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Repetitive transcranial magnetic stimulation as an alternative therapy for dysphagia after stroke: A systematic review and meta-analysis

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Abstract

Objectives: A meta-analysis and systematic review was conducted to investigate the potential effects of repetitive transcranial magnetic stimulation on dysphagia in patients with stroke, including different parameters of frequency and stimulation site.

Methods: PubMed, Embase, MEDLINE databases and the Cochrane Library, were searched for randomized controlled studies of repetitive transcranial magnetic stimulation treatment of dysphagia published before March 2016.

Results: Six clinical randomized controlled studies of a total of 163 stroke patients were included in this meta-analysis. A significant effect size of 1.24 was found for dysphagic outcome (mean effect size, 1.24; 95% confidence interval (CI), 0.67–1.81). A subgroup analysis based on frequency showed that the clinical scores were significantly improved in dysphagic patients with low frequency repetitive transcranial magnetic stimulation treatment ($P<0.05$) as well as high frequency repetitive transcranial magnetic stimulation treatment ($P<0.05$). A stimulation site stratified subgroup analysis implied significant changes in stroke patients with dysphagia for the unaffected hemisphere ($P<0.05$) and the bilateral hemisphere stimulation ($P<0.05$), but not for the affected hemisphere ($P>0.05$). The analysis of the follow-up data shows that patients in the repetitive transcranial magnetic stimulation groups still maintained the therapeutic benefit of repetitive transcranial magnetic stimulation four weeks after the last session of repetitive transcranial magnetic stimulation therapy ($P<0.05$).

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Conclusion: This meta-analysis indicates that repetitive transcranial magnetic stimulation has a positive effect on dysphagia after stroke. Compared with low-frequency repetitive transcranial magnetic stimulation, high-frequency repetitive transcranial magnetic stimulation may be more beneficial to the patients. This meta-analysis also supports that repetitive transcranial magnetic stimulation on an unaffected – or bilateral – hemisphere has a significant therapeutic effect on dysphagia.

Keywords
Repetitive transcranial magnetic stimulation, stroke, dysphagia, meta-analysis

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Introduction

Dysphagia is a major complication which occurs in 55% to 65% after stroke patients[1,2] and is often accompanied by malnutrition, pneumonia and dehydration.[3] While many stroke patients recovered their swallowing function within a few weeks after acute stroke, the extent of recovery varies widely from patient to patient.[4] To shorten the recovery time and improve the recovery rate in patients with dysphagia, various therapeutic methods have been explored.[2,5]

Recently, various brain stimulations, e.g. repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation have emerged as promising therapies for swallowing disorders. It is well known that low-frequency rTMS leads to inhibition effectively, whereas high-frequency rTMS leads to excitation effectively on cerebral cortex. One study[6] showed that rTMS over the swallowing motor cortex induced the excitability of direct corticobulbar projections to the swallowing muscles. Several studies reported that rTMS is effective in the recovery of swallowing function following stroke, but other studies did not support the findings.[7–14]

A recent systematic review has evaluated the total effects of rTMS on dysphagia after stroke.[15] However, the effect of different parameters of rTMS on dysphagia has not been investigated. It is not clear if a difference in rTMS parameters or other factors may have affected the outcome of the treatment in different studies. This study was performed to evaluate the published data of the effects of different rTMS parameters on stroke patients with dysphagia.

Materials and methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16] There were no specific protocols for this systematic review and meta-analysis.

Search strategy

PubMed, Cochrane Library, MEDLINE and Embase were searched to identify relevant clinical studies published in English till 15 March 2016. The following subject headings and terms were used in conjunction with a sensitive search strategy. The search group was: ('dysphagia' or 'swallowing disorders' or 'deglutition disorders' or 'swallowing dysfunction') and ('stroke' 'cerebral apoplexy' or 'cerebrovascular accident') and ('repetitive transcranial magnetic stimulation' or 'rTMS').

