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Theta burst stimulation versus high-frequency repetitive transcranial magnetic stimulation for poststroke dysphagia

A randomized, double-blind, controlled trial

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) of high-frequency (10 Hz) on suprahyoid motor cortex has been an evidence-based treatment for poststroke dysphagia. Intermittent theta burst stimulation (iTBS) can be performed in 3 minutes compared with 20 ± 5 minutes for 10 Hz rTMS. This study aimed to ensure the clinical efficacy, safety, and tolerability of iTBS compared with 10 Hz rTMS for patients with poststroke dysphagia.

Method: In this randomized, double-blind, single-center, controlled trial, 47 participants were randomly assigned to iTBS (n = 24) and rTMS (n = 23) group. Each participant received iTBS or rTMS daily at suprahyoid motor cortex of affected hemisphere for 10 consecutive days. The outcomes were assessed at baseline, immediately, and 2 weeks after intervention, including water-swallowing test, standardized swallowing assessment, Mann assessment of swallowing ability, Murray Secretion Scale, Yale Pharyngeal Residue Severity Rating Scale, Penetration-Aspiration Scale, and motor evoked potential (MEP) of bilateral suprahyoid muscle.

Results: There were no significant differences between groups. There was a significant improvement on all rating scales and MEP after rTMS and iTBS. No significant differences on water-swallowing test, Mann assessment of swallowing ability, standardized swallowing assessment, Murray Secretion Scale scores, and MEP were observed between groups. In particular, there was significant differences on Penetration-Aspiration Scale scores (viscous liquid: mean difference = 1.016; 95% CI: 0.32–1.71; effect size: 0.360; $P = .005$) and the residue rate of pyriform fossa (viscous liquid: mean difference = 0.732; 95% CI: 0.18–1.28; effect size: 0.248; $P = .010$) in between-group. Comparing the differences over the changes of all rating scales, only the residue rate of epiglottis valley between groups was found to be significantly different (dilute liquid: mean difference = –0.567; 95% CI: –0.98 to –0.15; $P = .009$). There was no severe adverse effect and high dropout rates in both groups.

Conclusion: The clinical efficacy, safety, and tolerability of iTBS showed non-inferior to 10 Hz rTMS for patients with poststroke dysphagia. The present study can be used to improve the clinicians' knowledge and clinical decision skills on iTBS and rTMS for poststroke dysphagia.

Abbreviations: FEES = fiberoptic endoscopic evaluation of swallowing, iTBS = intermittent theta burst stimulation, MASA = Mann assessment of swallowing ability, MEP = motor evoked potential, MSS = Murray Secretion Scale, PAS = Penetration-Aspiration Scale, RMT = determination of resting motor threshold, rTMS = repetitive transcranial magnetic stimulation, SSA = standardized swallowing assessment, TBS = theta burst stimulation, WST = water-swallowing test, YPRS = Yale Pharyngeal Residue Severity Rating Scale.

Keywords: double-blind randomized controlled trial, dysphagia, intermittent theta burst stimulation, stroke, transcranial magnetic stimulation

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1. Introduction

Stroke, as a common cerebrovascular disease, is the primary cause of disability worldwide.[1] About 29% to 81% of survivors after stroke are left with dysphagia, which is characterized by varying degree of eating disorders, choking cough, salivation, and abnormal pronunciation. Dysphagia is associated with increased risk of malnutrition and pneumonia, and leads to prolonged hospital stay, poor prognosis, and mortality.[2–4] Repetitive transcranial magnetic stimulation (rTMS), as a noninvasive neuromodulation technique, is an emerging choice for poststroke dysphagia.[5] Previous clinical studies and meta analyses have demonstrated the efficacy and safety of low-frequency or high-frequency rTMS located in motor cortex for treating poststroke dysphagia.[3,6–9]

rTMS is approved by the US Food and Drug Administration. At present, the conventional protocol of rTMS for poststroke dysphagia consists of 5 Hz or 10 Hz rTMS for 20 ± 5 minutes per time, which contributes to long treatment duration and high cost and further limits the processing capacity of rTMS.[9] Therefore, shortened treatment duration is beneficial to improving the acceptability and cost-effectiveness of rTMS.

Theta burst stimulation (TBS), proposed initially by Huang et al, is a new pattern of rTMS and simulates the frequency of the released pulses in the hippocampus.[10] Intermittent TBS (iTBS), induces synaptic long-term potentiation. It delivers 600 pulses just in 3 minutes, but show similar or more forceful excitatory effects than conventional 10 Hz rTMS.[11] A pilot trial has shown that iTBS is superior to sham stimulation for poststroke dysphagia.[12] Our early clinical research also supports the effect of iTBS on the improvement of poststroke dysphagia.[13] Yet the core issue is whether the efficacy of iTBS and conventional rTMS is comparable. If iTBS within 3 minutes compares favorably with 10 Hz rTMS, the capacity, cost, and acceptability of rTMS would augment several times, widely improving its clinical applications. Clinicians will spend less time but can achieve the same effect as rTMS mode, and reducing the intervention time can significantly improve patient compliance. This will further inspire researchers to apply iTBS to other poststroke dysfunction. Unfortunately, there is currently no study comparing the efficacy of iTBS and conventional rTMS on poststroke dysphagia.

