Review Article

Repetitive Transcranial Magnetic Stimulation for the Treatment of Lower Limb Dysfunction in Patients Poststroke: A Systematic Review with Meta-Analysis

Mahboubeh Ghayour-Najafabadi, PhD,* Amir-Hossein Memari, MD,† Lida Hosseini, PhD,† Ardalan Shariat, PhD,† and Joshua A. Cleland, PT, PhD‡

Purpose: To investigate the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in recovery of lower limb dysfunction in patients poststroke. *Participants and Methods:* Cochrane Central Register of Controlled Trials, Medline, ISI web of knowledge, EBSCO, Embase, Cumulative Index to Nursing and Allied Health Literature and Scopus. *Results:* Fifteen trials with 385 patients were included. Results showed that rTMS had a significant effect on balance (standard mean difference [SMD] = .38; 95% confidence interval [CI], .07: .69; $I^2 = 51\%$) and mobility (SMD: −.67; 95% CI, −1.08: −.26; $I^2 = 72\%$). However, rTMS had no significant immediate effects on the lower limb subscale of the Fugl-Meyer Assessment (FMA-L) (SMD = .01; 95% CI, −.29: .31; $I^2 = 0\%$). Continued effects of rTMS was also found to be significant during the follow-up period (SMD = .46; 95% CI, .09: .84; $I^2 = 14\%$). *Conclusion:* rTMS was found to result in positive effects on mobility, balance and long-term prognosis of FMA-L. However data indicated that there is insufficient evidence for the effectiveness of rTMS in improving lower limb function.

Key Words: Patients poststroke—balance—rTMS—disability, lower extremity motor function

Introduction

Stroke is one of the most frequent causes of death and adult disability worldwide.[1,2] The burden of stroke will increase over the next 20 years as a result of the aging of population.[3,4] Approximately 80% of patients with stroke suffer from motor impairments that typically result in a reduction in muscle strength and coordination.[5] Balance and walking impairments commonly seen in people with stroke can result in an increase in falls and a reduction in the ability to independently perform activities of daily living.[6-8] There is an urgent need to identify strategies to maximize function and reduce the social and economic burden poststroke. Rehabilitation often includes the use of different forms of physical and or occupational therapy which focus on high-intensity, repetitive, task oriented and task specific practice in all stages poststroke.[5,9] Furthermore, there are several benefits to recovering more rapidly or gaining functional independence for patients and their families. Thus, to facilitate neural recovery, new rehabilitation techniques (e.g., brain stimulation) are being developed to improve the quality of life of stroke survivors.[3,5] Recently repetitive transcranial magnetic stimulation (rTMS), a noninvasive brain stimulation method has been introduced in the field of stroke

From the *Department of Motor Behavior, Faculty of Physical Education and Sport Science, University of Tehran, Tehran, Iran; †Sports Medicine Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran; and ‡Franklin Pierce University, Manchester, New Hampshire.

Received July 25, 2019; revision received August 29, 2019; accepted September 10, 2019.

Address correspondence to Mahboubeh Ghayour-Najafabadi, PhD, Department of Motor Behavior, Faculty of Physical Education and Sport Science, University of Tehran, Tehran, Iran. E-mail: m.ghayournaj@ut.ac.ir.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104412

rehabilitation.[10-12] Indeed rTMS is applied to target a particular area of the brain.[13] The rTMS can potentially modulate the cortical excitability of the brain by decreasing or increasing the activity of neural synapses which can improve motor control.[3] The rTMS method has been examined in the treatment of several diseases such as depression, tinnitus, movement disorders and obsessive compulsive disorder.[3,14,15]

To address the question of our study, there are only 2 published reviews[16,17]; examining the clinical efficacy of rTMS on motor recovery in patients poststroke. Existing reviews are not typical systematic reviews or meta-analysis and have shown conflicting results as some indicate no support for rTMS use in motor function recovery, some recommend rTMS results in only short-term motor recovery and the other suggests to use rTMS in combination as adjunctive therapy in patients poststroke.[3,16] Hao et al, did not find any significant improvement of motor function poststroke using rTMS.[3] Ayache et al, found brain stimulation in combination with noninvasive cortical stimulation can provide short-term effects on various aspects of poststroke motor function.[17] Hatem et al, also support the effectiveness of brain stimulation on recovery of motor function.[16] Altogether, the potential therapeutic effect of rTMS in patients poststroke has yet been debated.

Therefore the purpose of this systematic review was to examine the latest evidence for the use of rTMS on lower limb dysfunction in patients poststroke. The specific research questions were as follows: Is the rTMS effective in improving function of the lower limbs after stroke? And which aspects of lower limb function have been influenced by rTMS in patients poststroke?

Participants and Methods

This study was a systematic review and meta-analysis written according to the preferred reporting items for systematic reviews and meta-analyses.[18] Also, this review was registered with PROSPERO a priori on 14.02.2018 (ID: CRD42018088598). We included clinical trials with predefined characteristics in design, participants, intervention, primary outcome measures and secondary outcome measures. We included patients poststroke (not later than 10 years after stroke) with any level of disability, acuity and chronicity (Adults >18). The rTMS was as a non-invasive treatment that transports repetitive pulses of an MRI-strength magnetic field from a coil placed over the scalp. Studies using ipsilateral or bilateral treatment with different range of frequency or duration of rTMS in patients poststroke were included. Sham treatment and other conventional treatments were considered as alternative interventions. The location of rTMS had to be on the primary motor cortex (M_1) and or cerebellum. Compared treatments could include a control, sham, or other intervention (placebo), exercise group, etc. Studies had to include primary and secondary outcomes that reported lower limb function reporting walking speed, mobility, speed ability, balance, gait and disability. (e.g., 6-10 meter walking test (MWT), timed up and go (TUG), Berg Balance Scale (BBS), postural assessment scale for stroke patients (PASS), Barthel Index (BI), Fugle Meyer assessment (FMA), Brunnstorm recovery stages (BRS), biodex system, motion analysis, Modified Modified Ashworth Scale (MMAS)).

