Repetitive Transcranial Magnetic Stimulation for Post-stroke Dysphagia: a Meta-analysis

Nicole A. Bernardo-Aliling,[1] Adovich S. Rivera[2] and Paul Matthew D. Pasco[3]

[1]*Department of Neurosciences, Philippine General Hospital, University of the Philippines Manila*
[2]*Institute of Health Policy and Development Studies, National Institutes of Health, University of the Philippines Manila*
[3]*Section of Adult Neurology,Department of Neurosciences, College of Medicine and Philippine General Hospital, University of the Philippines Manila*

ABSTRACT

Background. Dysphagia is common among post-stroke patients, causing disability due to malnutrition and pneumonia. Repetitive transcranial magnetic stimulation (rTMS) is a novel treatment modality to address this complication.

Objective. The study aimed to compare real versus sham rTMS in treating post-stroke dysphagia.

Methods. PubMed, Ovid, ClinicalKey, Herdin, and Google Scholar databases were searched from their earliest record to 31 July 2015 for randomized controlled trials that used rTMS to treat post-stroke dysphagia. The Jadad scale was used to assess the quality of the studies. The weighted mean difference (WMD) between baseline and post-treatment mean for Penetration Aspiration Scores (PAS) measured in the experimental and control groups were extracted for subsequent meta-analyses.

Results. Three studies were analyzed. The WMD in PAS score between rTMS and control using liquid bolus two weeks after treatment in two good quality studies was -1.14 (95% confidence interval (CI) = -1.80 – -0.48, P = 0.001, I^2 = 0.0%), and after four weeks was -1.83 (CI = -3.22 – -0.44, P = 0.010, I^2 = 0.0%).

Conclusion. Treatment of post-stroke dysphagia with rTMS improved PAS on subgroup analyses of studies using liquid bolus after two weeks, and between real and sham treatment after four weeks.

Key Words: dysphagia, meta-analysis, stroke, transcranial magnetic stimulation

Introduction

Dysphagia is a common complication post-stroke, estimated to range from 37% seen under cursory screening techniques, to a maximum of 78% using instrumental testing.[1] This outcome begets other complications, the most common of which is pneumonia. Development of pneumonia after stroke was associated with mortality at thirty days and one year, longer length of stay, and dependency at discharge.[2] In-hospital feeding would be facilitated through nasogastric tubes, which do not confer complete protection against aspiration and subsequent pneumonia.[3] For intractable dysphagia, percutaneous endoscopic gastrostomy (PEG) insertion is one of the methods employed in as much as 3.4% of stroke patients in a local tertiary hospital.[4] However, this procedure is not without its own complications.

The gold standard procedure used to detect dysphagia is through the videofluoroscopic swallowing study (VFSS), also known as the videofluoroscopic modified barium swallow (VMBS).[5] From this, scoring of degrees of aspiration have been developed. One of these functional rating scales is the Penetration Aspiration Scale (PAS), which is an eight point ordinal scale ranging from no aspiration/no material entering the airway, penetration or entering through the larynx, and aspiration which is food entering the airway, which garners the maximum score of eight.[6]

Conventional swallowing therapy, the cornerstone of dysphagia rehabilitation, includes several techniques. These include exercises aimed at strengthening muscles, and improving movement and coordination. Possible exercises may include the Mendelsohn maneuver (the patient hold the larynx up, either using the muscles of the neck or with the hand, during the swallow for an extended period of time), the Masako maneuver (patient protrudes tongue and then swallows), Shaker exercise, and gargling, among others. Other strategies include postural changes (head turn and chin tuck postures) and multiple swallows. These therapies are usually provided in addition to dietary modifications. Consistency- and texture-modified diets are utilized to facilitate progression of swallowing. Thickeners may be added to liquids for this purpose.[7]

Alternative interventions have also come to fore in terms of dysphagia treatment. Traditional Chinese Medicine,

