reportedly occurs as a complication in 37% to 78% of patients with stroke.[2] Dysphagia may lead to serious adverse clinical outcomes such as malnutrition, dehydration, aspiration pneumonia, or even death.[3,4] Thus, it is necessary to intervene as early as possible in patients with post-stroke dysphagia.

Various therapeutic approaches have been used to promote swallowing function in patients with dysphagia, such conventional dysphagia training (oral and facial sensory stimulation, swallowing muscle exercises, and compensatory techniques),[5] pharyngeal electrical stimulation,[6] neuromuscular electrical stimulation (NMES),[7–9] and repetitive transcranial magnetic stimulation (rTMS).[10–14] NMES and rTMS are two noninvasive approaches that have been widely used for rehabilitation of dysphagia. NMES stimulates the anterior neck muscles by surface electrodes, leading to the excitement of related peripheral nerve fibers and eventual improvements in neurophysiological and clinical outcomes.[8] rTMS directly delivers cortical stimulation and improves cortical neuroplasticity and swallowing function.[15] Thus, rTMS has attracted much more attention in rehabilitation.

The therapeutic effects of rTMS depend on various stimulation parameters (pattern, frequency, intensity, and number of pulses), the stimulation side, the patient's disease status, and other factors.[16] No unified rTMS treatment has yet been developed. Evidence indicates that high-frequency (HF) (>5-Hz) rTMS increases cortical excitability, whereas low-frequency (LF) (<1-Hz) rTMS decreases cortical excitability.[17,18] Therefore, HF rTMS (HF-rTMS) is delivered to the ipsilesional hemisphere to enhance cortical excitability. In contrast, LF rTMS (LF-rTMS) is applied to the contralesional hemisphere to inhibit cortical excitability. A few studies have shown the effectiveness of either HF-rTMS over the ipsilesional side or LF-rTMS over the contralesional side in patients with post-stroke dysphagia.[8,12,13,19,20] However, which protocol is more effective remains controversial. Interestingly, Park et al.[21] reported that 5-Hz HF-rTMS over the contralesional pharyngeal motor cortex potentially improved the recovery of post-stroke dysphagia. Moreover, multiple-site rTMS has become a focus of research.[10,22] Two recent studies showed that bilateral HF-rTMS significantly improved swallowing function.[10,22] In these studies, HF-rTMS was applied over the healthy hemisphere and the affected side. It appears that the combination of rTMS with other recovery approaches, such as drugs, pharyngeal electrical stimulation, NMES, conventional rehabilitation, and task-oriented mirror therapy, achieves better therapeutic effects.[22–25]

In the present study, we evaluated whether rTMS combined with NMES has an advantage over NMES alone and whether the combination of bilateral rTMS (HF-rTMS over the ipsilesional hemisphere and LF-rTMS over the contralesional hemisphere) with NMES is more effective than the combination of unilateral rTMS (HF-rTMS over the ipsilesional hemisphere or LF-rTMS over the contralesional hemisphere) with NMES.

Methods

Participants

Patients with their first-ever stroke complicated with dysphagia were consecutively recruited from June 2016 to December 2017 from the neurologic rehabilitation outpatient clinic at the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University and the 102nd Hospital of PLA. The inclusion criteria were as follows: 1) the patient met the diagnostic criteria for stroke as confirmed by brain magnetic resonance imaging; 2) the patient was 50 to 75 years of age; 3) stroke onset occurred <2 months previously; and 4) the patient had normal consciousness, stable vital signs, dysdipsia, and dysphagia upon admission to this study. The exclusion criteria were as follows: 1) brain trauma or other central nervous system diseases; 2) unstable arrhythmia, fever, infection, epilepsy, or use of sedation drugs; 3) poor cooperation due to serious aphasia or cognitive disorders; and 4) contraindications to magnetic or electrical stimulation. This study was approved by the hospital ethics committee, and all participants provided written informed consent. The study design and flow chart are illustrated in Figure 1.

