Therapeutic role of rTMS on recovery of dysphagia in patients with lateral medullary syndrome and brainstem infarction

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ABSTRACT

Background There is some evidence for a therapeutic effect of repetitive transcranial magnetic stimulation (rTMS) on dysphagia in hemispheric stroke.

Aim To compare the effect of active or sham rTMS applied to the motor area of both hemispheres in patients with acute lateral medullary infarction (LMI) or other brainstem infarctions.

Material and method The study included 22 patients with acute ischaemic stroke who had severe bulbar manifestation. 11 patients had LMI, and 11 had another brainstem infarction. They were randomly allocated to receive active (n=11) or sham (n=11) rTMS of the oesophageal motor cortex. Each patient received 300 rTMS pulses at 3 Hz and an intensity of 130% resting motor threshold to each hemisphere for five consecutive days. Clinical ratings of dysphagia and motor disability were assessed before and immediately after the last session, and then again after 1 and 2 months.

Results There were no significant differences in baseline clinical assessment of swallowing between active and sham groups. Active rTMS improved dysphagia compared with sham rTMS in both groups of patients, (p=0.001 for both); the LMI group also improved the scores in the Barthel Index. All improvements were maintained over 2 months of follow-up (p=0.001).

Conclusion These findings suggest that rTMS could be a useful adjuvant strategy in neurorehabilitation of dysphagia due to LMI or other brainstem infarction, although further assessment is necessary in multicentre clinical trials.

INTRODUCTION

Wallenberg syndrome (WS) is well defined clinically, and lateral medullary infarction (LMI) is one of its most frequent causes. Although the combinations of the various signs and symptoms are helpful for the clinical diagnosis of WS, the presence of the different signs and symptoms may vary from patient to patient.[1 2] Among these symptoms and signs, dysphagia has been reported in 51–94% of the patients with WS,[1 2] and in most cases this is initially severe enough to require nasogastric feeding. It usually improves rapidly, and the patient can return to oral feeding within 1 to 2 months after the stroke.[3 4] However, in some patients, dysphagia does not recover for many months or even years.[5 6]

The major swallowing centres of the nucleus tractus solitarius (NTS) and nucleus ambiguous (NA) and the reticular formation around them are located in the dorsolateral medulla oblongata.[7 8] Dysphagia after stroke increases the risk of death, mainly as a consequence of pneumonia which is implicated in one-third of stroke deaths.[9] While the reflexive component of swallowing depends on swallowing centres in the brainstem, initiation of swallowing is a voluntary action that involves the integrity of motor areas of the cerebral cortex.[8] The cortex seems to initiate activity in the brainstem swallowing centres causing the sequence of muscular contraction in the pharynx and oesophagus that is competed by peristalsis.[10] Recently, transcranial magnetic stimulation (TMS) has been used to study the cortical input to swallowing control[11–13] and has revealed that the topographic representation of oesophageal motor function in the human cerebral cortex is bilateral but with consistent interhemispheric asymmetry unrelated to handedness.

In a number of recent studies, poststroke motor and dysphagia performance has been improved after daily treatment sessions with repetitive TMS (rTMS) using an excitatory frequency of 3 Hz[14–16] in patients with hemispheric ischaemic stroke due to occlusion of territories of the middle cerebral artery. In the present study, we have tested the effect of 3 Hz rTMS on dysphagia in patients after vertebrobasilar stroke either in brainstem or producing the lateral medullary syndrome. Our hypothesis was that stimulation of the cortical motor area of each hemisphere would maximise functional plasticity of the connections from both hemispheres.

SUBJECTS AND METHODS

Subjects

The present study included 22 patients with acute ischaemic stroke with bulbar manifestation (dysphagia, nasal regurgitation). Eleven patients had LMI, and 11 patients had brainstem infarction. All patients were admitted to the Stroke Unit, Department of Neurology Assiut University Hospital, and Assiut, Egypt. The diagnostic criteria of LMI were: vertigo, nausea, vomiting and nystagmus; ataxic gait and ipsilateral limb ataxia; impaired pain and temperature sensation on the ipsilateral face and the contralateral body, dysphagia, hoarseness and ipsilateral weakness of the palate and vocal cords, and decrease in the gag reflex; and ipsilateral Horner syndrome.[17] Diagnostic criteria of other brainstem infarction with pontomedullary dysfunction were: bilateral long tract motor or sensory signs; crossed motor or sensory signs; dissociative sensory loss on one-half of the body, with pain and temperature sensation

more involved than propioception; cerebellar signs; Horner syndrome and involvement of lower four cranial nerves.