Inclusion and exclusion criteria

Previously published studies were assessed using the following criteria: (1) the studies were randomized and controlled; (2) the patients were diagnosed with stroke (ischemic or haemorrhagic) by clinically relevant examinations (computed tomography, magnetic resonance imaging); (3) the dysphagia and oral pharyngeal dysfunction of the stroke patients were confirmed by video fluoroscopic swallowing studies, in which the researchers provided original data or sufficient information about

Table1. Main characteristics of included studies.

First author	Year	Age	Stroke duration	No. of participants (Exp./Ctr.)	Method of control	Main clinical score	Follow-up?	Adverse effects
Khedr[8]	2009	57.3 (12.5)	2 weeks	26 (14/12)	Sham stimulation	DG	1 and 2 months	—
Khedr[7]	2010	56.4 (15)	1–3 month	22 (11/11)	Sham stimulation	DG	1 and 2 months	—
Kim[9]	2013	66.4 (12.3)	<3 month	30 (20/10)	Sham stimulation	PAS	No	—
Park[11]	2013	73.7 (3.8)	55.9 (16.3) day	18 (9/9)	Sham stimulation	PAS	4 weeks	—
Lim[10]	2014	59.8 (11.8)	<3 month	29 (14/15)	CDT	PAS	4 weeks	One subject complained of headache
Du[13]	2016	58.3 (2.9)	7.7 days	38 (26/12)	Sham stimulation	SSA	1, 2 and 3 months	—

—: no description in the study; CDT: conventional dysphagia therapy; Ctr.: control group; DG: dysphagia grade; Exp.: experimental group; PAS: penetration aspiration scale; SSA: standardized swallowing assessment.

dysphagia occurred during pre- and post-treatment in experimental trials and control trials; and (4) the interventions should be the same between experimental and control trials except for the rTMS in the experimental trials. Exclusion criteria included: (1) the dysphagia was caused by another disease (head injury, cancer, infection, etc.); (2) certain publications that did not offer original data, such as reviews, meta-analysis, systematic review, letters, or proceedings; and (3) if the study was a case report.

Study quality and data extraction

Two experienced reviewers independently assessed the studies using the inclusion/exclusion criteria described above. The extracted data and descriptive information included the surname of the first author, the year of the publication, style of study, stroke duration, the number of the study subjects, method of control, main clinical scores, follow-up and adverse effect. The posttreatment main clinical scores of the experimental and control trials were included: The functional dysphagia scale, penetration aspiration scale or dysphagia grade. The baseline information of the six included studies is shown in Table 1.

The mean and standard deviation (SD) of outcomes were used in the meta-analysis. The mean and SD of primary clinical outcomes were obtained from the tables published in each study. If the direct results were not provided, the data was obtained from the histograms by using the GetData Graph Digitizer software (http://getdata-graph-digitizer.com) or from the corresponding author. Any disagreements were resolved by discussing and by consulting with a third reviewer.

Statistical analysis

The effect-size was calculated by a standardized mean difference (SMD) for clinical scores of post-treatment in experimental and control trials. A 95% confidence interval (CI) was evaluated using a Z test. The heterogeneity between each group was tested by the Cochran's Q statistic and an I^2 test.[17] If heterogeneity did not exist among the included groups (the Q test displayed that $P>0.05$ or $I^2<50\%$), the fixed-effect model was used. Otherwise, if the Q test result was significant ($p<0.05$ or $I^2>50\%$), the random-effect model was used in the meta-analysis. The subgroup analysis was used to find out sources of the heterogeneity. The random-effect model for small sample studies with higher weight generally leads to a relatively conservative result.[18] All statistical analyses were conducted using RevMan5.2 statistical software (Cochrane Collaboration, Oxford, UK).