rTMS protocols

rTMS was delivered by a magnetic stimulator (CCY-IV; YIRUIDE Inc., Wuhan, China) with a 70-mm figure-of-eight coil. Eligible patients were randomly divided into four groups according to a random distribution table: the sham rTMS plus NMES (Sham-rTMS/NMES), ipsilesional rTMS plus NMES (Ipsi-rTMS/NMES), contralesional rTMS plus NMES (Contra-rTMS/NMES), and bilateral rTMS plus NMES (Bi-rTMS/NMES) groups. All participants underwent 10 rTMS sessions and 10 NMES sessions during a 2-week period (5 days/week, from Monday to Friday). rTMS was delivered during NMES with a sequence of HF-rTMS over the affected hemisphere followed by LF-rTMS over the unaffected hemisphere. The HF-rTMS parameters were as follows: 10 Hz, 3-s stimulation, 27-s interval, 15 min, 900 pulses, and 110% intensity of resting motor threshold (rMT) at the hot spot. The LF-rTMS parameters were as follows: 1 Hz, total of 15 min, 900 pulses, and 80% intensity of rMT at the hot spot. In the Sham-rTMS/NMES group, 10-Hz sham rTMS was delivered to the hot spot for the mylohyoid muscle at the ipsilesional hemisphere followed by 1-Hz sham rTMS over the corresponding position of the contralesional hemisphere. In the Ipsi-rTMS/NMES group, 10-Hz real rTMS was delivered to the hot spot for the mylohyoid muscle at the ipsilesional hemisphere followed by 1-Hz sham rTMS over the corresponding position of the contralesional hemisphere. In the Contra-rTMS/NMES group, 10-Hz sham rTMS was delivered to the hot spot