Seven patients had left LMI, and four patients had right LMI. In the brainstem infarction group, six patients had crossed signs, and five patients had bilateral long tract motor signs. The MRI findings supported the presence of LMI or brainstem infarction on one side in all cases.

The mean age was 56.4±15 years for the LMI group, and the mean age of the brainstem infarction group was 58.2±10.4 years. Each group was subdivided randomly into active and sham rTMS subgroups. Eleven patients received active rTMS, and 11 patients received sham rTMS. All patients were admitted at the Stroke Unit, Department of Neurology Assiut University Hospital, and Assiut, Egypt. Each patient fulfilled the inclusion criteria as follows: patients must be conscious and have ischaemic cerebrovascular stroke (LMI or other brainstem infarction with pontomedullary dysfunction and documented by MRI) for the first ever and within 1–3 months from the onset with a degree of dysphagia ranging from grade III to IV.[18] Because of the severity of vertigo and dysphagia, we could not perform neurophysiology studies in those patients. All patients apart from two in the sham treatment group (another brainstem infarction group who died) completed the trial and follow-up periods.

Exclusion criteria included head injury or neurological disease other than stroke, unstable cardiac dysrhythmia, fever, infection, hyperglycaemia, epilepsy and prior administration of tranquiliser. We excluded patients with intracranial metallic devices or with pacemakers or any other device. Patients who were unable to give informed consent because of severe anaesthesia or cognitive deficit were not included. All patients provided fully informed consent. The local Ethics Committee had approved the experimental protocol.

Methods

Each patient underwent a full clinical and neurological assessment. Diagnosis of dysphagia depended on answers to a swallowing questionnaire[19] confirmed by bedside examination.[20] The examiner asked the patients to swallow a small volume of water (cup) and watched for signs of dysphagia (coughing, oral residue, delayed swallow, throat clearing, choking and reduced laryngeal elevation). Other signs—loss of liquid from the mouth, dyspraxia or poor coordination of the muscles, facial weakness, breathlessness and changes in voice quality after swallowing—were also observed.[20]

The degree of dysphagia (DD) was graded as follows: (DD-I) there was no clinical signs and symptoms of dysphagia; grade II (DD-II) very mild dysphagia was suspected by clinical examination, but the patient never complained of dysphagia; for grade III (DD-III), the patient complained of dysphagia, and other clinical signs supported this, but non-oral feeding was not necessary at the time of investigation; for grade IV (DD-IV), the patient had obvious clinical signs and symptoms of dysphagia, including aspiration, and dysphagia was severe enough to necessitate non-oral feeding.[18]

Motor disability functional ability

Grip strength was assessed according to the Hemispheric Stroke Scale.[21] The National Institutes of Health Stroke Scale[22] and Barthel index scale (BI)[23] were assessed for each patient. All patients received the same conventional therapy and medical treatment (anticoagulant 'low-molecular-weight heparin' plus acetyl salicylic acid and Piracetam 2000–4000 mg/day) in the first week followed by acetyl salicylic acid and Piracetam alone.

Repetitive transcranial magnetic stimulation

Device

A Dantec Keypoint electromyograph was used to collect the signal (Dantec, Skovlunde, Denmark). Electromyography parameters included a bandpass of 20–1000 Hz and a recording time window of 200 ms. Single and rTMS were performed with a commercially available 90 mm figure-of-eight coil connected to a Mag-Lite r25 stimulator (Dantec Medical, Skovelund, Denmark).

rTMS sessions

The patients were randomly classified into two groups: the first group received active rTMS, and the second group received sham rTMS for each type of infarction (LMI and other brainstem infarction).

Active rTMS was applied for 10 min every day for five consecutive days. A session of stimulation consisted of 10 trains of 3 Hz stimulation, each lasting for 10 s, and then repeated every minute given through a figure-of-eight coil with the centre of coil positioned over the provisional oesophageal cortical area of both hemispheres (the best site for stimulation about 3 cm anterior and 6 cm lateral to the vertex).[13] The intensity of stimulation was set to 130% of the resting motor threshold for the first dorsal interosseous muscle (FDI) of the unaffected hemisphere. Sham rTMS was applied using the same parameters but with the coil held so that the edge was in contact with the head, while the remainder was rotated 90° away from the scalp in the saggital plane to reproduce the noise of the stimulation as well as some of its local sensation. However, as the patients had never experienced rTMS previously, they did not know whether they were receiving active or sham rTMS. All patients, whether in the active or sham group, received single-pulse TMS to determine the resting motor threshold.

Those patients in the sham group who had received single-pulse TMS were informed that the rTMS therapy would use a much lower intensity of stimulation than was required for testing and that they would experience no muscle twitching during stimulation.