Therefore, a randomized, double-blind, single-center, controlled trial was conducted to compare iTBS with conventional 10 Hz rTMS for poststroke dysphagia. It is hypothesized that compared with conventional 10 Hz rTMS, iTBS would not reveal a significant inferiority in efficacy, safety, and tolerability for poststroke dysphagia.

2. Materials and methods

2.1. Study design

This study was a randomized, double-blind, single-center, controlled trial with blinded participants and evaluators. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (Approval No.: 2021ER066-1).

We completed a preliminary trial with 10 patients before the formal trial to evaluate the sample size. In the preliminary trial, we randomly divided 10 participants into two groups, and received iTBS and rTMS (see sections 2.3–2.4 for specific parameter settings), and performed the standardized swallowing assessment (SSA) before the intervention and 2 weeks after the intervention (T2). On this basis of the estimation, SSA level of patients in the iTBS group was 29.76 ± 2.62 (mean ± standard deviation) at T2, and the SSA level of patients in the rTMS group was 27.45 ± 2.48 (mean ± standard deviation) at T2. A sample size of 22 participants per group for 0.8 power was required to detect the assumed difference between means with a .05 significant level. Considering the short follow-up time, it is assumed that 10% of the patients in each group stopped treatment and/or lost follow-up. Finally, the sample size of 25 subjects in each group was determined. The randomization table was generated centrally by the computer of North Sichuan Medical College and was put in sequentially numbered opaque and sealed envelopes. Participants were randomly assigned to iTBS group (n = 25) or rTMS group (n = 25) via sequentially numbered opaque and sealed envelopes that contained the product assignment provided by an independent staff. For the iTBS group, iTBS was performed on the motor cortex of the suprahyoid muscle on the affected side; the rTMS group was also treated with rTMS on the motor cortex of the suprahyoid muscle on the affected side.

Each participant received iTBS or rTMS daily at motor cortex of affected hemisphere for 10 consecutive days. After stimulation, each patient received same amount of conventional dysphagia therapy including oral exercise training, oral sensory training, swallowing organ training, direct feeding training, swallowing auxiliary techniques for 30 minutes every day.[14]

The outcome measures were assessed at baseline (T0, before intervention), immediately after intervention (T1, post-intervention), and 2 weeks after intervention (T2, follow-up).

2.2. Participants and setting

Fifty patients diagnosed with poststroke dysphagia by the Rehabilitation Department of the Affiliated Hospital of North Sichuan Medical college were recruited from February 1, 2020 to June 1, 2021. All patients met the following inclusion criteria:

(1) supratentorial stroke (unilateral ischemic or hemorrhagic stroke, 2 weeks ≤ duration ≤ 3 months) confirmed by computed tomography or magnetic resonance imaging with the first onset;
(2) patients aged 18 to 78 years;
(3) dysphagia lasting >2 weeks after stroke;
(4) infiltration or aspiration confirmed by fiberoptic endoscopic evaluation of swallowing (FEES);
(5) water-swallowing test (WST) ≥ grade 3;
(6) signing the relevant informed files.

The exclusion criteria included:

(1) a history of swallowing problems due to other neurological conditions, such as Parkinson's disease, dementia, and motor neuron disease;
(2) history of intractable epilepsy;
(3) intracranial and/or cardiac metal implants;
(4) unstable vital or in the acute phase of the disease;
(5) patient with poor cognitive function.

Three patients dropped out for personal reasons unrelated to this study. Eventually, 47 completed the study (Fig. 1).