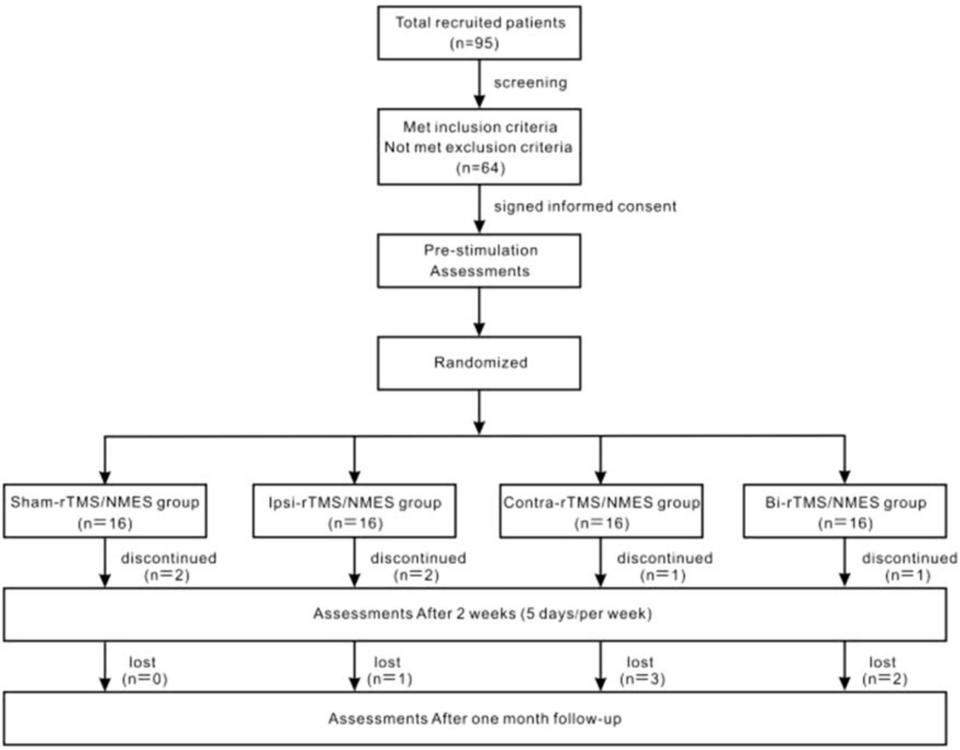

Figure 1. Flow diagram of this study

for the mylohyoid muscle at the ipsilesional hemisphere followed by 1-Hz real rTMS over the corresponding position of the contralesional hemisphere. In the Bi-rTMS/NMES group, 10-Hz real rTMS was delivered to the hot spot for the mylohyoid muscle at the ipsilesional hemisphere followed by 1-Hz real rTMS over the corresponding position of the contralesional hemisphere. In all groups, the same rTMS pulses were applied (900 pulses for the ipsilesional side and 900 pulses for the contralesional side). Sham rTMS was delivered using a vertical coil tilt, generating the same noise as real rTMS without cortical stimulation.

Measurement of motor evoked potentials

Before rTMS, motor evoked potentials (MEPs) were measured using a magnetic stimulator (CCY-IV; YIRUIDE Inc.) with an electromyography device. The participants were seated on a reclining armchair. To determine the mylohyoid hot spot area, the coil was placed on the optimal site for cortical areas representing the mylohyoid muscle in the contralesional hemispheres to elicit the maximal MEP responses. Thus, we applied rTMS at the hot spot. The rMT was defined as the minimal stimulation intensity for producing an MEP with a >50-μV peak-to-peak amplitude in 5 of 10 consecutive trials by delivering single-pulse TMS on the hot spot at submaximal stimulation. The hot spot and rMT at the ipsilesional hemisphere were determined by the hot spot and rMT at the contralesional hemisphere according to the symmetry of the brain. MEPs were measured again after the stimulation course and at the end of follow-up.

NMES

NMES was performed using a modified hand-held battery-powered electrical stimulator (HL-08178B; Changsha Huali Biotechnology Co., Ltd., Changsha, China) for 30 minutes once daily. Two channels of electrodes were placed on each side of the cervical midline. The channels of one set were placed between the digastric muscle and hyoid bone, while the channels of the other set were placed between the thyroid cartilage and cricoid cartilage. The waveform generated by the stimulator was a rectangular symmetric biphasic wave mode with a pulse width of 700 ms and frequency of 30 to 80 Hz. The current intensity was 7 to 10 mA depending on the tolerance of the participants. The participants were required to provide continuous feedback and perform continuous swallowing until a mild tingling, burning, or scratching sensation appeared, indicating that the current was at the appropriate level.

Assessment of swallowing function and dysphagia

Before stimulation, after the stimulation course, and at the end of follow-up, dysphagia and swallowing function were evaluated by the same doctor, who was well trained and blinded to the clinical information.

Dysphagia was assessed using the Dysphagia Outcome and Severity Scale as previously described.[26] The degree of dysphagia (DD) was categorized into four grades: Grade I, no clinical signs or symptoms; Grade II, very slight dysphagia suspected by clinical examination without complaint of dysphagia by the patient; Grade III, complaint of dysphagia and the presence of other supportive clinical signs without the need for non-oral feeding; and Grade IV, significant clinical signs and symptoms including aspiration, serve dysphagia, and the need for non-oral feeding. The Standardized Swallowing Assessment (SSA) was used to evaluate the swallowing function.[27,28] The SSA comprises three sections. The first section includes the level of consciousness, head and trunk control, breathing, lip closure, soft palate movement, laryngeal function, pharyngeal reflex, and voluntary cough, and the score for this section ranges from 8 to 23 points. The second section includes laryngeal movement, repetitive swallowing, choking, stridor, and vocal quality, and the score for this section ranges from 5 to 11 points. The score is obtained after the patient swallows 5 mL of water three times. The third section of the SSA is performed if all items in the first two sections are achieved, and its score ranges from 5 to 12 points. This score is obtained after the patient swallows 60 mL of water. Thus, the total score for the SSA ranges from 18 to 46 points, and higher scores indicate poorer swallowing function.