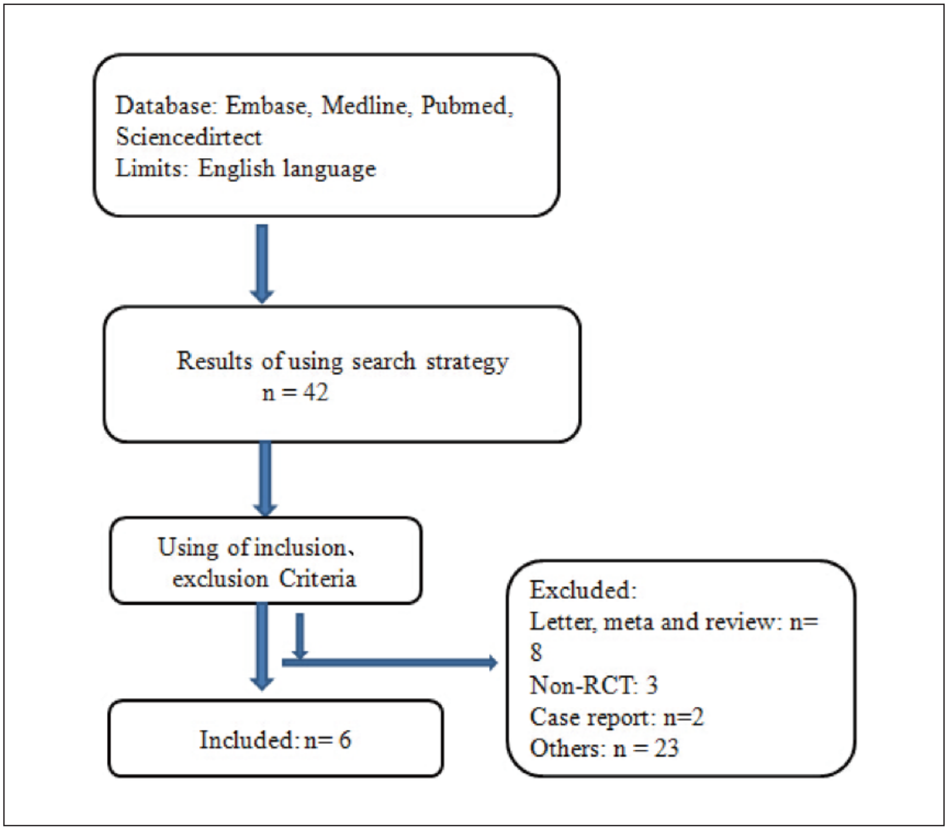

Figure 1. Flowchart summarizing the selection process.

Results

Information of included studies

Of the 43 original studies found in the databases, six randomized controlled studies (nine groups) of a total of 163 stroke patients with dysphagia and who received rTMS intervention were included for meta-analysis (Figure 1).

Three studies included six experimental groups[7,9,13] and another three studies included three experimental groups.[8,10,11] Three studies[9,10,13] used low-frequency rTMS to treat patients with dysphagia. Other studies used high-frequency rTMS.[7,8,11] The stimulation sites of those included studies comprised of the bilateral oesophageal motor cortex,[7] affected oesophageal motor cortex[8,9,13] and unaffected oesophageal motor cortex.[9,10,11] Some included studies[7,8,10,11,13] also had follow-up patients after four weeks or one month of rTMS treatment. The baseline information of the included rTMS studies is shown in Table 2.

Quality of the studies

The risk of bias for the nine study groups has been evaluated by two reviewers by using Cochrane Collaboration guidelines; and the results are presented in Figure 2. The risk of bias was low except the blinding of outcome data.

Quantitative data synthesis

The Q and I^2 tests (posttreatment experiment and control group) analyses with SMD along with the random effect model were used to test the heterogeneity in the meta-analysis. A significant heterogeneity

Table 2. Main parameter of rTMS.