Patients were followed-up after the fifth session, and then at the end of the first and second month after the last session. The blind primary outcome measure was the score on the dysphagia rating scale, and the secondary outcomes measures were: hand grip strength, as well as NIHSS and Barthel scales. These measures were evaluated by a trained neurologist who was blind to the type of rTMS. Patients were informed as to which group they had been allocated at the end of the last assessment.

Note that we chose 130% RMT because a high intensity such as this can spread as much as 2–3 cm from the coil in healthy subjects and therefore was chosen because it would target as wide an area of damaged tissue as possible. In addition, the threshold of oesophageal motor cortex is much higher than the motor threshold of the hand area where RMT was measured.

Statistical analysis

At the baseline assessment (ie, before 3 Hz rTMS), the mean values of different scales between both groups were compared using the Mann–Whitney U test for independent samples. The mean±SE were used to represent data. The level of significance was set at $p<0.05$. A two-factor ANOVA for repeated-measurements analysis of variance with 'treatment' (ie, active or sham rTMS) and 'time' (before versus after treatment) as the main factors was used to compare the differential effect of the

Table 1 Basal clinical assessment of active and sham groups, prerepetitive transcranial magnetic stimulation (rTMS) of lateral medullary infarction and other brainstem infarction

	Lateral medullary infarction group			Other brainstem infarction group		
	N=11			N=11		
	Active rTMS N=6	Sham rTMS N=5	p Value	Active rTMS N=5	Sham rTMS N=6	p Value
Age (years)	56.7±16	58±17.5	0.782	55.4±9.7	60.5±11	0.226
Sex (male/female)	6/0	5/0	–	2/3	3/3	0.819
Duration of stroke (weeks)	6±4.15	5.5±0.2	0.513	3.2±0.8	3.7±0.8	0.287
Hand-grip strength	2±0.9	3±0.7	0.081	5.2±1.5	3.3±0.8	0.926
National Institutes of Health Stroke Scale	10.3±2.7	12±2.1	0.137	14±1.9	12.5±2.7	0.358
Barthel index	51.7±17.8	39±11.4	0.097	31±9.6	33.3±14.7	0.926
Dysphagic grade	3.5±0.6	3.8±0.4	0.326	3.8±0.5	3.8±0.4	0.892

rTMS conditions (active-rTMS vs sham-rTMS) on changes in dysphagia rating and hand-grip strength and BI. When necessary, a Greeenhouse–Geisser correction was applied to correct for non-sphericity.

RESULTS

There was no significant difference between patients who received active rTMS or sham rTMS, either in the LMI group or in the other brainstem infarction group in age, dysphagia grade, grip strength, NIHSS and BI at the baseline assessment (pre rTMS sessions). Details are given in table 1.

At the baseline assessment, seven patients had dysphagia grade VI (requiring non-oral feeding), and only four patients had dysphagia grade III within the active rTMS group, while in the sham group, nine patients had grade VI dyphagia, and only two cases had dysphagia grade III.

rTMS and LMI

Five days of active rTMS produced a substantially greater improvement in dysphagia than sham TMS, and this improvement was maintained over a 2-month follow-up. Repeated-measures ANOVA showed a significant interaction of group (active vs sham rTMS)×time (pre-, postsession, first- and second-month follow-up; F=12, df=2.3 (20.7); p=0.0001) (figure 1A).

Clinical scores (NIHSS and BI) improved in all patients during the course of follow-up, with this being significantly larger in the active rTMS group for the BI but not NIHSS. A two-way ANOVA with repeated measures showed a significant interaction (group×time) for the BI measure (F=13.7, df=2.4(22.4); p=0.001) (figure 1B,C).

Although hand grip strength and NIHSS were improved over period of study in both patient groups, there was no significant difference between active and sham rTMS treatment (F=0.39, df=1.9 (17.3), p=0.67) and F=0.48, df=1.1 (10.2), p=0.52, respectively) (figure 1D).

rTMS and other brainstem infarction

Five days of rTMS produced a substantially greater improvement in dysphagia in the active compared with the sham group that was maintained over a 2-month follow-up. A repeated-measures ANOVA showed a significant interaction of group (active vs sham rTMS)×time (pre-, postsession, first- and second-month follow-up) (F=14.3, df=2.1 (19); p=0.001) that was due to the fact that patients who received active rTMS improved to a greater extent than in the sham group (figure 2A).