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Corresponding author: Nicole A. Bernardo-Aliling, MD
Section of Adult Neurology
Department of Neurosciences
Philippine General Hospital
University of the Philippines Manila
Taft Ave. Ermita, Manila, 1000 Philippines
Telephone: +632 5548400 local 2401
Email: nicole.bernardo@gmail.com

thermal stimulation, antihypertensives, antiplatelet agents, decontamination of the digestive tract, transcranial direct stimulation (tDCS), neuromuscular electrical stimulation (NMES), and repetitive transcranial magnetic stimulation have all been evaluated for their role in dysphagia.[7,8] NMES was shown to have an unclear role for the treatment of dysphagia while traditional techniques also have inconsistent outcomes.[8,9]

This report examined the role of rTMS, another emerging modality, and its role in the rehabilitation of post-stroke patients presenting with dysphagia. Repetitive transcranial magnetic stimulation (rTMS) uses a magnet instead of an electrical current to activate the brain. It was first developed in 1985, and has been studied as a possible treatment for mental disorders most notably for depression and psychosis. A typical rTMS session lasts 30 to 60 minutes and does not require anesthesia. An electromagnetic coil is held against the forehead near an area of the brain, then short electromagnetic pulses are administered through the coil. The magnetic pulse easily causes small electrical currents that stimulate neurons in the targeted brain region. Depth of effect usually reaches up to two inches from the surface facing the device only. Generally, the person will feel a slight buzz on the head as the pulses are administered. Discomfort may be felt at the site on the head where the magnet is placed, and the muscles of the scalp, jaw or face may contract. Mild headache or brief lightheadedness may be felt. It is theorized that the procedure could cause a seizure, although documented incidences of this are uncommon. A recent large-scale study on the safety of rTMS found that most side effects, such as headaches or scalp discomfort, were mild or moderate, and no seizures occurred. Because the treatment is new, however, long-term side effects are unknown.[7,9]

This review and meta-analysis aimed to evaluate the efficacy of rTMS in the treatment of post-stroke dysphagia. Specifically, this analysis looked into the short-term impacts on PAS scores.

Materials and Methods

A. Criteria for inclusion of studies

1. Type of studies

All relevant published randomized controlled trials using rTMS for the treatment of post-stroke dysphagia were identified. Studies must have objective outcome measures for dysphagia pre- and post-treatment with rTMS.

2. Types of participants

Studies with the following subjects were included: aged older than 40 years of either sex who had stroke of either cerebral hemisphere with hemiplegia or hemiparesis and dysphagia, the stroke must have been documented via computed tomography or magnetic resonance imaging, and dysphagia was evaluated through videofluoroscopy.

3. Types of interventions

The authors aimed to include double-blind, randomized controlled trials that compared real rTMS to sham rTMS. Studies with other comparisons to rTMS were also considered, such as: conventional dysphagia therapy, use of rTMS on an area stimulating the abductor pollicis brevis muscle.

4. Types of outcome measures

The weighted mean difference (WMD) between baseline and post-treatment mean for Penetration Aspiration Scores (PAS) measured in the experimental and control groups were extracted for subsequent meta-analyses.

B. Search methods for identification of studies

A literature search was done in several databases (PubMed, Ovid, ClinicalKey, Herdin, and Google Scholar) from their earliest record to 31 July 2015 for relevant abstracts using the terms “repetitive transcranial magnetic stimulation” + “stroke” + “dysphagia”. A review of bibliographies of retrieved studies was also done to locate additional unpublished studies. Full texts and additional information regarding the relevant studies were sought by correspondence with the authors through electronic mail.

C. Data collection and analysis

1. Study selection

Two of the authors screened the abstracts of potential studies according to the aforementioned inclusion criteria. Full text articles of those that fulfilled all the criteria were evaluated.

2. Data extraction

A standard table was filled with the necessary data on each of the studies (Appendix 1). The needed information included: population and sample sizes, inclusion and exclusion criteria of each trial, mention of blinding, random assignment, age and sex of patients, stroke types, time post-stroke, devices used, type of intervention (rTMS methodology), experimental procedure, primary and secondary outcomes, and results. Two authors independently filled the extracts the needed data then met to resolve any inconsistencies.

3. Data analyses

The authors used Stata Data Analysis and Statistical Software for data processing. The random effects model was used because of the risk of heterogeneity between studies. Forest plots were used to summarize the data, and the I^2test used to demonstrate heterogeneity.