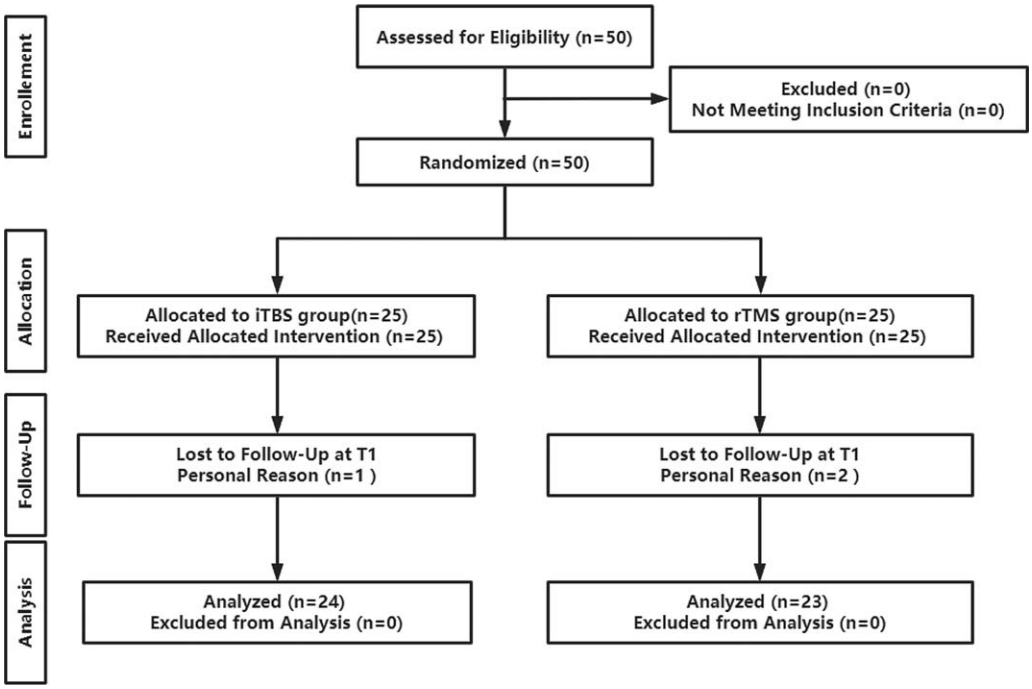

Figure 1. Flow chart. T1 = immediately after the intervention.

2.3. Determination of resting motor threshold (RMT)

Before intervention, RMT should be assessed by a physical therapist who was not clear about the assignment. Patients sat relaxed on an armchair. The targeted site was detected according to the international 10–20 systems for electrode placement. This study used a TMS System (nagneuro60 stimulator, Nanjing Weiss Medical Technology Co., Ltd., Nanjing, China) and a figure-of-eight coil. And electromyography data were recorded from the suprahyoid muscle via surface electrodes.[15] The coil was positioned on the motor cortex of unaffected side. The single-pulse stimulation was primarily triggered at 30% of the maximum output intensity, then the stimulus intensity was increased gradually until the largest consistent motor evoked potential (MEP) response from the contralateral thumb short abductor muscle was induced.[14,16] Keep the stimulus intensity constant, and the coil was moved slightly around the site with an interval of 0.5 to 1.0 cm until five consecutive highest MEP recordings were obtained, which of site was termed as "hot spot."[17,18] After "hot spot" determined, the RMT was obtained by gradually reducing the intensity. RMT was defined as the minimal intensity, at which MEP of at least 50 μV could be drawn out in 5 of 10 consecutive sessions.[16]

2.4. TMS intervention

Due to the design and settings of the study, it was not possible to blind the treatment research staff involved in the study. We arranged for an experienced therapist to conduct TMS intervention. The iTBS protocol was delivered at an intensity of 100% of RMT, 3 pulses of 50 Hz bursts repeated at 5 Hz (2 s on and 8 s off) for a total of 192 seconds (600 pulses) on the "hot spot" of affected hemisphere. rTMS group contained 10 Hz and 100% RMT with 2 s trains at an intertrain interval of 18 seconds for 20 minutes (1200 pulses) on the same position.[14]

2.5. Swallowing function assessments

WST, SSA, and Mann assessment of swallowing ability (MASA) were assessed to quantify severity of dysphagia by a physical therapist who was not clear about the assignment. A physiotherapist, blinded to group assignment, evaluated the swallowing function to score WST, MASA, and SSA before each FEES. WST was divided into five grades from 1 to 5, with lower grades reflecting poorer swallowing function.[19] SSA score ranged from 18 to 46, with higher scores reflecting more serious dysphagia.[20] The highest MASA score was 20 to 100, with lower scores reflecting worse dysphagia.[21] WST, MASA, and SSA have been proven to have a good reliability and validity in the assessment of dysphagia.[19–22]

2.6. Fiberoptic endoscopic evaluation of swallowing

The speech therapist carried out FEES based on the Standard Manual guide.[23] Each nostril was visually examined so that the endoscope could pass through fluently without the application of local anesthetics or vasoconstrictors to the nasal mucosa, which eliminated any potential adverse anesthetic reactions and guaranteed security of this check.[24]

First, patients were asked to swallow saliva and observed whether that accumulated in the bottom of tongue, pharynx, and larynx. Next, each patients were given 5 ml dilute liquid and viscous liquid orderly. All processes were conserved in a digital video file. A speech therapist and a physical therapist, both blinded to group allocation, graded the Murray Secretion Scale (MSS), The Yale Pharyngeal Residue Severity Rating Scale (YPRS), and Penetration-Aspiration Scale (PAS).