Study design was randomized controlled trials, cross-over trials. Five electronic databases were searched up until the15th October 2018: Cochrane Central Register of Controlled Trials (studies from 1970 in 15th October 2018), Medline (studies from 1967 to 15th October 2018), Embase and ISI web of science (studies from 1981 to 15th October 2018), EBSCO Cumulative Index to Nursing and Allied Health Literature (studies from 1970 to 15th October 2018), Scopus (studies from 1983 to 15th October 2018). The search query was organized using following terms:

Cerebrovascular disorders, basal ganglia, cerebrovascular disease, brain ischemia, poststroke, stroke, hemiplegia; brain stimulation, repetitive transcranial magnetic stimulation, rTMS, TMS; randomized controlled trials, random allocation, controlled clinical trials, control groups, sham intervention, clinical trials, double-blind method, cross-over studies; gait, lower limb function, motor function, lower extremity, balance, postural control, mobility and walking.

Two authors (M.Gh and L.H) independently reviewed all identified trials based on titles, abstracts and keywords of records and excluded duplicate and unrelated citations. The full text articles for remaining studies were reviewed based on the previously defined inclusion criteria. After identifying any disagreements related to inclusion of studies, a third author made the final decision (A.M).

For eligible studies in this systematic review, we included individuals with stroke who had been treated using rTMS, compared with a control, sham, or other conservative interventions. In the current systematic review, only randomized controlled trials were included. Studies were included if the participants were more than 18 years of age and if the full text was published in English. In addition, based on the Cochrane "risk of bias" tool, only moderate to high-quality studies were included. Two reviewers (L.H and M.GH) independently completed the quality assessment. A third author (A.M) who was blinded to the previous assessment scores, resolved any disagreements.

Examination of the quality of studies was performed based on the Cochrane "risk of bias" tool.[19] The Cochrane risk of bias tool includes a report and a judgment (low-risk of bias, high-risk of bias, or unclear risk of bias) for each of the selected studies that are described in Figure 2.

Kappa statistics were used for interrater agreement between the reviewers who screened the studies (kappa values determine inter observer agreement with weighted ranging from .688 to .912 that was good to excellent).[20] Meta-analyses of study outcomes were executed wherever possible using RevMan (The Nordic Cochrane

Centre, Copenhagen, Denmark). Effect size was reported by the standardized mean difference (SMD) with a 95% confidence interval (CI). Effect size of .2 was considered as small, .5 as moderate, and .8 as large.[21] The heterogeneity among trials was examined with the I^2 statistic that the score was classified as following: 25% as a small, 50% as a moderate, and 75% as a large degree of heterogeneity.[22]

Additionally, 2 independent reviewers (M.GH and L.H) used the Grading of Recommendations Assessment, Development and Evaluation approach[23] to determine the level of evidence of pooled findings; then each meta-analysis was categorized as below.[24]

- High-quality evidence: It is unlikely to modify our confidence in the estimate of effect by more research.
- Moderate-quality evidence: It is likely to find a significant change in our confidence in the evaluation of effect and may modify the evaluation by further research.
- Low-quality evidence: It is expected to find a significant change on our confidence in the estimate of effect and can probably modify the estimate by additional research.
- Very low−quality evidence: All findings are very uncertain.

To rate the overall quality of the evidence for each meta-analysis, the evidence was downgraded by one level for every following domain:

(1) Study design and risk of bias (decreased if > 25% of the participants were from trials with a high-risk of bias that was defined as the Cochrane Risk of bias scale)
(2) Findings variability (decreased if substantial heterogeneity was found on visual inspection or the I^2 value > 50%)
(3) Indirectness (the results generalizability decreased if > 50% of the participants were not in the target group)
(4) Reliability (decreased if < 400 participants were assigned in the analysis for continuous data)
(5) Other (publication bias).[25]

Results

We identified 18,475 articles from the initial electronic search and 1940 of those were removed as duplicates. After screening title/keyword an additional 16,410 were removed. The remaining 125 records were assessed for full text eligibility. Of these, after full-text review, 110 articles were excluded for various reasons. Finally, we included 15 trials in this systematic review and meta-analyses (Fig. 1). Of the included studies four were cross-over designs.[6,21-23]

Based on the Cochrane risk of bias tool, random sequence generation was achieved in 86.6% of studies (low-risk), allocation concealment was achieved in 53.3% of trials (low-risk), blinding participants was achieved in 80% of trails (low-risk), blinding of outcome assessment was achieved in 66.6% of trails (low-risk), 93.3% studies reported no attrition bias (low-risk). There was insufficient information provided in the articles for us to make a judgment on other bias (Fig. 2). Results of Grading of Recommendations, Assessment, Development and Evaluations system used in the review were shown in Figure 3.

Across the trials, a total of 385 participants aged between 18[23] and 85[6] years old, were enrolled. Also, 63.3% of the participants were male. The mean time after stroke ranged from 10 days[25] to 1 year, with 53.3% of the trials carried out after 6 months. 73.3% of studies included patients with hemiparesis. Five studies included subjects with walking ability between 6 and 20 m.[21,26-29]

Fourteen trials[6,10,21,23,25-34] investigated rTMS on the primary motor cortex (M_1), and one trial[24] investigated rTMS on the cerebellum. The length of rTMS sessions ranged from 10 minutes to 20 minutes. Frequency of sessions ranged from 5 [23,24,31] to 7 [25,33] sessions per week. The duration of intervention ranged from 5-days[10,24] to 15 weeks.[10] From the 15 trials, 14 trials had experimental and sham groups though one of them had 3 arms with 2 intervention groups and a sham group and another trial had 2 active groups (high rTMS group and low rTMS group).[34] There is also a trial which used a single dose in terms of cross over study.[27]

The frequency of the electrical stimulation was 1 [23,24] or 10 [6,9] Hz, and pulse width ranged from 900[24,33] to 2000[22] ms (Table 1). The sham intervention was the same activity as the experimental intervention without real stimulation.

Results showed that lower limb function was assessed as primary and secondary outcomes using 10MWK,[29,24] TUG,[28] BBS,[6,24,28,34] PASS,[33] BI,[28,34] FMS,[21] BRS,[10] motion analysis,[26] MMAS,[23] and FAC.[25] Finally, side effects of rTMS were reported by 9 trials.[6,21,24-26,30,32,33] Results indicated that in only 1 study, participants experienced tingling scalp pain and dizziness as side effects after the intervention.[33]

The effect of rTMS on balance in 200 participants was examined by pooling data after intervention from 5 trials[24,28,31,33,34] and one of them was cross-over study in which we pooled data at the end of second period of the study[6] and they used same balance measures including Performance-Oriented Mobility Assessment (POMA), PASS, BBG (Fig. 4a). Meta-analysis showed that rTMS improved balance compared to sham (SMD = .38; 95% CI, .07: .69; I^2 = 51%).