Table 1. Summary of studies using rTMS to treat post-stroke dysphagia

Study no.	Authors, Published year	Participants (Exp1/ Control)	Intervention	Control	Characteristics of Participants	Assessment Timing	Outcomes	Quality Assessment
1	Park, et al, 2013	18 (9/9)	5Hz rTMS over contra-lesional pharyngeal motor cortex for 10 min per day for 2 weeks	Sham	Post-stroke dysphagia persisted over 1 month post-ictus	At 2 weeks and 2 weeks post treatment	**PAS** VDS	5
2	Lim, et al, 2014	29 (14/15)	rTMS and NMES over contra-lesional cortex	Conventional dysphagia therapy	Subacute (<3 months) stroke with dysphagia	After 2 and 4 weeks	**PAS** FDS PTT ASHA NOMS	3
3	Lee, et al, 2015	24 (12/12)	rTMS once a day for 10 mins on 10 consecutive days on lesion side	rTMS of APB site	Subacute stroke patients with dysphagia	Soon after and 4 weeks after rTMS	**PAS** FDS DOSS	1
4	Michou et al, 2013	18 (6 per arm, both real and sham)	rTMS PES PAS	Sham	Stroke with dysphagia 6 weeks post-ictus	Immediately and 30mins after treatment	cPA BTT	
5	Cheng, et al, 2015	4 (2/2)	10 sessions of active rTMS for 2 weeks	Sham	Chronic post-stroke dysphagia (at least 2 years)	After 1 week and 1 month	SAPP, VFSS, OPSE	
6	Khedr, et al, 2008	26 (14/12)	Real TMS: 10 min daily x 5 days, 10 trains of 3Hz, lasting for 10s repeated each min	Sham	5th-10th day post-stroke with dysphagia	After 5th session, 30 and 60 days after	DOSS MEP BI grip strength	
7	Verin, Leroi, 2008	7	rTMS at 1 Hz was applied for 20 min per day every day for 5 days	**None**	Post-stroke dysphagia more than six months or earlier	After 1 and 3 weeks	**PAS**	