MSS is an outcome to assess the accumulation of oropharyngeal secretion, indicating the extent of impairment of the larynx's capacity of removal.[25] YPRS, a credible imaging tool based on its anatomic definition, was divided into five grades according to

the location and the amount of residue, with higher scores indicating worse dysphagia.[26] PAS, an 8-point multidimensional index of airway invasion, was adopted to record the airway penetration (entering the laryngeal vestibule) and aspiration (entering below the level of the vocal cords) for each swallow.[27] MSS, YPRS, and PAS have been proven to have a good reliability and validity in the assessment of dysphagia.[25,28,29]

2.7. Suprahyoid muscle MEP assessment

Referring to past TMS trials, to evaluate the excitability of bilateral suprahyoid motor cortex, one pair of bipolar silver-silver chloride electrodes was delivered on the right and left suprahyoid muscle, each 1 cm lateral to the midline, respectively, to monitor suprahyoid muscle MEPs. Measured from the center of the electrodes, the inter-electrode distance for each pair of electrodes was 2 cm.[30] The MEPs of bilateral suprahyoid muscle were recorded by the single-pulse TMS located on "hot spot" of the contralesional suprahyoid motor cortex. In brief, the left MEP reflected the excitability of the right suprahyoid motor cortex and the right MEP reflected that of left.

To avoid the cortical evoked responses induced without intention, all patients tried to remain relaxed during the research, minimizing swallowing, coughing, or talking. A total of 10 MEPs per side of the suprahyoid muscle were recorded at each time point.

2.8. Statistical analyses

SPSS 22.0 (SPSS Inc., Chicago, IL) was utilized to analyze. The Shapiro-Wilk test was used to assess if the scores conformed a normal distribution. The changes of within-group over time were evaluated using paired *t*-test. To assess the differences of swallowing function scores along therapy timeline, the change value "Δ" was figured out from the baseline to each time point. Univariate ANOVA was adopted to evaluate the differences of characteristics at baseline and changes from the baseline to each time point between groups. The Kruskal–Wallis and Friedman tests were used to assess latency and amplitude of MEPs. The Cohen's *d* and Morris ppc2 were used to assess effect size of all the variables.[31] The significance level was set at .05.

3. Results

3.1. Participants

A sum of 47 participants (aged 66.2 ± 10.9 years, 34 males) completed the research without severe adverse effects, of whom, three participants dropped out due to personal reasons, including one in iTBS group and two in rTMS group. There were no significant differences in gender, age, poststroke duration, stroke type, and side of paresis between groups. And no significant differences in scores of WST, MASA, SSA, MSS, YPRS, and PAS were found at baseline (Table 1).

Table 1

Characteristics of behavior and swallowing function assessment at baseline.

Variables	iTBS group (n = 24)	rTMS group (n = 23)	*P*
Age (years)	67.5 ± 10.6	64.8 ± 11.3	.401
Gender			
Males	16 (67%)	18 (78%)	.385
Females	8 (33%)	5 (22%)	
Time from stroke to recruitment (days)	25.1 ± 11.74	29.9 ± 17.11	.251
Stroke type (ischemic:hemorrhagic)	6:18	7:16	.685
Lesion site (right:left)	14:10	11:12	.481
WST	4.25 ± 0.53	4.43 ± 0.59	.265
MASA	80.96 ± 8.16	80.91 ± 8.24	.985
SSA	31.04 ± 5.09	32.83 ± 4.97	.23
MSS	1.70 ± 0.86	1.96 ± 0.88	.332
YPRS (severity of vallecula residue)			
Dilute liquid	2.29 ± 0.95	2.74 ± 0.86	.099
Viscous liquid	2.75 ± 0.79	2.43 ± 0.84	.194
YPRS (severity of pyriform sinus residue)			
Dilute liquid	2.83 ± 1.27	2.91 ± 0.79	.799
Viscous liquid	2.25 ± 0.74	2.78 ± 1.17	.063
PAS			
Dilute liquid	4.54 ± 2.46	5.69 ± 1.89	.078
Viscous liquid	2.83 ± 1.90	3.91 ± 2.46	.099

iTBS = intermittent theta burst stimulation, MASA = Mann assessment of swallowing ability, MSS = the Murray Secretion Scale, PAS = Penetration-Aspiration Scale, rTMS = repetitive transcranial magnetic stimulation, SSA = standardized swallowing assessment, WST = water-swallowing test, YPRS = The Yale Pharyngeal Residue Severity Rating Scale. N or mean ± standard deviation.