The effect of rTMS on mobility of patients on 100 participants was examined by pooling data after intervention from 3 trials[23,28,35] that one of them was a cross-over study [23] and they used TUG as an outcome measure (Fig. 4b). In one trial we pooled data related to real and sham separately after the second period of the study.[23] Meta-analysis revealed that there was a significant improvement in rTMS group compared to sham group on mobility (SMD: −.67; 95% CI, −1.08: −.26; I^2 = 72%).

The effect of rTMS on the lower limb subscale of the Fugl-Meyer Assessment (FMA-L) was examined on 177

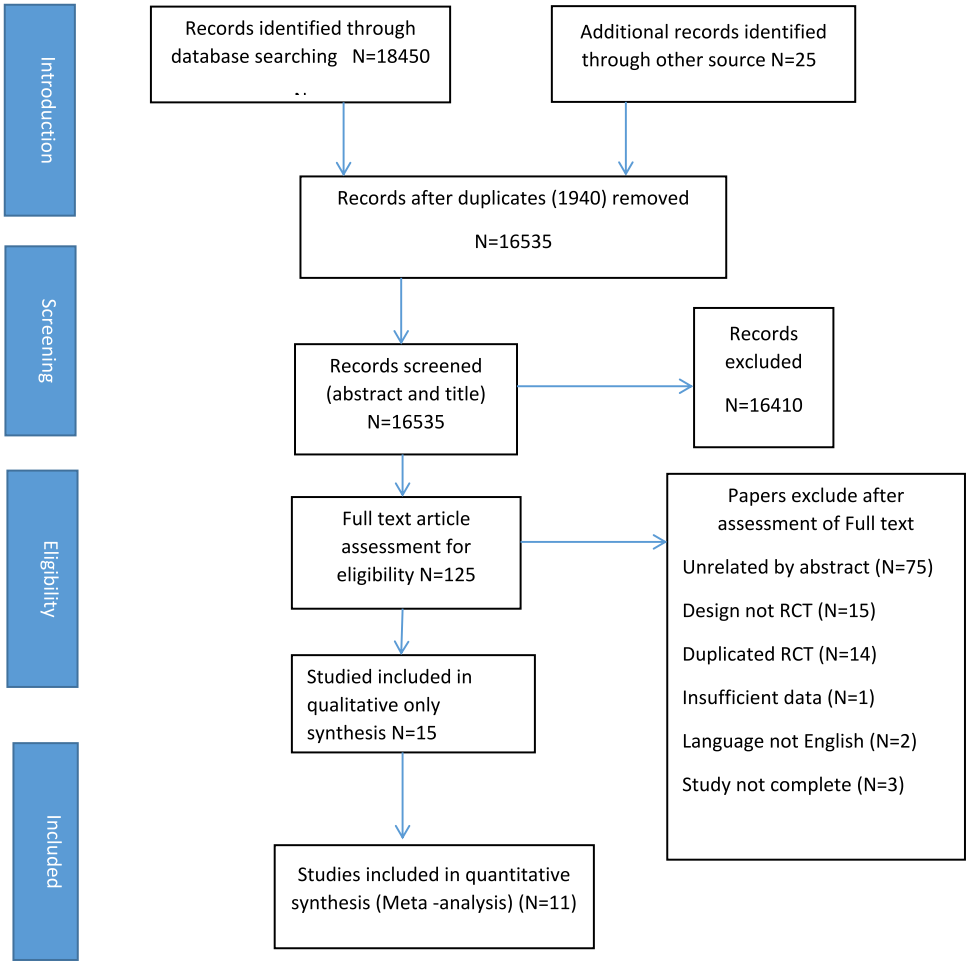


Figure 1. *PRISMA flow chart. Abbreviation: PRISMA, preferred reporting items for systematic reviews and meta-analyses.*

participants by pooling data after interventions from 6 trials [21,23,25,26,30,33] (Fig. 4c). Meta-analysis revealed that there was no significant improvement in rTMS compared to sham on FMA-L (SMD = .01; 95% CI, −.29: .31; $I^2 = 0\%$). Two of included studies had cross-over design in which we pooled data related to real and sham separately after the second period of the study.[21,23] The long-term effect of rTMS on FMA-L in 117 participants was examined by pooling data from 4 trials, 2 of them were cross-over studies and all used the FMA with a follow-up duration of 1 to 3 months. In cross-over trials, we pooled data related to real and sham separately after the second period of the study. Meta-analysis revealed that there was significant improvement in rTMS group compared to sham group on FMA-L at the follow-up (SMD = .46; 95% CI, .09: .84; $I^2 = 14\%$) (Fig. 4d).

Discussion

We completed a systematic review with meta-analysis to investigate the effects of rTMS on improving lower limb function in patients poststroke. Our results showed that rTMS resulted in improved balance and mobility. Our findings also showed rTMS can result in long-term improvements over sham in some variable. Finally, the result of this systematic review found rTMS to be more beneficial than sham on mobility and balance with a large effect size. Our findings also provide preliminary evidence that rTMS is more beneficial than sham on mobility, balance and long-term effects in FMA-L with a high effect size. However, results provided evidence that rTMS did not have a positive effect on FMA-L compared to sham.