Name of group	Repetitive transcranial magnetic stimulation				
	Frequency	Stimulation location (oesophageal cortical area)	Intensity	Number of pulse a day	Total time
Khedr 2009[8]	3 Hz	Affected hemisphere	120% rMT	300 pulses	1 week
Khedr 2010a[7]	3 Hz	Bilateral hemisphere	130% rMT	300 pulses	1 week
Khedr 2010b[7]	3 Hz	Bilateral hemisphere	130% rMT	300 pulses	1 week
Kim 2013a[9]	1 Hz	Unaffected hemisphere	100% MT	1200 pulses	2 week
Kim 2013b[9]	5 Hz	Affected hemisphere	100% MT	1000 pulses	2 week
Park 2013[11]	5 Hz	Unaffected hemisphere	90% MT	500 pulses	2 week
Lim 2014[10]	1 Hz	Unaffected hemisphere	100% rMT	1200 pulses	2 week
Du 2016a[13]	3 Hz	Affected hemisphere	90% rMT	1200 pulses	1 week
Du 2016b[13]	1 Hz	Unaffected hemisphere	100% rMT	1200 pulses	1 week

MT: motor threshold; rMT: resting motor threshold; rTMS: repetitive transcranial magnetic stimulation.

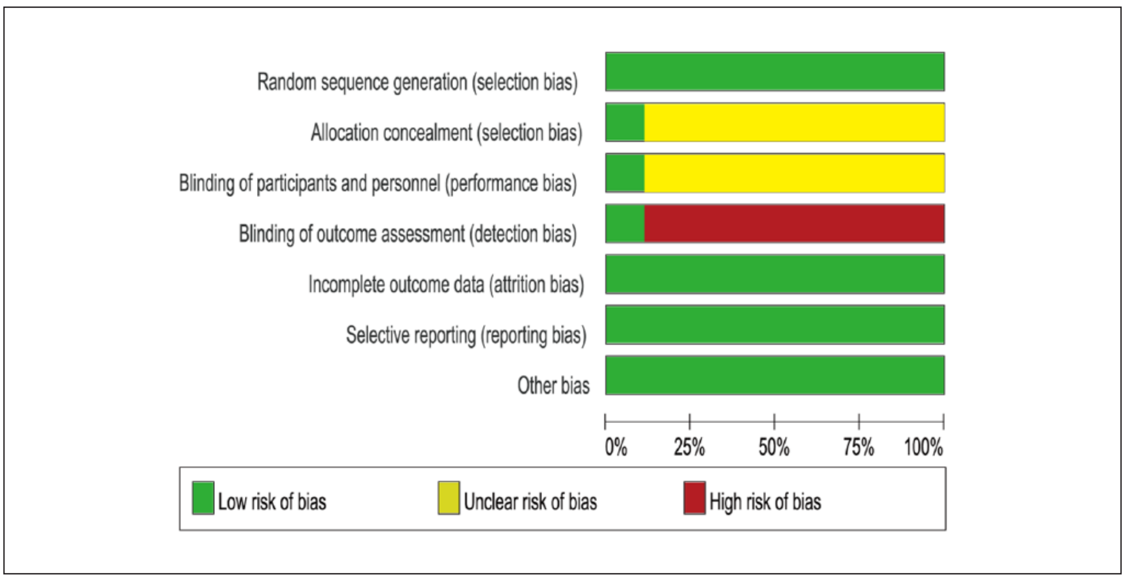

Figure 2. Risks of bias assessment for nine groups.

(p=0.004, I^2=65%) was found in the studies. To find out the source of heterogeneity, two subgroup analyses were conducted: Frequency (low frequency and high frequency) and stimulation location (unaffected hemisphere, affected hemisphere and bilateral hemisphere). The meta-analysis result showed significant improvement in dysphagia after rTMS treatment (Z=4.28, P<0.001; SMD=1.24, 95% CI=0.67 to 1.81) (Figure 3).

Within-frequency subgroup analysis showed significant differences in posttreatment clinical scores in dysphagia between the rTMS and the control groups. The clinical scores of dysphagia were higher in the high-frequency subgroup (Z=2.96, P=0.003; SMD=1.38, 95% CI=0.47 to 2.29) than in the low-frequency subgroup (Z=3.93, P<0.0001; SMD=1.02, 95% CI=0.51 to 1.53) (Figure 4).