3.2. Swallowing function assessments

The WST, MASA, SSA, MSS, and PAS scores of the two groups at T1 and T2 were significantly improved compared with T0 ($P < .05$). No significant differences between groups were found at T1 on WST (mean difference = .397; 95% confidence interval [CI]: –0.28 to 1.08; effect size: 0.011; $P = .247$), MASA (mean difference = –0.254; 95% CI: –5.01 to 4.51; effect size: 0.026; $P = .915$), SSA (mean difference = 1.683; 95% CI: –2.73 to 4.05; effect size: 0.243; $P = .698$), MSS (mean difference = –0.038; 95% CI: –0.49 to 0.41; effect size: 0.353; $P = .866$), and PAS scores (dilute liquid: mean difference = 0.534; 95% CI: –0.93 to 2.01; effect size: 0.306; $P = .467$; but viscous liquid: mean difference = 1.016; 95% CI: 0.32–1.71; effect size: 0.360; $P = .005$). No significant differences also could be detected at T2 for WST (mean difference = 0.386; 95% CI: –1.09 to 0.32; effect size: 0.645; $P = .277$), MASA (mean difference = 2.705; 95% CI: –1.086 to 7.27; effect size: 0.354; $P = .239$), and SSA (mean difference = 1.248; 95% CI: –2.15 to 4.65; effect size: 0.140; $P = .464$) (Table 2).

YPRS scores were based on the residue rate of thick and thin liquid of the pyriform fossa and the epiglottis valley. The results suggested no significant differences at T1 in the residue rate of dilute liquid (mean difference = –0.119; 95% CI: –0.65 to 0.41; effect size: 0.628; $P = .654$) and viscous liquid (mean difference = –0.161; 95% CI: –0.587 to 0.264; effect size: 0.173; $P = .449$) on the epiglottis valley and no significant differences at T1 in that of dilute liquid (mean difference = 0.312; 95% CI: –0.19 to 0.82; effect size: 0.285; $P = .219$) of the pyriform fossa in both groups. Only the residue rate of viscous liquid (mean difference = 0.732; 95% CI: 0.18–1.28; effect size: 0.248; $P = .010$) of the pyriform fossa at T1 showed the difference in both groups (Table 2).

Due to differences in some of the results between groups, we further performed a statistical analysis on the changes in SSA, YPRS, and PAS scores between two groups. No significant differences could be detected in SSA, YPRS, and PAS scores when comparing the changes between groups directly (Fig. 2). If comparing the differences over the changes of the residue rate of dilute liquid of the epiglottis valley between groups, the

Table 2

Comparison of clinical outcomes between 2 groups.

Variables	Time	iTBS group (n = 24)	rTMS group (n = 23)	Mean difference	Lower 95% CI	Upper 90% CI	*P*
WST							
	T0	4.25 ± 0.53	4.43 ± 0.59	0.184	–0.14	0.51	.265
	T1	3.16 ± 1.08	3.52 ± 1.24	0.397	–0.28	1.08	.247
	T2	3.13 ± 1.23	2.74 ± 1.18	0.386	–1.09	0.32	.277
MASA							
	T0	80.96 ± 8.16	80.91 ± 8.24	–0.045	–4.85	4.76	.985
	T1	85.17 ± 8.84	84.91 ± 7.26	–0.254	–5.01	4.51	.915
	T2	85.21 ± 9.62	87.91 ± 5.17	2.705	–1.086	7.27	.239
SSA							
	T0	31.04 ± 5.09	32.83 ± 4.97	1.784	–1.17	4.74	.23
	T1	29.13 ± 5.97	29.78 ± 5.55	1.683	–2.73	4.05	.698
	T2	27.71 ± 6.03	28.96 ± 5.52	1.248	–2.15	4.65	.464
MSS							
	T0	1.70 ± 0.86	1.96 ± 0.88	0.248	–0.26	0.76	.332
	T1	1.13 ± 0.74	1.09 ± 0.74	–0.038	–0.49	0.41	.866
YPRS (severity of epiglottis valley residue)							
Dilute liquid	T0	2.29 ± 0.95	2.74 ± 0.86	0.447	–0.09	0.98	.099
	T1	2.25 ± 0.99	2.13 ± 0.81	–0.119	–0.65	0.41	.654
Viscous liquid	T0	2.75 ± 0.79	2.43 ± 0.84	–0.315	–0.79	0.17	.194
	T1	2.29 ± 0.81	2.13 ± 0.63	–0.161	–0.587	0.264	.449
YPRS (severity of pyriform fossa residue)							
Dilute liquid	T0	2.83 ± 1.27	2.91 ± 0.79	0.079	–0.54	0.71	.799
	T1	2.17 ± 1.01	2.48 ± 0.67	0.312	–0.19	0.82	.219
Viscous liquid	T0	2.25 ± 0.74	2.78 ± 1.17	0.533	–0.04	1.1	.063
	T1	1.83 ± 0.82	2.57 ± 1.04	0.732	0.18	1.28	.010*
PAS							
Dilute liquid	T0	4.54 ± 2.46	5.69 ± 1.89	1.154	–0.14	2.44	.078
	T1	3.29 ± 2.56	3.83 ± 2.42	0.534	–0.93	2.01	.467
Viscous liquid	T0	2.83 ± 1.90	3.91 ± 2.46	1.079	–0.21	2.37	.099
	T1	1.38 ± 0.71	2.39 ± 1.53	1.016	0.32	1.71	0.005*

iTBS = intermittent theta burst stimulation, MASA = Mann assessment of swallowing ability, MSS = the Murray Secretion Scale, PAS = Penetration-Aspiration Scale, rTMS = repetitive transcranial magnetic stimulation, SSA = standardized swallowing assessment, WST = Water-swallowing test, YPRS = The Yale Pharyngeal Residue Severity Rating Scale. N or mean ± standard deviation. T0 = baseline before stimulation; T1 = immediately after stimulation; T2 = 3 weeks after cessation of stimulation.