Statistical analysis

SPSS for Windows, Version 16.0 (SPSS, Inc. Chicago, IL, USA) was used for the statistical analysis. For the baseline clinical information, one-way analysis of variance or the chi-square test was used to compare mean values of continuous or categorical variables between the groups, respectively. Comparisons with different groups were performed using repeated-measures analysis of variance followed by Bonferroni's test. A P value of <0.05 was considered statistically significant.

Results

Of 95 initially recruited patients with stroke, 64 were eligible for inclusion in this study (we excluded 16 patients with multiple infarctions confirmed by magnetic

Table 1. Demographic and clinical characteristics of participants

	Sham-rTMS/NMES group (n = 16)	Ipsi-rTMS/NMES group (n = 16)	Contra-rTMS/NMES group (n = 16)	Bi-rTMS/NMES group (n = 16)	P
Age (years)	55.9 ± 8.9	56.8 ± 9.7	56.5 ± 10.1	53.1 ± 10.6	0.17
Sex (F/M)	8/6	6/7	6/6	9/4	0.66
Days from stroke onset to rTMS	26.4 ± 7.4	20.8 ± 6.9	23.3 ± 8.7	24.4 ± 5.6	0.28
Stimulation side (R/L)	7/7	5/8	7/5	6/7	0.94
Stroke location					0.28
Subcortical	8	4	7	8	
Brain stem	5	9	5	5	
SSA score	37.2 ± 5.1	35.6 ± 6.4	34.5 ± 4.9	34.5 ± 5.7	0.15
DD score	3.9 ± 0.9	3.7 ± 0.7	3.4 ± 0.8	3.6 ± 0.7	0.12

Data are presented as mean ± standard deviation or number of patients
rTMS, repetitive transcranial magnetic stimulation; NMES, neuromuscular electrical stimulation; Sham-rTMS/NMES, sham rTMS plus NMES; Ipsi-rTMS/NMES, ipsilesional 10-Hz rTMS plus NMES; Contra-rTMS/NMES, contralesional 1-Hz rTMS plus NMES; bilateral rTMS plus NMES; F, female; M, male; R, right; L, left; SSA, Standardized Swallowing Assessment; DD, degree of dysphagia

resonance imaging, 7 patients with consciousness disturbance, and 8 patients who declined rTMS therapy). Six patients discontinued treatment (two in the Sham-rTMS/NMES group, two in the Ipsi-rTMS/NMES group, one in the Contra-rTMS/NMES group, and one in the Bi-rTMS/NMES group). Six patients were lost to follow-up (one in the Ipsi-rTMS/NMES group, three in the Contra-rTMS/NMES group, and two in the Bi-rTMS/NMES group) (Figure 1). There were no significant differences in the baseline clinical information among the four groups (Table 1).

As shown in Figure 2(a) and (b), the percentage change in cortical excitability of patients with post-stroke dysphagia significantly increased over time in either the affected or unaffected hemisphere in the Bi-rTMS/NMES, Ipsi-rTMS/NMES, and Sham-rTMS/NMES groups ($P < 0.05$). In the Contra-rTMS/NMES group, however, the percentage change in cortical excitability in the unaffected hemisphere significantly decreased after the stimulation course ($P < 0.05$) (Figure 2(a)). The increase in the other three groups was maintained for at least 1 month (Figure 2(a)). Interestingly, cortical excitability in the Sham-rTMS/NMES group seemed to decline after follow-up (Figure 2(a) and (b)), suggesting that rTMS plus NMES may have a more sustained effect on excitability than NMES alone. Compared with the Ipsi-rTMS/NMES or Contra-rTMS/NMES group in the affected hemisphere, the Bi-rTMS/NMES group displayed a significantly greater percentage change ($P = 0.017$ and $P = 0.024$, respectively) (Figure 2(a)), suggesting the synergic effect of bilateral stimulation.