Although previous meta-analyses examined the effect of rTMS on upper limb function in stroke patients,[3,16,17] as far as we know, this is the first review to show the effects of rTMS on lower limb function specially on mobility and FMA-L in patients poststroke.[36]

Results showed that rTMS had a positive effect on balance and mobility. The results were in agreement with Ayache et. al. found that rTMS with a frequency (from 1HZ to 10HZ) could be safe and effective on motor function in patients poststroke.[17] However, these effects only

Bias	Authors' judgement	Support for judgement
Chieffo et al. 2014		
Random sequence generation (selection bias)	Low risk	2 blank-coded magnetic cards (A and B)
Allocation concealment (selection bias)	Low risk	Active or sham modes were determined by a switch controlled through the assigned magnetic Card.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and examiner
Blinding of outcome assessment (detection bias All outcomes	Low risk	Assessor and treating personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 subject left the study because of cardiac disease and was therefore not included in the statistical analysis
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	Short washout period, with a carryover effect up to the second baseline measurements for the real treatment.
Chang et al. 2010		
Random sequence generation (selection bias)	Low risk	Using the table of random sampling numbers
Allocation concealment (selection bias)	Low risk	2:1 raito
Blinding of participants and personnel (performance bias) All outcomes	Low risk	participate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed their rTMS sessions
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Unclear	None known
Kim et al. 2014		
Random sequence generation	Low risk	by a computer

Figure 2. *Cochrane risk of bias.*

(selection bias)		
Allocation concealment (selection bias)	Low risk	opaque envelopes (2-to-1 ratio)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	patients
Blinding of outcome assessment (detection bias All outcomes	Low risk	assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients in the real rTMS group and 4 in the sham rTMS group were lost to follow-up for reasons not related to the intervention
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	patients in our study are heterogeneous in the baseline function and anatomical structures involved in PCS
Rastgoo et al. 2016		
Random sequence generation (selection bias)	Low risk	through random assignment by individuals
Allocation concealment (selection bias)	unclear	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and physiotherapist
Blinding of outcome assessment (detection bias All outcomes	Unclear	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six patients (3 in each group) refused to do second intervention
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	assessments and treatment were done by a same physiotherapist and the localisation of the cerebral lesion was not same and this may affect the patients' response to the intervention
Choi et al. 2016		
Random sequence generation	Low risk	randomized by other healthcare

Figure 2. *Continued*

(selection bias)		professional who did not participate in this study
Allocation concealment (selection bias)	unclear	Insufficient in formation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	patients
Blinding of outcome assessment (detection bias All outcomes	High risk	No one
Incomplete outcome data (attrition bias) All outcomes	Low risk	were excluded from the study due to the following reasons
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear	None known
Lin et al. 2015		
Random sequence generation (selection bias)	low risk	1:1 ratio (with a block of 2)
Allocation concealment (selection bias)	unclear	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and physical therapists
Blinding of outcome assessment (detection bias All outcomes	Low risk	assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient was transferred to another hospital for personal reasons before treatment completion
Selective reporting (reporting bias)	High risk	At the pre-test, all the participants were unable to finish the TUG test within 2 min. At the post-test, 11 Group E patients and 4 Group C patients could complete the TUG test within 2 min
Other bias	High risk	The PT was customized for each individual patient. Thus, the extent of similarity between the therapies administered to both groups, as well as the contribution of this factor to the present results, remains unclear.
Sasaki et al. 2017		
Random sequence generation (selection bias)	High risk	according to the date of admission
Allocation concealment	Unclear	Insufficient information

Figure 2. *Continued*

(selection bias)		
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Therapists and patients
Blinding of outcome assessment (detection bias All outcomes	Low risk	physical therapist
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed their rTMS sessions
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	High risk	patients represented a heterogeneous group with regard to stroke type and baseline stroke severity
Wang et al. 2012		
Random sequence generation (selection bias)	Low risk	Block randomization (with a block size of 2)
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	participants
Blinding of outcome assessment (detection bias All outcomes	Low risk	assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 did not complete the intervention (2 in the control group and 2 in the experimental group)
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Unclear	None known
Cha & Kim 2015		
Random sequence generation (selection bias)	Low risk	blindly drawing cards
Allocation concealment (selection bias)	Low risk	envelope containing two cards that were each marked as EG and CG
Blinding of participants and personnel (performance bias) All outcomes	high risk	subjects and their therapists were aware of their groups
Blinding of outcome assessment (detection bias All outcomes	Low risk	assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed their rTMS sessions
Selective reporting (reporting	Low risk	The study protocol is available and

Figure 2. *Continued*

bias)		all of the study's pre -specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	the subjects in this study were recruited from a selfselected group of patients, who are able to walk independently and are highly motivated. Thus, the findings of this study may not be generalized to the entire stroke population with a variety of functional levels
Cha & Kim 2017		
Random sequence generation (selection bias)	Unclear	This randomization was performed by a third party unaware of the nature of the study
Allocation concealment (selection bias)	Low risk	sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physicians
Blinding of outcome assessment (detection bias All outcomes	Unclear	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed their rTMS sessions
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Unclear	None known
Kakuda et al. 2013		
Random sequence generation (selection bias)	Low risk	random
Allocation concealment (selection bias)	Unclear	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and examiner
Blinding of outcome assessment (detection bias All outcomes	Low risk	assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed their rTMS sessions
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified (primary and secondary) outcomes

Figure 2. *Continued*

		that are of interest in the review have been reported in the pre-specified way
Cha et al. 2014		
Random sequence generation (selection bias)	Low risk	blindly draw one of the cards
Allocation concealment (selection bias)	Low risk	envelope with two cards
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Insufficient information
Blinding of outcome assessment (detection bias All outcomes	Unclear	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed their rTMS sessions
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Unclear	None known
Other bias	Unclear	None known
Forogh et al. 2017		
Random sequence generation (selection bias)	Low risk	Insufficient information
Allocation concealment (selection bias)	unclear	None known
Blinding of participants and personnel (performance bias) All outcomes	Low Risk	Insufficient information
Blinding of outcome assessment (detection bias All outcomes	Low risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 patients withdraw from study
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Unclear	None known
Guan 2017		
Random sequence generation (selection bias)	Low risk	computer
Allocation concealment (selection bias)	Low risk	Sealed envelop
Blinding of participants and	Low Risk	Insufficient information

Figure 2. *Continued*

personnel (performance bias) All outcomes		
Blinding of outcome assessment (detection bias All outcomes	Low risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	15 patients withdraw from study in follow up
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Unclear	None known
Vaziri et al.2014		
Random sequence generation (selection bias)	Low risk	Simple random
Allocation concealment (selection bias)	unclear	None Known
Blinding of participants and personnel (performance bias) All outcomes	High risk	None known
Blinding of outcome assessment (detection bias All outcomes	High risk	None known
Incomplete outcome data (attrition bias) All outcomes	Low risk	15 patients withdraw from study in follow up
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre -specified outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Unclear	None known

Figure 2. *Continued*

remained for short time (several weeks) beyond the time of stimulation on various motor aspects. Similarly, Hatem et al., indicated that rTMS could be combined with other rehabilitation therapies for patients with stroke with an emphasis to improve motor limb function.[16] However there was further result which our meta-analysis could not indicate the benefits of rTMS on some of the motor assessment scale.[3] Furthermore, although never reported so far, we showed the continued effects of rTMS by identifying a significant improvement on FMA-L in follow-up period.