* Significant difference was observed in both groups (*$P < .05$).

differences became significant (mean difference = –0.567; 95% CI: –0.98 to –0.15; $P = .009$).

3.3. Suprahyoid muscle MEP assessment

The amplitude of MEPs of the suprahyoid muscle representing the ipsilesional hemisphere increased significantly at T1 and T2 compared with baseline in both groups (rTMS groups at T1: mean difference = 381.29; 95% CI: 49.57–379.34; $P = .013$; rTMS groups at T2: mean difference = 490.82; 95% CI: 215.88–640.37; $P < .001$; iTBS groups at T1: mean difference = 333.03; 95% CI: 77.48–358.73; $P = .004$; iTBS groups at T2: mean difference = 535.08; 95% CI: 176.48–628.36; $P = .001$). The amplitude of MEPs of the suprahyoid muscle representing the contralesional hemisphere increased significantly at T1 compared with T0 for iTBS group and the amplitude on that increased significantly at T2 compared with T0 for rTMS group (iTBS groups at T1: mean difference = 216.57; 95% CI: 34.23–217.13; $P = .009$; rTMS groups at T2: mean difference = 170.11; 95% CI: 88.30–235.42; $P < .001$). There were no significant between-group differences in the amplitude of MEPs of ipsilesional hemisphere at neither T1 nor T2 ($P > 0.05$). Both groups showed that the amplitude of MEPs of suprahyoid muscle in the contralesional hemisphere were significantly higher than that in the ipsilesional hemisphere at T2. No differences in latency of MEP were observed (Table 3).

3.4. Safety and tolerability

No serious adverse effects were found in the iTBS group and the rTMS group. The dropout rates of the participants were 1/25 (the iTBS group) and 2/25 (the rTMS group), and participants dropped out due to personal reasons ($P > .05$).

4. Discussion

According to our understanding, this is the first randomized controlled trial comparing iTBS with 10 Hz rTMS on poststroke dysphagia. The results provide strong evidence that iTBS is non-inferior to conventional 10 Hz rTMS in improving poststroke dysphagia. The finding showed no obvious differences in clinician-based evaluations of WST, MASA, SSA, MSS, YPRS, PAS scores, and MEPs of suprahyoid muscle, a significant reduction in dysphagia symptoms at T1 and T2, and a significant increase in amplitude of MEP of suprahyoid muscle on the affected side between both groups, as well as severe adverse effects and dropout rate. These outcomes hint the 3 minutes iTBS protocol might perform comparably to the conventional 20 ± 5 minutes 10 Hz rTMS protocol as an intervention for poststroke dysphagia.

The existed studies have demonstrated that the suprahyoid muscles were dominated by bilateral motor cortices, and such domination often was asymmetric. Neurophysiologically, swallowing function maintained via mechanism of interhemispheric