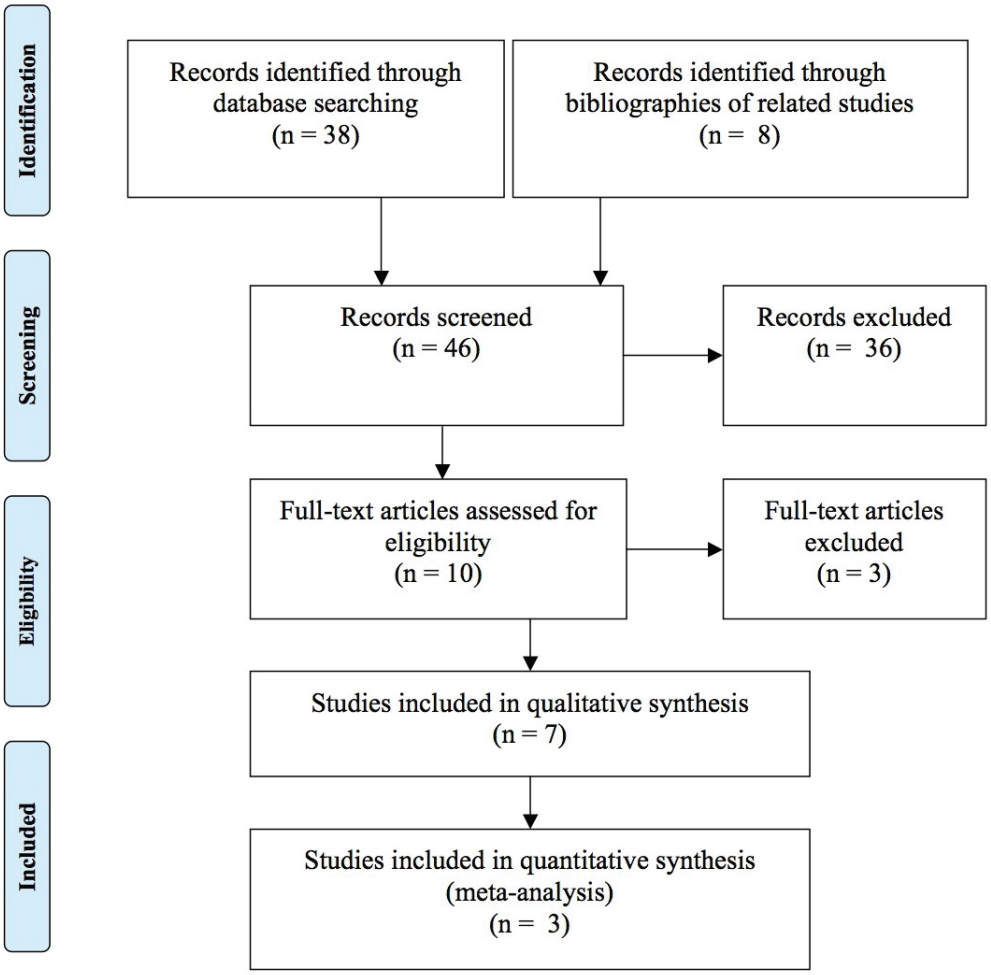
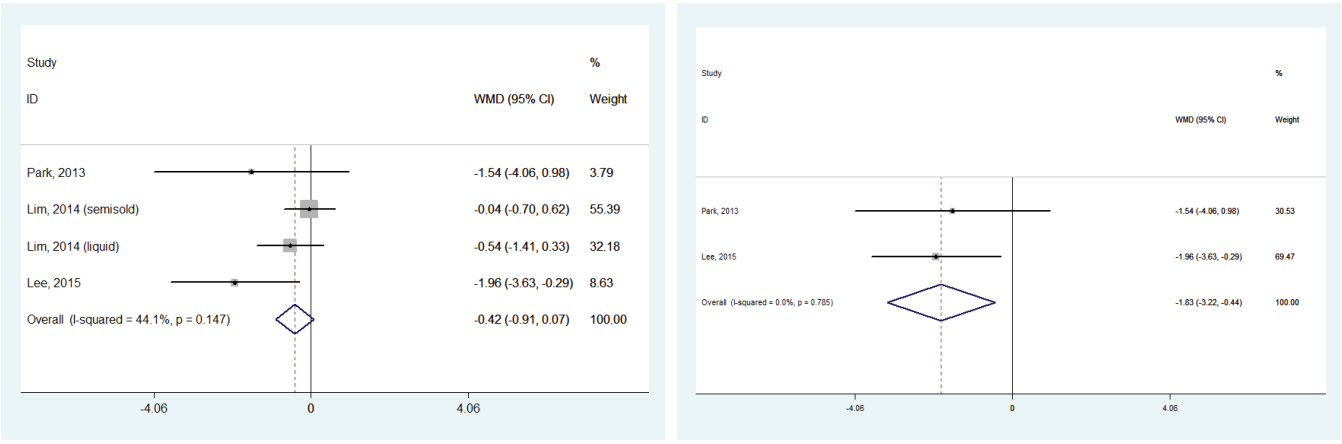


Figure 1. Flow diagram of the evaluation process for the inclusion or exclusion of studies.

A B

Figure 2. (A) Forest plot of weighted mean difference (WMD) in PAS at two weeks post rTMS, and (B) Forest plot of WMD in PAS with liquid arm subgroup analysis.



A B

Figure 3. (A) Forest plot of weighted mean difference (WMD) in PAS at four weeks post rTMS, and (B) Forest plot of WMD for real vs sham rTMS at four weeks post rTMS.

4. Risk of bias assessment

Three independent raters appraised the included studies using the Jadad scale and Cochrane Collaboration Handbook Criteria version 5.1.

Jadad criteria include: randomization, blinding, an account of all patients,[10] while Cochrane criteria examined: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting (Appendices 2 and 3).