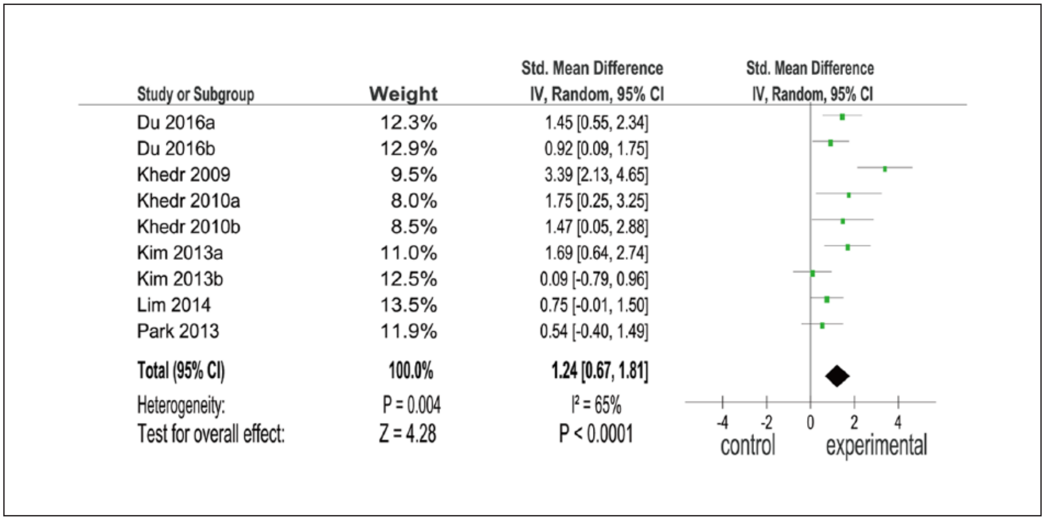

Figure 3. Forest plot: SMD in effect of rTMS on dysphagia and 95% CI.