We found significant time and treatment interaction differences in the SSA score ($F = 3.34$, $P = 0.038$) but not in the DD score ($F = 5.67$, $P = 0.74$). As illustrated in Figure 3 and Figure 4, significant improvements were observed in all four groups as reflected by the decrease in the SSA scores ($F = 4.56$, $P < 0.05$) or DD scores ($F = 5.12$, $P < 0.05$) for dysphagia following stimulation. These results suggest that in all groups, improvement of swallowing function was achieved and maintained for the

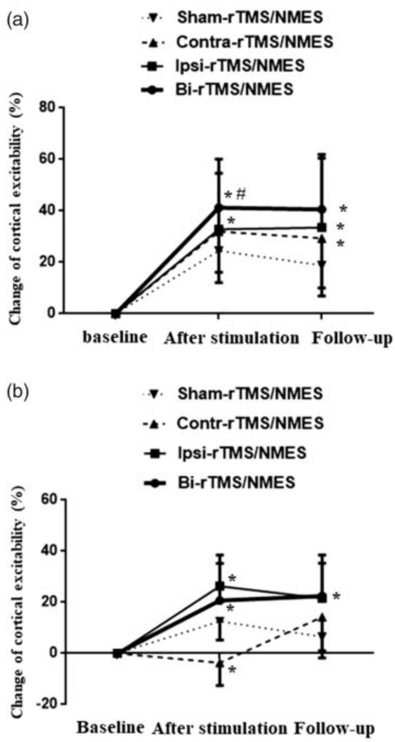

Figure 2. Effect of different stimulation protocols on the percentage change of cortical excitability. (a) Effect of different stimulation protocols on the percentage change of affected cortical excitability as reflected by the mylohyoid MEP amplitude. *$P < 0.05$ indicates a significant difference compared with the Sham-rTMS/NMES group, and #$P < 0.05$ indicates a significant difference compared with the Ipsi-rTMS/NMES or Contra-rTMS/NMES group. There was no difference between the Ipsi-rTMS/NMES and Contra-rTMS/NMES groups. (b) Effect of different stimulation protocols on the percentage change of unaffected cortical excitability as reflected by the mylohyoid MEP amplitude. *$P < 0.05$ indicates a significant difference compared with the Sham-rTMS/NMES group. The percentage change of cortical excitability was calculated by the following formula: (MEP amplitude after stimulation course or at the end of follow-up − MEP amplitude before stimulation) / MEP amplitude before stimulation × 100%. MEP, motor evoked potential; rTMS, repetitive transcranial magnetic stimulation; NMES, neuromuscular electrical stimulation; Sham-rTMS/NMES, sham rTMS plus NMES; Ipsi-rTMS/NMES, ipsilesional 10-Hz rTMS plus NMES; Contra-rTMS/NMES, contralesional 1-Hz rTMS plus NMES

1-month follow-up period. Further comparison analysis revealed that the alteration of the SSA score or DD score in the Bi-rTMS/NMES group was markedly higher than that in the other three groups at the end of stimulation ($P = 0.02$, $P = -0.03$, and $P = 0.005$) and still higher than that in the NMES group at the 1-month follow-up ($P = 0.01$). There was no significant difference in the SSA scores among the Bi-rTMS/NMES, Contra-rTMS/NMES, and Ipsi-rTMS/NMES groups at the 1-month follow-up. Similarly, the DD scores displayed greater improvement in the Bi-rTMS/NMES group than in the Ipsi-rTMS/NMES and Contra-rTMS/NMES groups at the end of stimulation ($P = 0.017$ and $P = 0.021$, respectively), but not after the 1-month follow-up.