Results

A. Study selection

A total of 46 potentially relevant articles were identified after electronic search was conducted (Figure 1). After removing duplicates, articles written in other languages apart from English, and others that did not meet the criteria stated above, only ten full-text articles were evaluated. Three articles were excluded; one study aimed to measure long-term plasticity instead of clinical excitability, another only induced virtual lesions instead of having actual post-stroke patients, and the third paired associated stimulation instead of rTMS. Only seven studies were retained for further evaluation. The characteristics of the included studies are summarized in Table 1.

Of the seven studies included in the qualitative analysis, only three studies had analyzable data and similar outcomes. The included studies were evaluated using the Jadad scale. Three independent assessors performed the evaluation to minimize bias. Only two studies had a Jadad score of ≥3, and considered goodquality studies. Meta-analysis of the outcomes of these three studies was done. Three other studies were included in the systematic review but subsequently excluded.

B. Primary outcome measures

Two of the three evaluated RCTs had results at two weeks post-treatment with rTMS. These are also the studies found to have good quality scores. Figure 2A illustrates a non-statistically significant decrease in PAS, with a WMD of -0.29 ([-0.66, 0.09] p = 0.133), and there was significant heterogeneity among studies (I^2 = 79.2%, p for heterogeneity = 0.008). The semisolid arm of one study appeared to be the source of heterogeneity. Removing this arm demonstrated a significant WMD of -1.14 ([-1.8, -0.48] p = 0.001). No further significant heterogeneity was found (I^2= 0), shown in Figure 2B.

All three RCTs showed results four weeks post-rTMS. WMD was not statistically significant at -0.42 [-0.91, 0.07] p = 0.091, with still a significant heterogeneity among studies (I^2 = 44.1%, p for heterogeneity = 0.147). Subgroup analysis including only good quality studies showed similar results (WMD = -0.645 [-1.464.0.173]. I = 0%). Unlike the two-week outcome, there was no significant change in PAS if the semi-solid arm of one of the studies was removed in the analysis (WMD = -0.645 [-1.464.0.173]. I^2 = 0%). Finally, subgroup analysis was done to include only the studies that compared real vs sham rTMS. There was a significant WMD of -1.83 ([-3.22, -0.44] p = 0.010), with non-significant heterogeneity (I^2 = 0.0%, p for heterogeneity 0.785).

Discussion

This meta-analysis aimed to determine the effectiveness of rTMS for rehabilitation of post-stroke dysphagia with the decrease in PAS as the primary outcome. As a burgeoning mode of treatment, and due to the limitations inherent to each study design, no large RCTs investigating this aspect of use on rTMS have been successfully completed. As such, combining the sample sizes of all trials brought the total n = 71, a significant sample size in terms of power of analysis. However, still due to these small sample sizes, heterogeneity was significant in the overall analysis of the main outcomes. Aside from sample sizes, there were differences in the experimental designs of each study. This is also expected, as the use of rTMS has yet to have standardized guidelines even in its more established uses (ie, depression[9]). The number of sessions, use of sham versus control or standard swallow therapy, and application of rTMS to the lesion or contra-lesional site, were also not standardized among the studies assessed. Differences in the population sampled (ie, stroke type and duration) also contributed to heterogeneity of the studies. It is recommended that future investigators explore the possibility of creating a standardized protocol for treatment with rTMS.

Cerebrovascular disease is among the top causes of morbidity in the world. With the improvement in management of stroke and the concomitant improvement of survival, several practitioners are now facing issues in taking care of post-stroke patients. Dysphagia is a devastating consequence of stroke which affects the patients' nutrition and quality of life. It also puts the patient at increased risk of pneumonia and re-hospitalization. There is a need to look into the efficacy of new treatments for the possibility of adding new management options. Treatment of post-stroke dysphagia with rTMS over the intact and affected swallowing motor cortices translated to improved scores on one functional outcome rating for aspiration, PAS. This treatment effect was only statistically significant using subgroup analysis that measured dysphagia to liquids at two weeks after treatment, and after four weeks and in comparing real rTMS versus sham rTMS. Overall analysis of the three included RCTs at two weeks and four weeks post-rTMS did not show a significant decrease in PAS.

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Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

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10. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996; 17(1):1–12.