Sample size and number of participants were small and may not have adequate power to detect a difference between the groups. There were different stimulation protocols across studies; however the most appropriate rTMS protocol for motor recovery in patients poststroke is still unclear. The comparability of some outcomes was questionable due to diversity of motor function assessment measures used across trails. Length of follow-up was primarily short-term. Most of the trails only reported the outcome at the end of the intervention period or within 1 month of being treated with rTMS. Indeed, the long-term effects of rTMS have not been clarified yet. Although we included 15 trials in the review, we pooled only 3-6 trails for meta-analysis for FMA, balance, walking speed and follow-up in 2 groups (rTMS and sham). Thus the pooled subjects were under 400 in each meta-analysis.

outcomes	Patients (n)	Included RCT (n)	Quality assessment						Summary of finding
			Risk of bias	inconsistency	indirectness	imprecision	Publication bias	Overall quality of evidence	SMD
Balance	200	5RCTs Cha2013 Cha 2015 Forogh Kim lin	Not serious Risk of bias	serious	Not serious	Serious	detected	low	0.38 {(0.07)-(0.68)}
Walk evaluation	100	3RCTs Cha2015 Elkhoy rastgoo	Not serious Risk of bias	serious	Not serious	Serious	undetected	low	-./67 {(-.1.08)-(-0.29)}
FMA-L	177	6RCTs Change	Not serious	Not serious	Not serious	Serious	undetected	low	0.01 {(-0.29)-(0.31)}
		Cheffio Guan Lin Rastgoo wang	Risk of bias						
Follow-up in FMA-L	117	4RCTs Chang Cheiffo Guan Rastgoo	Not serious Risk of bias	Not Serious	Not serious	Serious	detected	low	0.46 {(0.09)-(0.84)}

Figure 3. *Quality assessment and summary of findings using the GRADE approach.*

Since the existing level of evidence is not yet satisfactory, practitioners should use rTMS in lower limb dysfunction cautiously. The findings of this study have a number of important implications for future practice or research. However, by using more rigid including criteria, practitioners may find patients who will benefit more from brain stimulation trials. Furthermore it would be interesting for researchers to consider the following recommendations in their future studies:

1) Examining the effects of high- and low-frequency rTMS on lower limb motor function patients post-stroke. (Noted that the underlying mechanisms of high- and low-frequency rTMS are quite different).
2) Comparing subgroups under different phases of stroke on effects of rTMS.
3) Exploring the long-term effects of rTMS on motor function during the follow-up phase in patients post-stroke.
4) Recruiting larger sample sizes to examine the cost benefit analysis on rTMS therapy in patients with stroke.

A major limitation was the relatively small number of pooled studies for each meta-analysis that may affect the level of evidence of our findings. Another limitation of this review was that the included cross over studies did not report the results by different periods. Thus we had to use the final results for meta-analysis. Another caveat of the existing literature was a lack of sufficient data on timeline of rTMS used for either short-term or long-term benefits. Furthermore the adverse effects were not reported by all studies included in the review. Finally, most of studies did not discuss the possible mechanisms underlying effects of stimulation on lower limb function.

In conclusion, pooling a variety of rTMS conditions in poststroke, suggests that rTMS may be more effective than no treatment or sham for improving lower limb motor function in the immediate post-therapy to 30 day follow-up period. Although there are large effect sizes that support a recommendation for rTMS intervention, the existing level of evidence is still poor and further trials are mandatory to strengthen this preliminary finding.

Table 1. *Summary of included trials (N = 15)*

Study	Design	Participants	Intervention	Primary outcome	Secondary outcome	Adverse effects
Chieffo et al (2014)	Cross-over trial (CT)	Randomized = 10, remained after last Test/assessment = 9 Real - sham = 4 Sham-real = 5 Age = 25-80 Sex = 10 M Time since stroke: more than 6 months	Exp: Deep rTMS on hand or leg motor cortex; 11 sessions 20 HZ 1500 pulses 90% of motor threshold until 82% 30 trains at 20 Hz, 60-s inter-train interval Sham: sham-real and real-sham	Lower limb motor performance (FMA) Timing: 0, 3 weeks, 1 mon (washout) 3 weeks, 1 mon (washout) follow-up in cross-over study	Walking distance (10 MWT, 6 MWT)	No subject reported any adverse effects
Kim et al (2014)	RCT	Randomized = 32, remained after last test/assessment = 32 Real = 22 Sham = 10 Age = 64-67 Sex = 17 M/15 F Time since stroke: less than 6 months	Exp: low rTMS on cereblum 15 min*5/wk 1HZ 900 pulses 100% of motor threshold Sham: the coil was placed perpendicular to the scalp with the same parameters of stimulation to minimize current flow into the skull	Functional outcomes (10MWTand BBS) Timing: 0, 5 days, 35 days		No adverse events were reported in either group
Rastgoo et al (2016)	CT Cross-over study	Randomized = 20, remained after last test/assessment = 20 Real-sham = 10 Sham-real = 10 Age ≥18 Sex = 10M/10F Time since stroke: more than 6 months	Exp: rTMS the LE motor cortex 20min*5/wk 1 HZ 1000 pulses 90% of motor threshold	1) Muscle Spasticity (MMAS) 2) Motor neurone excitability (Hmax/Mmax ratio) Timing: 0, 5 days, 1 week after intervention, 1 mon (washout), 5 days, 1 week after intervention	1) Gait (TUG) 2) Lower limb subscale of the Fugl-Meyer Assessment (FMA)	No adverse events were reported by any of the patients
Choi et al (2016)	CT Cross-over study	Randomized = 30, remained after last test/assessment = 30 Real-sham = 15 Sham-real = 15 Age = 60-85 Sex = 27M/3F Time since stroke: more than 6 months	Exp: rTMS the leg motor area 10 min *10/wk *2 weeks 10 HZ 1000 pulses 90% of motor threshold Sham: real-sham, sham-real	Balance function (BBS) Timing: 0, 2 weeks,1 mon 2 weeks, 1 mon follow-up	Sensory limitation assessment (SOT)	None of the patient experienced serious adverse event