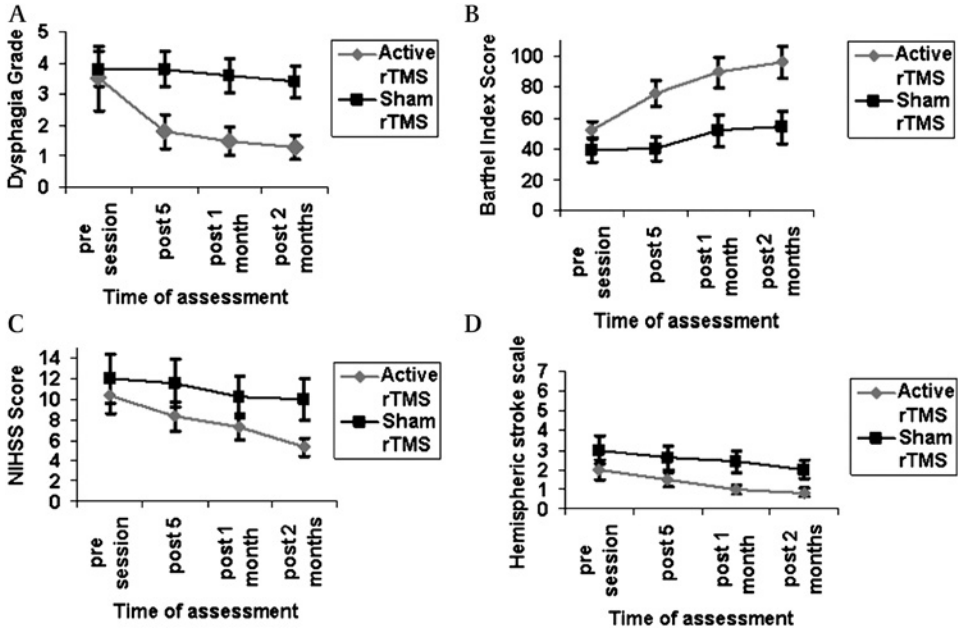

Figure 1 Changes in mean different rating scores of dysphagia (A), Barthel index (B), National Institutes of Health Stroke Scale (NIHSS) (C) and hand grip strength (D) at the four assessment points for the patients with lateral medullary infarction. The first assessment was immediately prior to commencing repetitive transcranial magnetic stimulation (rTMS) treatment (pre-), the second (postsession) was immediately after the end of the fifth session of rTMS, and the third and fourth assessment were immediately after the end of the first and the second months respectively. Each group separately shows a significant improvement. However, the mean scores of the patients who received active rTMS are significantly better than the sham group over the course of the treatment in Barthel Index scale only, while other rating scales showed no significant differences. Data are expressed as mean±SE.

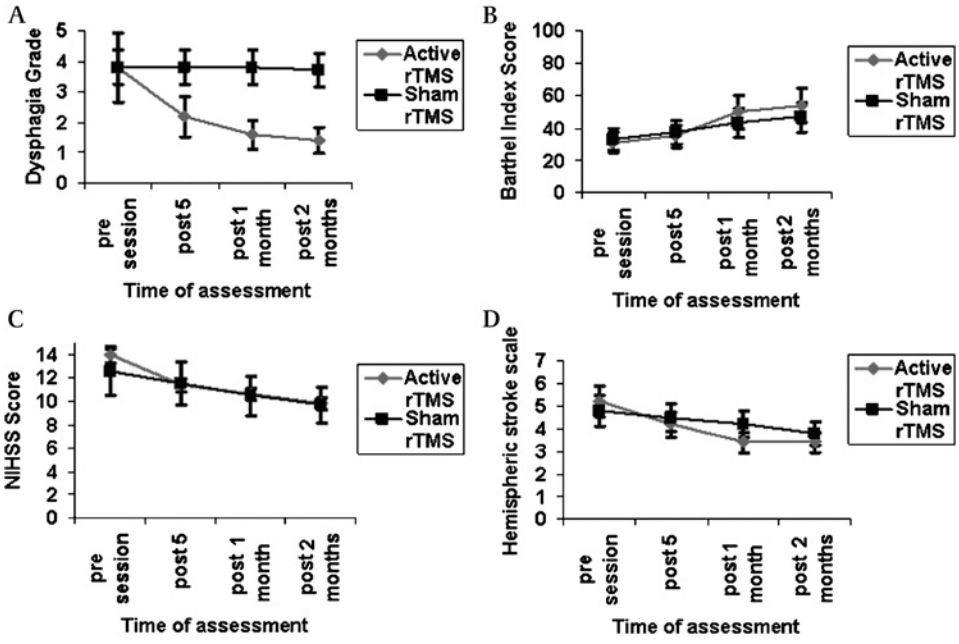

Figure 2 Changes in mean different rating scores of dysphagia (A), Barthel index (B), National Institutes of Health Stroke Scale (NIHSS) (C) and hand grip strength (D) at the four assessment points for the patients with brainstem infarction. The first assessment was immediately prior to commencing repetitive transcranial magnetic stimulation (rTMS) treatment (pre-), the second (postsession) was immediately after the end of the fifth session of rTMS, the third was immediately after the end of the first, and the fourth assessment was at the end of the second month. Each group separately shows a significant improvement. However, the mean scores of the patients who received active rTMS are significantly better than the sham group in the dysphagia rating score only over the course of the treatment, while no significant differences in the other scales were recorded between groups. Data are expressed as mean±SE.