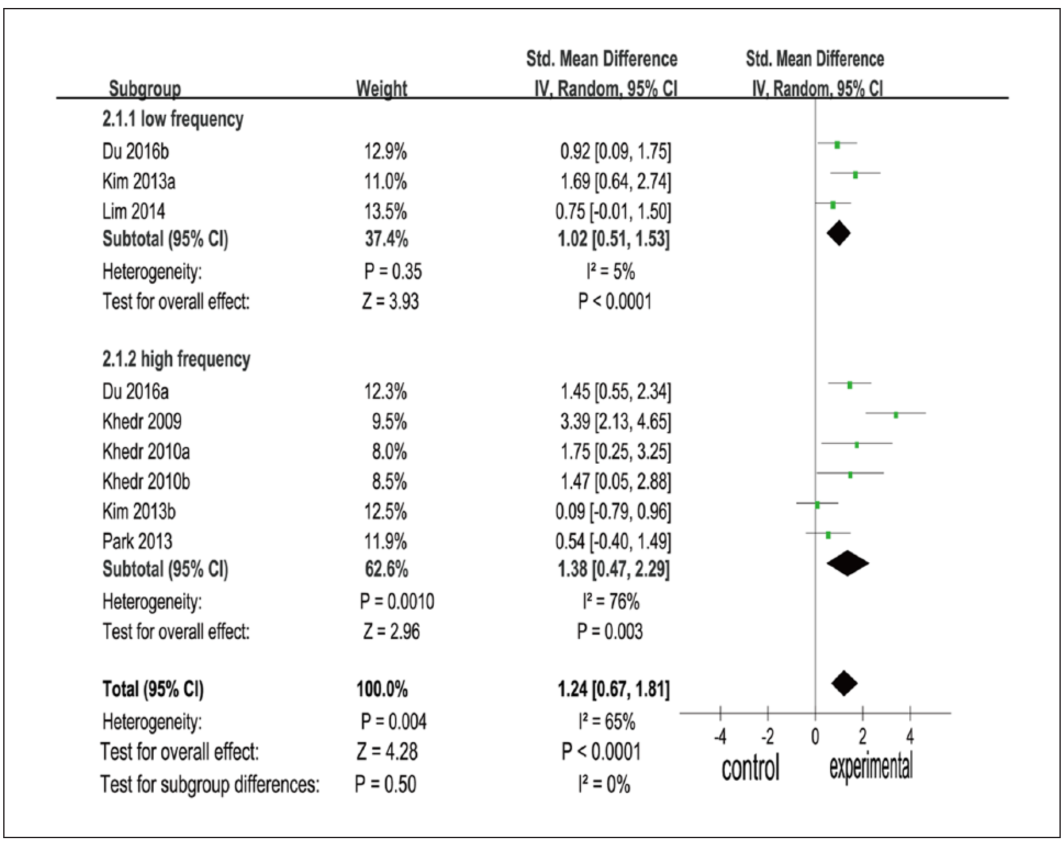

Figure 4. Forest plot: SMD in frequency subgroup and 95% CI.

Within-stimulation location subgroup analysis revealed significant improvement in deglutition disorder scores in the rTMS stimulation conducted in the unaffected hemisphere ($Z=4.09$, $P<0.0001$; SMD=0.91, 95% CI=0.48 to 1.35), and in the bilateral hemisphere stimulation ($Z=3.05$, $P=0.002$; SMD=1.60, 95% CI=0.57 to 2.63), but not in the affected hemisphere ($Z=1.81$, $P=0.07$; SMD=1.59, 95% CI=–0.14 to 3.31) (Figure 5).

Five studies[7,8,10,11,13] included follow-up data of four weeks after rTMS treatment. And the results show that rTMS treatment produced a sustained and significant improvement in deglutition as reflected in the dysphagia clinical scores in these stroke patients ($Z=3.78$, $P=0.0002$; SMD=1.91, 95% CI=0.92 to 2.90) (Figure 6).

Discussion

The result of our meta-analysis suggests that rTMS treatment effectively promoted the rehabilitation of swallowing function and dysphagia in stroke patients. This result agrees with that of Yang et al.[19] and Pisegna et al.[20] who reported a positive effect of rTMS on swallowing function recovery after stroke. Furthermore, stratification analysis showed that this effect is rTMS frequency- and hemisphere-dependent: High-frequency rTMS would be more effective than low-frequency rTMS for treating swallowing disorders; and stimulation of the affected hemisphere is not effective.

Within-frequency subgroup analysis shows a greater effect size in the high-frequency rTMS subgroup than that in the low-frequency rTMS subgroup. These results are in agreement with previous reports. Khedr et al.[7,8] used high-frequency (3 Hz) rTMS treatment on patients with dysphagia, and found better clinic outcomes of dysphagia in the high-frequency rTMS group than in sham group. Park et al.[11] used 5 Hz rTMS intervention on stroke patients with dysphagia, and found that swallowing function had significantly improved in the rTMS group. In a case report,[21] two weeks of 5 Hz rTMS stimulation on the stroke patient produced significant change on swallowing function. However, on the contrary, Kim et al.[9] found that low-frequency rTMS, but not high-frequency rTMS, significantly improved the functional dysphagia scale and penetration aspiration scale scores of dysphagia.

The analysis of the stimulation site revealed significantly improved swallowing function in the stroke patients with rTMS stimulation over the unaffected and bilateral oesophageal cortical, but not over the affected oesophageal cortical. Momosaki et al.[22] reported that 3.0 Hz rTMS applied bilaterally to the pharyngeal motor cortex induced a significant recovery in stroke patients with dysphagia. In a pilot study, Verin and Leroi[12] found rTMS was effective in improving post-stroke dysphagia and swallowing coordination after using rTMS stimulation over the unaffected hemisphere. Similar results were reported by others,[7,10,11] however, in a randomized controlled trial, Kim et al.[9] found that high-frequency rTMS stimulation on the affected hemisphere produced no change in swallowing function, whereas Du et al.[13] and Khedr et al.[8] found that high-frequency rMTS on the affected hemisphere had positive effects on dysphagia recovery after stroke. Thus, more studies are needed to validate the results of the rMTS impact on the affected hemisphere subgroups.