(*Continued*)

Table 1 (*Continued*)

Study	Design	Participants	Intervention	Primary outcome	Secondary outcome	Adverse effects
Sasaki et al (2017)	RCT	Randomized = 21, remained after last test/assessment = 21 Real = 11 Sham = 10 Age = 25-85 Sex = 13M/8F Time since stroke: less than 6 months	Exp: rTMS the leg motor area 10 min*10/wk*5 days 10 HZ 1000 pulses 90% of motor threshold Sham: without stimulation	1) Lower limb Motor function (BRS) 2) Trunk function (ABMS II) 3) Cognitive Function (MMSE) Timing: 0, 5 days		Author does not mention to adverse event
Chang et al (2010)	RCT	Randomized = 28, remained after last test/assessment = 28 Age = 27-78 Sex = 17M/11F Time since stroke: less than 6 months Real = 18 Control = 10	Exp: rTMS motor cortex 50s*10/wk*10 days 10 HZ 1000 pulses 90% of motor threshold Con: sham	1) Motor function of upper limb and hand (MI-A, BBT and FMA-UL), 2) Motor function of lower limb (MI-L and FMA-LL) Timing: 0,10 days, 3 mon after post- test for follow-up	1) Mobility and functional independence (FAC, and MBI)	No adverse side effects were reported
Wang et al (2012)	RCT	Randomized = 28, remained after last test/assessment = 24 Age = 40-60 Sex = 15M/9F Time since stroke: more than 6 months Exp = 12 Con = 12	Exp: rTMS leg area of the motor cortex 10 min*10/wk*14 days 1 HZ 600 pulses 90% of motor threshold Con: sham	1) Corticomotor excitability (MEPs) 2) Motor Performance (FMA and spatial and temporal parameters of gait performance) 3)Walking performance (GAITRite system) Timing: 0, 2 weeks		None of the participants reported any adverse events
Cha and kim et al (2014)	RCT	Randomized = 24, remained after last test/assessment = 24 Age = 40-57 Sex = 14M/10F Time since stroke: More than 6 months Real = 12 Sham = 12	Exp: HrTMS bilateral leg motor areas 20 min*5/wk*4 weeks 10 HZ 2000 pulses 90% of motor Con: LrTMS 20 min*5/wk*4 weeks 1 HZ , 1200 puls	1) Motor cortex excitability(MEP) 2) balance function (BI and the BBS) Timing: 0, 4 weeks		Authors does not mention to adverse events

Table 1 (*Continued*)

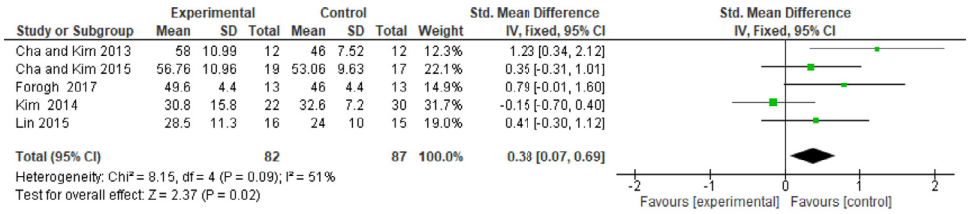
Study	Design	Participants	Intervention	Primary outcome	Secondary outcome	Adverse effects
Kakuda et al (2013)	RCT Cross-over study	Randomized = 18, remained after last test/assessment = 18 Real-sham = 9 Sham-real = 9 Age = 30-70 Sex = 13M/5F Time since stroke: more than 6 months	Exp: rTMS bilateral leg motor areas and sham 20 min*2session in 24 h 10 HZ 2000 pulses 90% of motor threshold Sham: sham and rTMS	1)Walking function (walking velocity) 2) Energy efficiency of walking (PCI) Timing: before, immediately after, and 10 and 20 min after each stimulation with 24 h wash out Not report		Authors does not mention to adverse events
Lin et al (2015)	RCT	Randomized = 32, remained after last test/assessment = 31 Age = 18-80 Sex = 21M/11F Time since stroke: less than 6 months Exp = 16 Con = 15	Exp: rTMS M1 15 min*15/wk*2 weeks 1 HZ 900 pulses 130% of motor threshold Con: sham group	1) Ability of a patient to maintain or change a given posture (PASS) Timing: 0, 2 weeks	1) Static and dynamic balance (POMA-b) 2) Ability to perform advanced mobility tasks (TUG) 3) ADL independence (BI) 4) neurological recovery of LE (FMA-LE)	A Group E patient reported dizziness, and a Group C patient reported tingling scalp pain
Cha and Kim et al (2015)	RCT	Randomized = 36, remained after last test/assessment = 36 Exp = 19 Con = 17 Age = 45-67; Sex = 19M/17F Time since stroke more than 6 months	EXP: rTMS on 2*10 min(20 min rTMS and 20 min MT) + mirror therapy 10 min* 5 days *4 weeks Con; sham + mirror therapy	1) Motor recovery (balance index, DLOS), BBS, and TUG) Timing: 0,4 weeks		Authors does not mention to adverse
Cha and Kim et al (2016)	RCT	Randomized = 30, remained after last test/assessment = 30 Exp1 = 10 Exp2 = 10 Con = 10 Age = 45-60 Sex = 14M/16F Time since stroke: stroke within more than 6 months	Exp1: just ankle strengthening exercise Exp2: rTMS motor cortex and ankle strengthening exercise 10 times*5/wk*8weeks 10 HZ 90% of motor threshold Con: rTMS group	1) Motor recovery (MEP) 2) Maximal muscle strength (Test of ankle joint muscle strength) 3) Walking (10MWT) Timing: 0, 8 weeks, 9 weeks		Authors does not mention to adverse

(*Continued*)