There were no significant differences between active and sham rTMS either in NIHSS, BI, or grip strength ($F=1.6$; df=1.2 (10.5) $p=0.23$ for NIHSS and $F=0.96$; df=1.1 (10.2), $p=0.36$ for BI, and $F=3.04$, df=1.9 (17); $p=0.076$ for grip strength) (figure 2B–D).

A repeated-measures ANOVA showed a no significant interaction involving subgroups (dysphagia grade III vs grade IV)× time (pre-, postsession, first- and second-month follow-up) ($F=1.9$, df=1.8 (16); $p=0.33$).

DISCUSSION

Dysphagia is usually managed using compensatory strategies (early nasogastric feeding, thickened fluids, percutaneous endoscopic gastrostomy (PEG) feeding), but rehabilitation strategies aiming to reduce the impairment are scarce and poorly supported by evidence. In the past 10 years, mainly due to work pioneered by Hamdy and colleagues, TMS, positron emission tomography (PET) and magnetoencephalography (MEG) studies have helped our understanding of the neural anatomy and physiology of swallowing.[11 24–27]

The main finding in this study was that five daily sessions of rTMS over the oesophageal motor cortex of both hemispheres can have a beneficial effect on dysphagia that is maintained for up to 2 months. We hypothesise that bilateral stimulation of the cortical swallowing motor areas increased the excitability of corticobulbar projections to brainstem swallowing nuclei which then led to an improvement in swallowing.

The effect on dysphagia was clear in both patient groups and was greater than the effect on other measures of general motor function. Indeed, almost all patients who received real rTMS recovered swallowing with different degrees of improvement immediately after the fifth session, and this improvement was maintained for at least 2 months, while patients who received sham rTMS still had overt dysphagia at the end of 2 months. This excellent response could be related partially to the fact that control of swallowing is usually bilateral, whereas the lesion in LMI is usually unilateral. Thus, the remaining intact ipsilateral premotor neurons and the contralateral centre in the medulla oblongata may eventually begin to operate and overcome the severity and long-term persistence of dysphagia. If so, the functional recovery that was observed in our patients could be due to rTMS having an effect to speed up this natural process of recovery. However, we cannot exclude other effects on less direct pathways from the cortex to the brainstem that could contribute to recovery in our patients, particularly those in the brainstem infarct subgroup in whom lesions were bilateral.

The absence of significant improvement in grip strength (from grade 3 to grade 2) after rTMS in LMI could be due to the fact that a recovery of grip strength may depend more exclusively on unilateral projections of the corticospinal tract from the contralateral hemisphere, and which cannot be replaced in function by intact projections that pass through the undamaged contralateral brainstem. It should also be noted that the initial mild weakness in LMI was due to the presence of ataxia, which in turn led to ill-sustained contractions and apparent weakness.

It is less clear why the clinical BI also improved more after real than sham rTMS, especially since there was no significant difference in effect on a second clinical measure, the NIHSS. It is known from both physiological and imaging studies that the effect of rTMS occurs not only at the site of stimulation but also in the surrounding connecting structures via activation of synaptic inputs to those sites.[15 28–30] These include right dorsal premotor cortex (PMd), bilateral ventral premotor cortex, supplementary motor area, somatosensory cortex, cingulate motor area, left posterior temporal lobe, cerebellum and caudate nucleus. It is possible that changes in activity in any or all of these regions could lead to some improvement in some overall clinical scores. The fact that no changes in BI were seen in the group of patients with brainstem infarction may be related to the severity of the initial weakness and bilateral lesions in many of these cases. Indeed, in a previous study of patients with stroke, Khedr *et al*[14] reported that patients with extensive infarction or dense hemiplegia did not respond well to rTMS.

Although our promising data suggest that rTMS may be a useful adjuvant therapy in addition to conventional treatment of specific syndrome of posterior fossa stroke, the number of patients was small, and further studies are needed to verify the findings before the technique can be applied more generally.

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Competing interests None.

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Patient consent Obtained.

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