Analysis of the follow-up data show that stroke patients in the rTMS group still maintained a better swallowing function than those patients in the control group four weeks after rTMS stimulation. This long-lasting effect suggests that rTMS has a long effective therapy for dysphagia, lasting for at least four weeks post-rTMS treatment. This result is in line with other findings.[7,10,11] Khedr et al.[8] reported that not only the swallowing function was changed significantly, but also the amplitude of the motor-evoked potential increased two months after rTMS treatment.

Although this meta-analysis has showed that rTMS has beneficial effects on dysphagia, the mechanism of rTMS has not been fully understood. The reflexive swallowing behaviour is known to be associated with the function of the swallowing motor areas of the cerebral cortex.[23] And the anatomical site of oesophageal motor function is located in the cerebral cortex of bilateral hemisphere.[24] According to Hamdy et al.,[25] the dominant hemisphere exerts the principal effect on the swallowing function and this dominant hemisphere is independent of handedness. The stroke patients with a damaged dominant hemisphere would suffer more severe dysphagia.

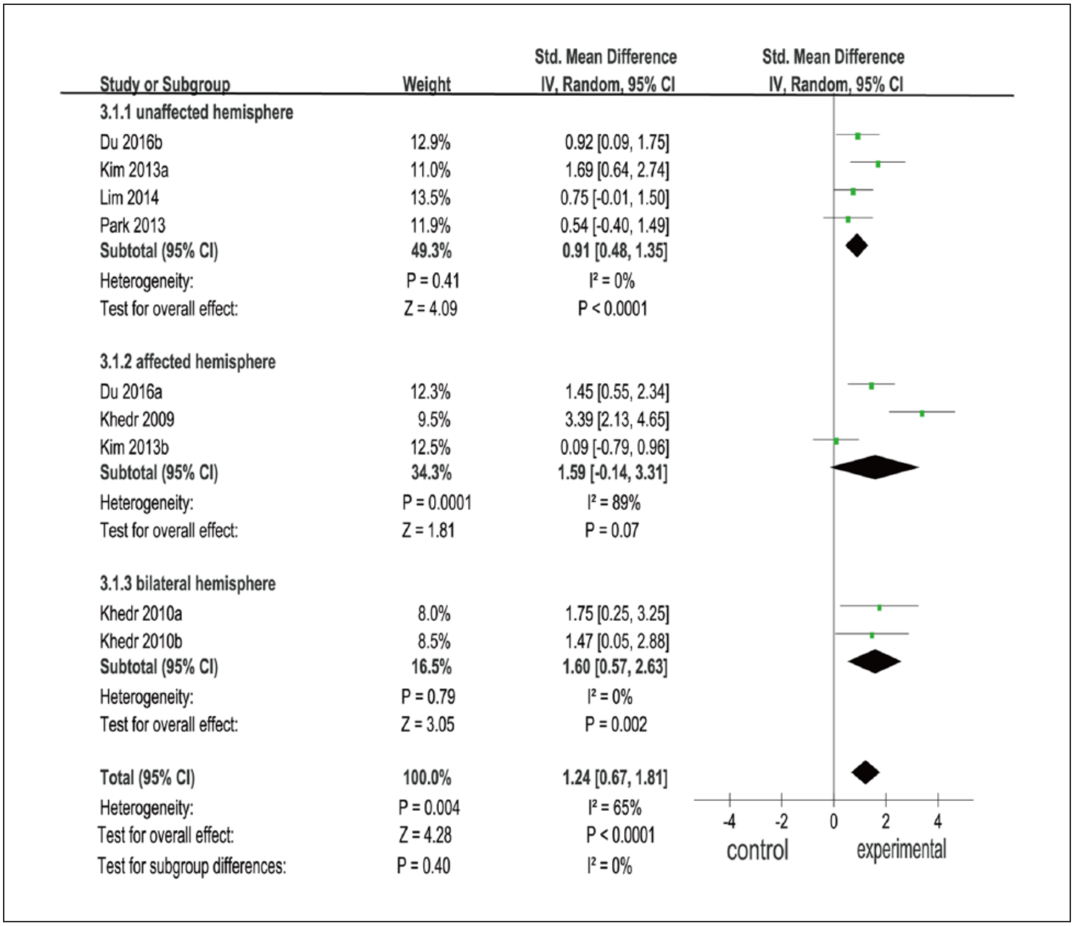

Figure 5. Forest plot: SMD in stimulation site subgroup and 95% CI.