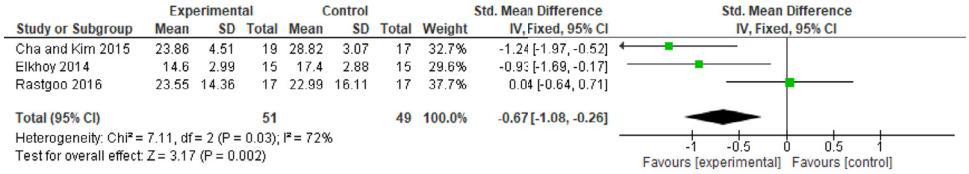
Table 1 (*Continued*)

Study	Design	Participants	Intervention	Primary outcome	Secondary outcome	Adverse effects
Forogh et. al (2017)	RCT	Randomized = 26, remained after last test/assessment = 15 Exp = 8 Sham = 7 Age = 53-79 Sex = 16M/10F years; 61.5% were male Time since stroke: more than 6 months	Exp: rTMS on M1 1 HZ 1200 pulses 20 min*5wk*3 weeks Con: sham	Static postural stability(BI), muscle strength: (MRC), Static and dynamic balance ability (BBS), Motor recovery (FMA) 0,3 weeks,15 weeks		Author does not mention to adverse effect
Gane et al 2017		Randomized = 42, remained after last test/assessment = 42 Real = 21 Sham = 21 Sex = 30M/12F Age = 43-67 Time since stroke: less than 6 months	Exp: M1 consecutive 10-day rTMS 10 HZ Con: sham	(NIHSS,BI, FMA-UL/LL), the degree of disability or dependence in the daily activities: (mRS), individually adjust the intensity (TMS, RMT)	0,10days, 1 month, 3 months, 6 months, and 1 year	None of the patients complained of discomfort after rTMS or sham rTMS
Vaziri et al 2014	RCT	Randomized = 12, remained after last test/assessment = 12 Age = 30-65 Time since stroke: more than 6 month Real = 6 Sham = 6	Exp: rTMS + rehabilitation program on M1 20 min*3wk*10 sessions Con: placebo rTMS + rehabilitation program	Dynometers: BI and FMI		No adverse side effects were reported during or after the study

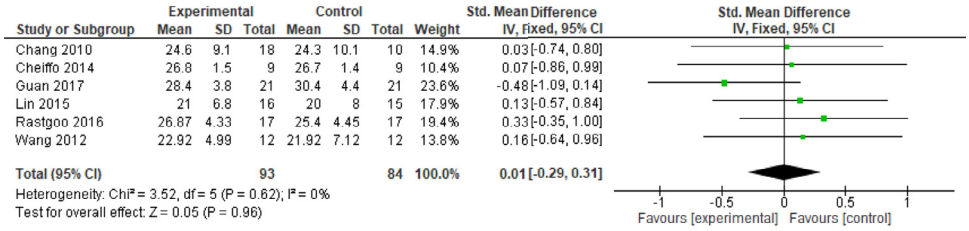
Abbreviations: ABMS II, Ability for Basic Movement Scale Revised; BBS, Berg Balance Scale; BBT, grip strength and the Box and Block test; BRS, Brunnstrom recovery stages; DLOS, dynamic limits of stability; FAC, functional ambulatory category; FMA, Fugl-Meyer assessment; FMA-LL, lower limb score in FMA; FMA-UL, score in the Fugl-Meyer assessment; FMA UL/LL, Fugl-Meyer assessment upper limb/lower limb; MBI, modified Barthel index; MEP, motor evoked potentials; MI-A, arm score in the Motricity Index; MI-L, leg score in MI; MMAS, modified modified Ashworth scale; MMSE, mini-mental state examination; MRC, Medical Research Council; MRS, modified rank score; NIHSS, National Institutes of Health Stroke Scale; PASS, Postural Assessment Scale for Stroke Patients; PCI, Physiological Cost Index; POMA-b, Tinetti Performance-oriented mobility assessment; RMT, resting motor threshold; SOT, sensory organization test; TUG, timed up and go; TMS, transcranial magnetic stimulation; 6MWT, the 6-minute walk test; 10MWT, 10 m walk speed test.



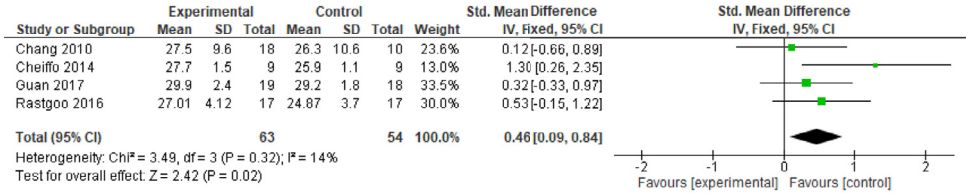
a. SMD (95%) of the effect of rTMS compared with Sham group on balance by pooling data from 5 trails



b. SMD (95%) of the effect of rTMS compared with Sham group on mobility evaluation by pooling data from 3 trails



c. SMD (95%) of the effect of rTMS compared with Sham group on (FMA-L) by pooling data from 6 trails



d. SMD (95%) of the effect of follow-up for rTMS compared with Sham group on lower extremity function by pooling data from 4 trails Abbreviations: IV, Inverse variance.

Abbreviations: IV, Inverse variance.

Figure 4. *SMD based on comparison.*

Conflict of Interest

Authors have no conflicts of interest to declare.

References

1. Kumar A, Gupta V. Discovery of neuroprotective antioxidants for the management of ischemic brain stroke. Discovery and development of neuroprotective agents from natural products. Elsevier; 2017. p. 377-399.
2. Wang W, Jiang B, Sun H, et al. Prevalence, incidence, and mortality of stroke in china: results from a nationwide population-based survey of 480 687 adults. Circulation 2017;135:759-771.
3. Hao Z, Wang D, Zeng Y, et al. Repetitive transcranial magnetic stimulation for improving function after stroke. Sao Paulo Med J 2013;131:440-450.
4. Shariat A, Ansari NN, Shaw BS, et al. Cycling training and functional electrical stimulation for poststroke patients. Rev Bras Med Esporte 2018;24:300-302.
5. de Rooij IJM, van de Port IGL, Meijer J-WG. Effect of virtual reality training on balance and gait ability in patients with stroke: systematic review and meta-analysis. Phys ther 2016;96:1905-1918.
6. Choi C-M, Kim J-H, Lee J-K, et al. Effects of repetitive transcranial magnetic stimulation over trunk motor spot