Discussion

Brain stroke is believed to lead to interhemispheric imbalance with increased excitability of the contralesional hemisphere and decreased excitability of the ipsilesional hemisphere.[29] This is based on the currently accepted principle that HF-rTMS increases cortical excitability whereas LF-rTMS decreases cortical excitability.[30] Thus, we applied 10-Hz rTMS over the affected hemisphere and 1-Hz rTMS over the unaffected hemisphere. Previous studies showed that 1-Hz rTMS over the unlesioned hemisphere[8,13] or 3-Hz rTMS over the lesioned hemisphere caused improvements in swallowing function in post-stroke patients.[12] In contrast to the above-mentioned accepted principle, some investigators applied HF-rTMS over the contralesional hemisphere. For example, HF-rTMS (5 Hz) over the contralesional hemisphere or bilateral HF-rTMS (10 Hz) over the ipsilesional and contralesional hemispheres still significantly promotes swallowing function in stroke patients with dysphagia.[10,21] Although no reports have described the

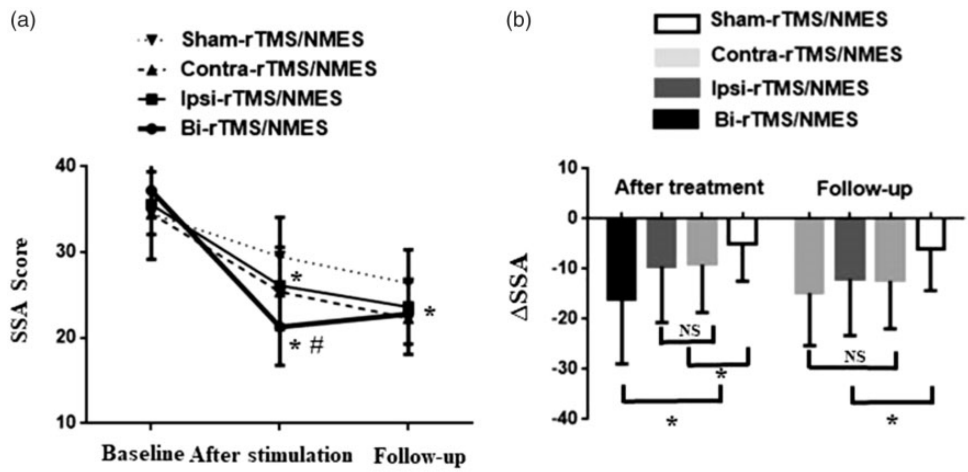

Figure 3. Improvement in swallowing function by different stimulation protocols. (a) Raw SSA scores at baseline, after treatment, and at the 1-month follow-up in the four groups. Remarkable improvement was observed in these groups. *$P < 0.05$ indicates a significant difference compared with the Sham-rTMS/NMES group, and #$P < 0.05$ indicates a significant difference compared with the Ipsi-rTMS/NMES or Contra-rTMS/NMES group. (b) Changes in SSA scores relative to baseline. Significant differences (*$P < 0.05$) are shown. SSA, Standardized Swallowing Assessment; rTMS, repetitive transcranial magnetic stimulation; NMES, neuromuscular electrical stimulation; Sham-rTMS/NMES, sham rTMS plus NMES; Ipsi-rTMS/NMES, ipsilesional 10-Hz rTMS plus NMES; Contra-rTMS/NMES, contralesional 1-Hz rTMS plus NMES

effect of 1-Hz rTMS (with appropriate intensity) over the affected hemisphere in post-stroke patients with dysphagia, we speculate that it would have some therapeutic effects. This may be largely attributed to the physical properties of magnetic stimulation, such as the quantum effect and magnetic spin effect.[31] Independent of frequency, the transcranial magnetic field would alter the atomic and molecular status of the disorder in the influenced brain area, eventually exerting a therapeutic effect. In the present study, bilateral rTMS (10 Hz over the contralesional area and 1 Hz over the ipsilesional area) combined with NMES was more effective than unilateral rTMS or NMES alone. This result is in agreement with a recent report describing the effect of 10-Hz rTMS over the contralesional and ipsilesional areas in post-stroke patients with dysphagia without the combination of NMES.[10] In contrast to our study, these authors applied bilateral HF rTMS. Additionally, they failed to observe the therapeutic effect of 10-Hz rTMS over the affected hemisphere. This may be related to the shorter stimulation duration (10 min, 500 pulses daily, 10 sessions) and smaller sample size. In the present study, however, swallowing function was significantly improved due to the longer stimulation duration (15 min, 900 pulses daily, 10 sessions) and combination with NMES.