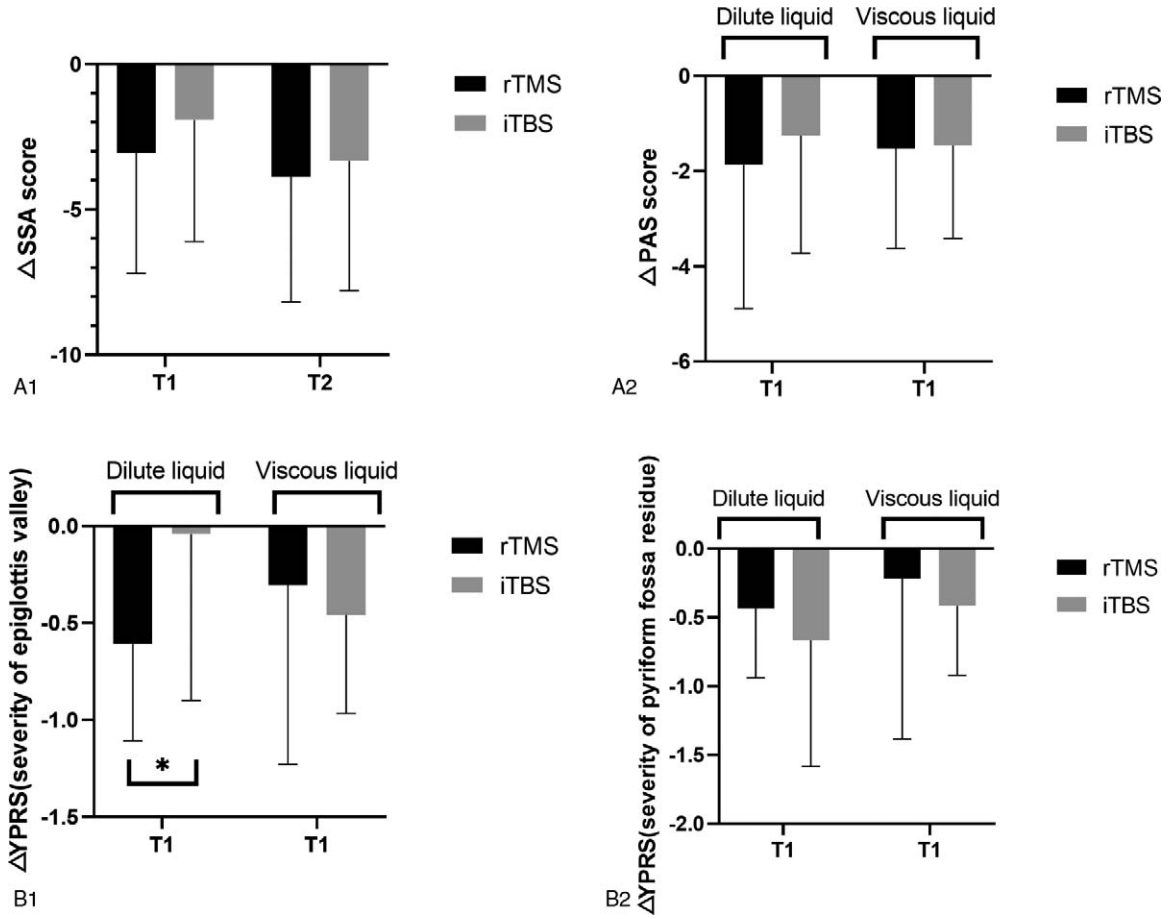

Figure 2. Swallowing function assessments based on clinical severity and fiberoptic endoscopic evaluation of swallowing (FEES). (A1) changes in the standardized swallowing assessment (SSA) score. (A2) Changes in the Penetration-Aspiration Scale (PAS) score. (B1) Changes in the Yale Pharyngeal Residue Severity Rating Scale (YPRS) in severity of epiglottis valley residue. (B2) Changes in the Residue Severity Rating Scale (YPRS) in severity of pyriform fossa residue. Error bars represent the standard deviation for each condition. (*) indicates that a significant difference was observed within both group (*$P < .05$); T0 = baseline before the intervention, T1 = immediately after the intervention, T2 = 2 weeks after cessation of the intervention.

inhibition.[32,33] The interhemispheric imbalance was considered as an abnormal increase in excitability of the unaffected hemisphere that exerted an inhibitory effect on the ipsilesional hemisphere via altered transcallosal inhibition pathway after stroke occurring, which eventually contributed to dysphagia.[34] It may be an effective way to promote the recovery of swallowing function after stroke clinically by adjusting cortical excitability and enhancing synaptic plasticity.[5]

This study analyzed the changes on swallowing function in patients with poststroke dysphagia after iTBS and rTMS. Studies have shown that iTBS and rTMS could increase the excitability of the stimulating cortex, and through the intermediate connecting fibers of the corpus callosum, the excitability of the contralateral brain area relatively reduced, and the excitability of both sides tended to be balanced.[5,35–37] At the same time, excitability changes would increase synaptic plasticity and further improve swallowing

Table 3

Value of the mylohyoid motor evoked potentials.

MEPs' parameters	Intervention	Hemisphere	T0	T1	T2
Amplitude (μV)	rTMS	Ipsilesional	519.1535 ± 241.06419	733.6109 ± 436.56993*	947.2804 ± 508.81151*
		Contralesional	442.1557 ± 218.51706	554.5061 ± 233.97681	604.0157 ± 252.95122*
	iTBS	Ipsilesional	502.5921 ± 292.64915	747.8529 ± 341.25736*	932.1700 ± 517.59311*
		Contralesional	468.4542 ± 375.37911	656.9067 ± 399.70593*	577.9367 ± 372.61419
Latency (ms)	rTMS	Ipsilesional	8.1509 ± 0.97666	7.8435 ± 0.20466	7.8370 ± 0.17851
		Contralesional	7.8196 ± 0.21038	7.8348 ± 0.18916	7.7152 ± 0.23857
	iTBS	Ipsilesional	8.3213 ± 1.10657	8.9375 ± 0.14084	8.9625 ± 0.08373
		Contralesional	7.8296 ± 0.19910	8.2854 ± 1.23107	7.9917 ± .50790

iTBS = intermittent theta burst stimulation, rTMS = repetitive transcranial magnetic stimulation, T0 = baseline before stimulation, T1 = immediately after stimulation, T2 = 3 weeks after cessation of stimulation. Mean ± standard deviation.