on balance function in stroke patients. Ann Rehabil Med 2016;40:826-834.
7. Naghdi S, Nakhostin Ansari N, Azarnia S, et al. Interrater reliability of the Modified Modified Ashworth Scale (MMAS) for patients with wrist flexor muscle spasticity. Physiother Theory Pract 2008;24:372-379.
8. Ansari NN, Naghdi S, Fakhari Z, et al. Dry needling for the treatment of poststroke muscle spasticity: a prospective case report. NeuroRehabilitation 2015;36:61-65.
9. Sasaki N, Kakuda W, Abo M. Bilateral high-and low-frequency rTMS in acute stroke patients with hemiparesis: a comparative study with unilateral high-frequency rTMS. Brain inj 2014;28:1682-1686.
10. Sasaki N, Abo M, Hara T, et al. High-frequency rTMS on leg motor area in the early phase of stroke. Acta Neurol Belg 2017;117:189-194.
11. Johnson NN, Carey J, Edelman BJ, et al. Combined rTMS and virtual reality brain−computer interface training for motor recovery after stroke. J Neural Eng 2018;15:160-168.
12. Iwański S, Leśniak M, Polanowska K, et al. Low frequency rTMS combined with visual scanning training in patients with poststroke visuospatial neglect. A randomized, double-blind, placebo-controlled study. Brain Stimulation 2018;11:11-22.
13. Corti M, Patten C, Triggs W. Repetitive transcranial magnetic stimulation of motor cortex after stroke: a focused review. Am J Phys Med Rehabil 2012;91:254-270.
14. Robinson R. For your patients-stroke rehabilitation: repetitive transcranial magnetic stimulation improves post-stroke walking speed. NeurologyToday 2018;18:21-23.
15. Yang Q, Chen S, Deng P, et al. Peripheral plus central repetitive transcranial magnetic stimulation (rTMS) for upper limb motor rehabilitation in chronic stroke-a case report. Ann Phys Rehabil Med 2018;61:215-216.
16. Hatem SM, Saussez G, della Faille M, et al. Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery. Front Hum Neurosci 2016;10: 442-448.
17. Ayache SS, Farhat WH, Zouari HG, et al. Stroke rehabilitation using noninvasive cortical stimulation: motor deficit. Expert Rev Neurother 2012;12:949-972.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS med 2009;6:197-201.
19. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions Version 5.1. 0. The Cochrane collaboration. Confidence intervals 2011.
20. Mandrekar JN. Measures of interrater agreement. J Thorac Oncol 2011;6:6-7.
21. Chieffo R, De Prezzo S, Houdayer E, et al. Deep repetitive transcranial magnetic stimulation with H-coil on lower limb motor function in chronic stroke: a pilot study. Arch Phys Med Rehabil 2014;95:1141-1147.
22. Kakuda W, Abo M, Watanabe S, et al. High-frequency rTMS applied over bilateral leg motor areas combined with mobility training for gait disturbance after stroke: a preliminary study. Brain Inj 2013;27:1080-1086.
23. Rastgoo M, Naghdi S, Nakhostin Ansari N, et al. Effects of repetitive transcranial magnetic stimulation on lower extremity spasticity and motor function in stroke patients. Disabil Rehabil 2016;38:1918-1926.
24. Kim W-S, Jung SH, Oh MK, et al. Effect of repetitive transcranial magnetic stimulation over the cerebellum on patients with ataxia after posterior circulation stroke: a pilot study. J Rehabil Med 2014;46:418-423.
25. Chang WH, Kim Y-H, Bang OY, et al. Long-term effects of rTMS on motor recovery in patients after subacute stroke. J Rehabil Med 2010;42:758-764.
26. Wang R-Y, Tseng H-Y, Liao K-K, et al. rTMS combined with task-oriented training to improve symmetry of interhemispheric corticomotor excitability and gait performance after stroke: a randomized trial. Neurorehabil Neural Repair 2012;26:222-230.
27. Kakuda W, Abo M, Nakayama Y, et al. High frequency rTMS using a double cone coil for gait disturbance. Acta Neurol Scand 2013;128:100-106.
28. Cha HG, Kim M-K. Therapeutic efficacy of low frequency transcranial magnetic stimulation in conjunction with mirror therapy for sub-acute stroke patients. J Magn 2015;20:52-56.
29. Cha HG, Kim MK. Effects of strengthening exercise integrated repetitive transcranial magnetic stimulation on motor function recovery in subacute stroke patients: a randomized controlled trial. Technol Health Care 2017;25:521-529.
30. Guan Y, Li J, Zhang X, et al. Effectiveness of repetitive transcranial magnetic stimulation (rTMS) after acute stroke: a one−year longitudinal randomized trial. CNS Neurosci Ther 2017;23:940-946.
31. Forogh B, Ahadi T, Nazari M, et al. The effect of repetitive transcranial magnetic stimulation on postural stability after acute stroke: a clinical trial. Basic Clin Neurosci 2017;8:405-409.
32. Vaziri PM, Bahrpeyma F, Firoozabadi M, et al. Low frequency repetitive transcranial magnetic stimulation to improve motor function and grip force of upper limbs of patients with hemiplegia. Iranian Red Crescent Med J 2014;16:851-861.
33. Lin Y-N, Hu C-J, Chi J, et al. Effects of repetitive transcranial magnetic stimulation of the unaffected hemisphere leg motor area in patients with subacute stroke and substantial leg impairment: a pilot study. J Rehabil Med 2015;47:305-310.
34. Cha H-G, Kim M-K, Nam H-C, et al. Effects of high frequency repetitive transcranial magnetic stimulation on function in subacute stroke patients. J Magn 2014;19: 192-196.
35. Elkholy SH, Atteya AA, Hassan WA, et al. Low rate Repetitive Transcranial Magnetic Stimulation (rTMS) and gait rehabilitation after stroke. Egypt J Neurol Psychiatry Neurosurg 2014;51:418-424.
36. Rogers LM, Madhavan S, Roth H, et al. Transforming neurorehabilitation of walking following stroke: the promise of non-invasive brain stimulation−a review. Restor Neurol Neurosci 2011;29:507-516.