Several studies of multiple-site combined stimulation or rTMS in combination with other effective approaches have been performed. For example, rTMS over six different cortical sites combined with cognitive training appeared to promote cognition in patients with Alzheimer's disease,[24] and HF-rTMS over the hand motor area combined with task-oriented mirror therapy training markedly ameliorated hand function in patients with acute stroke.[25] In the

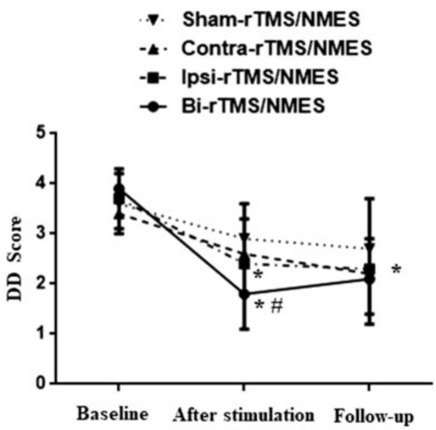

Figure 4. Effect of different stimulation protocols on the DD. Raw DD scores at baseline, after treatment, and at the 1-month follow-up in the four groups. Remarkable improvement was observed in these groups. *$P < 0.05$ indicates a significant difference compared with the Sham-rTMS/NMES group, and #$P < 0.05$ indicates a significant difference compared with the Ipsi-rTMS/NMES or Contra-rTMS/NMES group. DD, degree of dysphagia; rTMS, repetitive transcranial magnetic stimulation; NMES, neuromuscular electrical stimulation; Sham-rTMS/NMES, sham rTMS plus NMES; Ipsi-rTMS/NMES, ipsilesional 10-Hz rTMS plus NMES; Contra-rTMS/NMES, contralesional 1-Hz rTMS plus NMES

present study, we delivered rTMS over the bilateral or unilateral mylohyoid muscle cortical area combined with NMES. NMES has been shown to improve the swallowing function after stroke. When bilateral or unilateral rTMS was combined with NMES, additional therapeutic effects appeared. Consistent with previous reports, the effect of bilateral rTMS was better. Importantly, we failed to observe any adverse effects. These results suggest that bilateral rTMS combined with NMES may serve as an adjunctive strategy to conventional dysphagia treatment.

This study has some limitations. First, this was a small-sample, single-center investigation, and the results need to be further confirmed in larger-sample, multiple-center clinical trials. Second, we first applied HF-rTMS over the affected hemisphere and subsequently LF-rTMS over the unaffected hemisphere. However, whether similar effects would be achieved in the reverse order or with simultaneous and bilateral stimulation remains unclear. Finally, this study lacked a more precise assessment for dysphagia by a videofluoroscopic swallowing study.

In conclusion, our results showed that bilateral rTMS in combination with NMES has an advantage over unilateral rTMS/NMES or NMES alone and that unilateral rTMS/NMES is more effective than NMES alone in the treatment of post-stroke dysphagia.

Declaration of conflicting interest

The authors declare that there is no conflict of interest

Funding

This work was funded by the National Natural Science Foundation of China (No. 81471338 to X.Z., No. 81671284 to X.Z.), the Changzhou Sci & Tech Program Grant (No. CE20145045 to X. Z., No. CE20155051 to H.Y.), and the Changzhou High-Level Medical Talents Training Project (No. 2016CZLJ018 to X.Z.).

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