Included Studies in Meta-Analysis

1. Park JW, Oh JC, Lee JW, Yeo JS, Ryu KH. The effect of 5Hz high-frequency rTMS over contralesional pharyngeal motor cortex in post-stroke oropharyngeal dysphagia: a randomized controlled study. Neurogastroenterol Motil. 2013; 25(4): 324–e250. doi:10.1111/nmo.12063.
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Included Studies in Systematic Review

1. Cheng IK, Chan KM, Wong CS, Cheung RT. Preliminary evidence of the effects of high-frequency repetitive transcranial magnetic stimulation (rTMS) on swallowing functions in post-stroke individuals with chronic dysphagia. Int J Lang Commun Disord. 2015; 50(3):389-96. doi:10.1111/1460-6984.12144.
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Excluded Studies

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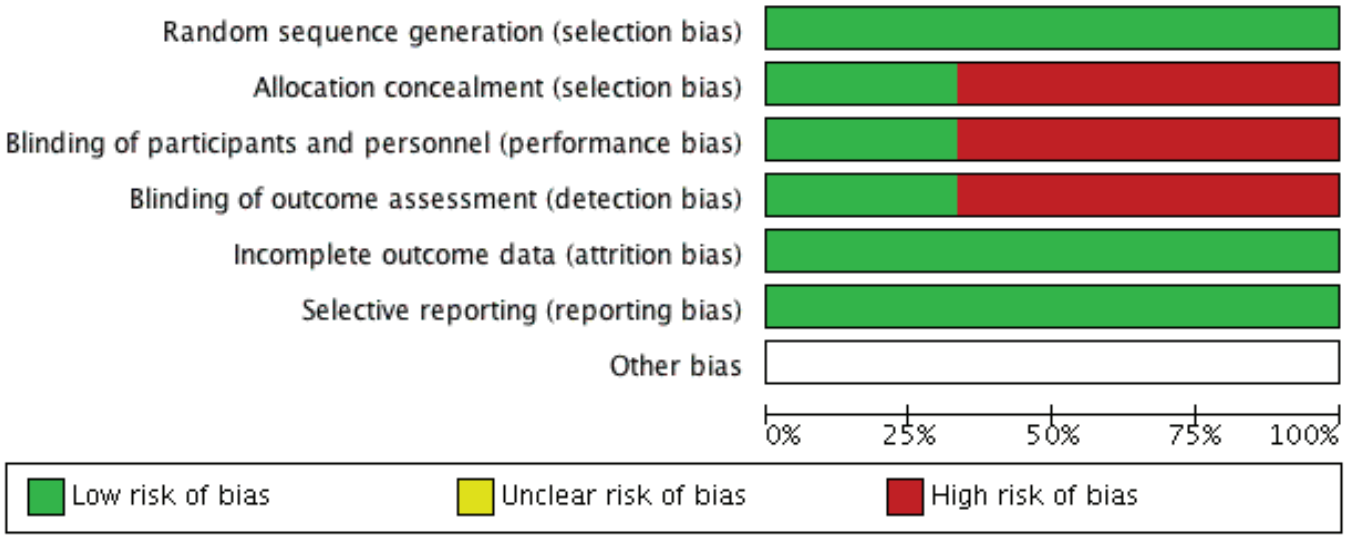
Appendices

Appendix 1. Data Extraction Table

	Study A
Study Title	
Authors	
Journal	
Year	
Research Design	
Population (N)	
Sample size (n)	
Inclusion criteria	
Exclusion criteria	
Blinding	
Random assignment	
Age of patients (y)	
Sex of patients	
Stroke types	
Time post-stroke	
Devices	
Control/Comparison	
Intervention	
Experimental Procedure	
Primary outcome	
Secondary outcome	
Results	

Appendix 2. Cochrane Collaboration Handbook Criteria Risk of Bias Summary



Appendix 3. Jadad Grading of Screened Studies for Meta-analysis

	Park, 2013			Lim, 2014			Lee, 2015		
Raters	AA	LD	RP	AA	LD	RP	AA	LD	RP
Randomization	2	2	2	2	2	2	0	0	0
Blinding	2	2	2	0	0	0	0	0	0
An account of all patients	1	1	1	1	1	1	1	1	1
TOTAL	5	5	5	3	3	3	1	1	1