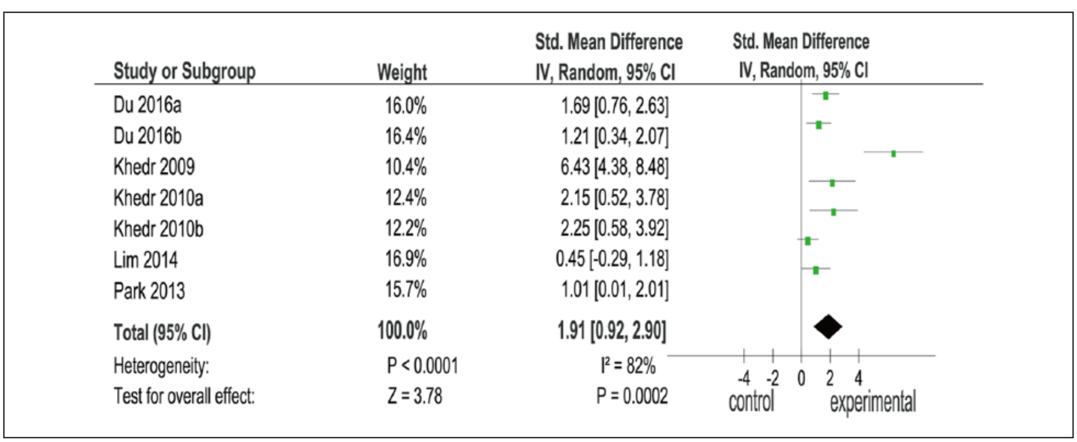

Figure 6. Forest plot: SMD in follow-up group and 95% CI.

The excitability is increased in the unaffected hemispheric cortex and is decreased in the affected hemispheric cortex after stroke.[26] The inter-hemispheric imbalance after brain injury, however, was found diminished after non-invasive brain stimulation.[21,22] As a non-invasive brain stimulation, high-frequency rTMS on the affected hemisphere or low-frequency rTMS over the non-affected hemisphere could promote inter-hemispheric rebalance.[27,28] Gow et al.[6] showed that rTMS (5 Hz) over the swallowing cortex increased the cortex excitability. Conversely, Mistry et al.[29] used inhibitory low-frequency rTMS (1 Hz) stimulation over pharyngeal cortex and found decreased cortex excitability of pharyngeal. Thus, the effects of rTMS appear to depend on the frequency of rTMS applied. Low-frequency ($\leqslant$1.0 Hz) rTMS led to inhibition, whereas high-frequency (>1.0 Hz) rTMS led to excitation in the stimulated brain region.[30]

This meta-analysis provided more convincing evidence of the true effect size with less random error of rTMS for stroke-related swallowing dysfunction than previously published individual studies. However, there were limitations of this study. First, because of the strict inclusion criteria, articles published in languages other than English, and articles with non-randomized controls were not included for analysis. Second, the number of included groups is relatively small, which might not offer enough statistical power to supports the results. Therefore, caution is needed when interpreting the results. Third, different swallowing scales and different rTMS parameters, such as frequency, stimulate site, intensity, duration, etc., across the studies may have also caused variations in the results.

Clinical messages

- The effect of high-frequency rTMS is better than low-frequency rTMS in this regard. rTMS treatment on the bilateral hemisphere or on the unaffected hemisphere may produce a better outcome than rTMS on the affected hemisphere.
- This therapeutic effect of rTMS is long-term, lasting for at least four weeks after the last session of rTMS treatment.

Declaration of Conflicting Interests

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