* Significant difference was observed compared to T0 within groups (*$P < .05$).

function.[5] These brain changes may clinically improve the swallowing function of patients with dysphagia after stroke. And the scores of WST, SSA, MASA, and MSS in both groups improved significantly. The current reports on these clinical changes were supported by Tarameshlu et al, Du et al and Zhang et al.[7,8,38]

Park et al observed that rTMS could reduce tracheal penetration and aspiration.[3] Penetration and aspiration belonged to one of the symptoms of dysphagia. Our research proved that both iTBS and rTMS could improve patients' osmotic aspiration and reduce PAS scores.

The findings of YPRS scores demonstrated the residue rate in the pyriform fossa and the epiglottis valley had various degrees of reduction in both groups, suggesting a lower risk of aspiration.[26] The changes of epiglottis valley residue of rTMS group were superior to that of iTBS group underlying the YPRS scores of dilute liquid (mean difference = –0.567; 95% CI: –0.98 to –0.15; $P = .009$). This discrepancy was probably related to the difference in the baseline of YPRS scores of dilute liquid of the epiglottis valley (iTBS, 2.29 ± 0.95; rTMS, 2.74 ± 0.86), but this difference was not statistically significant (mean difference = 0.447; 95% CI: –0.09 to 0.98; $P = .099$). At the same time, the results suggested no significant differences at T1 in the residue rate of dilute liquid (mean difference = –0.119; 95% CI: –0.65 to 0.41; effect size: 0.628; $P = .654$). Therefore, in general, the two groups had the same effect in improving residues.

In summary, the relief in symptoms and change in scores of participants in both groups would preserve assay sensitivity (i.e., the expected findings showed efficacy compared with sham stimulation) compared with our previous sham results.[13,39] Despite the dependable and consistent reduction in dysphagia symptoms drew, further efforts are needed to explicit the relevant mechanisms of rTMS to enhance overall outcomes.[9]

The results showed that the amplitude of MEPs of bilateral suprahyoid muscle improved after intervention in both groups, and the changes of amplitude on affected hemisphere performed higher than that on uneffected hemisphere. Moreover, the amplitude of MEPs on affected hemisphere rose persistently, implying that both iTBS and rTMS modulated excitability of affected hemisphere with a continuous effect, augmented neural plasticity and promoted the improvement of dysphagia. This result was consistent with previous research results.[5,35–37]

No discernible differences could be explored in adverse effects and the number of participants with intolerance to treatment between groups. Dropout rates were low in both groups (4–8%). This dropout rate showed no significant difference compared with that in a meta-analysis of 26 trials of neurostimulation therapies for poststroke dysphagia.[9]

It is worth noting that it is crucial to clarify the distinctions of the stimulation parameters for iTBS and rTMS. First, this study did not match the number of pulses of iTBS (600 pulses per session) to rTMS (1200 pulses per session). Previous studies proved that doubling the number of iTBS pulses did not consolidate the excitatory effect and even had an inhibitory effect.[40] Second, we delivered the stimulation at 100% RMT in both groups. Past meta-analysis had verified that insufficient stimulation intensity should be considered as a potential reason for lower efficacy in earlier rTMS trials.[9,41] Present conventional rTMS protocols were employed with stimulation of 90% to 120% RMT. The initial neurophysiological of iTBS researches adopted an intensity of 80% RMT.[10,35] Previous pilot studies of iTBS in poststroke dysphagia used similar low intensities, possibly owing to the uncertainty over the safety of iTBS at higher intensities.[12,17] Safety guidelines of TMS[42] did not rule a maximum stimulation intensity. The data from this study indicated that iTBS might be performed safely at 100% RMT in suprahyoid motor cortex without reducing tolerability.

Despite the strengths of this study, several limitations should be taken to consideration. The study exists an absence of sham stimulation as previous studies have discussed the efficacy of rTMS and sham stimulation in poststroke dysphagia.[12,17,9,41] The study involved the efficacy of iTBS versus conventional 10 Hz rTMS rather than sham stimulation.

Application of sham stimulation following iTBS could enable matching of treatment duration with conventional rTMS. However, it would require performing active and sham stimulation in the same session continuously, which would not blind the participants. Because active and sham stimulation could be easily distinguished if delivered to the same patient sequentially even with careful calibration.[43] So we abandoned the above procedure.

5. Conclusion

Taken together, this study proved that iTBS exerted similar efficacy, safety, and tolerability compared with conventional 10 Hz rTMS for poststroke dysphagia. The number of patients treated by each machine will be doubled or more per day after application of iTBS. In other words, iTBS has shown the potential to increase capacity, improve utilization rate, short waiting times, and reduce costs. The present study can be used to improve the clinicians' knowledge and clinical decision skills on iTBS and rTMS for poststroke dysphagia.

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