Clinical Neurophysiology 127 (2016) 1907–1913

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Repetitive transcranial magnetic stimulation for rehabilitation of poststroke dysphagia: A randomized, double-blind clinical trial

Juan Du [a,1], Fang Yang [b,*,1], Ling Liu [b,1], Jingze Hu [b], Biyang Cai [b], Wenhua Liu [b], Gelin Xu [b], Xinfeng Liu [a,b,*]

[a] Department of Neurology, Jinling Hospital, Second Military Medical University, Nanjing 210002, China
[b] Department of Neurology, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, China

ARTICLE INFO

Article history:
Accepted 30 November 2015
Available online 11 December 2015

Keywords:
Dysphagia
Ischemic stroke
Repetitive transcranial magnetic stimulation (rTMS)
Rehabilitation
Motor evoked potentials (MEPs)

HIGHLIGHTS

- Repetitive transcranial magnetic stimulation (rTMS) has been increasingly used to treat aphasia and motor impairment following stroke; however, little is known about its effect on swallowing function.
- We demonstrated the long-term neurophysiological effects of rTMS on swallowing recovery in stroke patients.
- Repetitive TMS might help improve swallowing function in patients with dysphagia at the early stage of stroke.

ABSTRACT

Objective: This randomized, sham-controlled, double-blind study was conducted to investigate the effects of high-frequency versus low-frequency repetitive transcranial magnetic stimulation (rTMS) on patients with poststroke dysphagia during early rehabilitation.
Methods: Forty patients with poststroke dysphagia were randomized to receive five daily sessions of sham, 3-Hz ipsilesional, or 1-Hz contralesional rTMS. Swallowing function, the severity of stroke and functional disability, and cortical excitability were examined before, immediately after five daily sessions, as well as the first, second, and third month after the last session.
Results: At baseline, no significant differences between groups were observed in terms of demographic and clinical rating scales. However, a significantly greater improvement in swallowing function as well as functional disability was observed after real rTMS when compared with sham rTMS, which remained 3 months after the end of the treatment sessions. In addition, 1-Hz rTMS increased cortical excitability of the affected hemisphere and decreased that of the non-affected hemisphere; however, 3-Hz rTMS only increased cortical excitability of the affected hemisphere.
Conclusion: rTMS (both high and low frequency) improved swallowing recovery in patients with poststroke dysphagia, and the effects lasted for at least 3 months.
Significance: rTMS appears to be a beneficial therapeutic modality for patients with dysphagia during the early phase of stroke.

1. Introduction

Dysphagia is a common and potentially fatal complication following stroke (Martino et al., 2005). It afflicts a large number of patients with hemispheric stroke (Martino et al., 2005) and brain-stem infarction (Horner et al., 1991). Poststroke dysphagia is associated with an increased risk of mortality, and it may lead to severe complications including malnutrition, dehydration, and aspiration pneumonia (Teasell et al., 1994; Dziewas et al., 2004; Martino et al., 2005). Most patients recover from dysphagia within

* Corresponding authors at: Department of Neurology, Jinling Hospital, Nanjing University School of Medicine, 305 East Zhongshan Road, Nanjing 210002, Jiangsu Province, China (F. Yang). Department of Neurology, Jinling Hospital, Second Military Medical University, 305 East Zhongshan Road, Nanjing 210002, Jiangsu Province, China. Tel.: +86 25 80863485; fax: +86 25 84664563 (X. Liu).
E-mail addresses: yangfang021011@163.com (F. Yang), xfliu2@vip.163.com (X. Liu).
[1] These authors contributed equally to this work and share first authorship.

http://dx.doi.org/10.1016/j.clinph.2015.11.045
1388-2457/

a few weeks, but the extent of recovery of swallowing varies widely from patient to patient (Martino et al., 2005). The treatment options for poststroke dysphagia remain limited despite its frequent occurrence. In recent years, effective neurostimulation techniques promoting cortical neuroplasticity have become available to improve swallowing function and reduce dysphagia-related complications (Ridding and Rothwell, 2007).

Repetitive transcranial magnetic stimulation (rTMS) is a safe, painless, and noninvasive method of stimulation for modulating cortical excitability (Ridding and Rothwell, 2007). Existing evidence has demonstrated that low-frequency (1 Hz) rTMS decreases the cortical excitability (Mansur et al., 2005; Fregni et al., 2006; Kobayashi et al., 2004), whereas high-frequency ($\geqslant$3 Hz) rTMS increases the cortical excitability (Peinemann et al., 2004; Pascual-Leone et al., 1998). A few studies found that rTMS over the swallowing motor cortex induced the excitability of direct corticobulbar projections to the swallowing muscles (Gow et al., 2004), thereby enhancing swallowing functions (Park et al., 2013; Khedr and Abo-Elfetoh, 2010). However, few studies have compared the effects of high-frequency versus low-frequency stimulation on dysphagia patients after stoke.

Thus, in the present prospective, randomized, sham rTMS-controlled, double-blinded clinical trial, we investigated the efficacy and safety of rTMS on poststroke dysphagia by comparing high-frequency, low-frequency, and sham rTMS groups, and continued follow-up for 3 months. In addition, we studied the changes in cortical excitability after treatment sessions.

2. Methods

2.1. Patients

Fifty-seven patients with poststroke dysphagia were recruited consecutively from April 2013 to January 2014. All patients were admitted to the Department of Neurology, Jinling Hospital, Jiangsu Province, China. Each patient fulfilled the following inclusion criteria: dysphagia secondary to first-ever monohemispheric ischemic stroke, single infarction as confirmed by a CT or MRI scan; and the time from onset of symptoms was <2 months. Exclusion criteria included other concomitant neurological diseases, fever, infection, prior administration of tranquilizer, severe aphasia or cognitive impairment, inability to complete the follow-up, and other contraindications for rTMS. All participants gave their informed written consent prior to their inclusion in the study, and this study was approved by the Internal Review Board of Jinling Hospital. This clinical trial was conducted and reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The details of the trial protocol are outlined in clinicaltrials.gov (ClinicalTrials.gov Identifier: ChiCTR-TRC-12003100). A flow chart for patient selection is shown in Fig. 1.

2.2. Clinical assessment

A neurologist conducted examinations to diagnose dysphagia and assess the severity of dysphagia. The diagnosis of dysphagia was based on a swallowing questionnaire (Parker et al., 2004) confirmed by bedside physical examination (Logemann et al., 1999). Patients were asked to swallow a small volume of water (cup), and any signs of dysphagia such as coughing, oral residue, delayed swallow, throat clearing, choking, and reduced laryngeal elevation were evaluated and recorded during swallowing. 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 and recorded (Logemann et al., 1999). Dysphagia was scored using the Standardized Swallowing Assessment (SSA) (Perry, 2001a,b; Perry and Love, 2001), the water swallow test (Suiter and Leder, 2008; DePippo et al., 1992), and degree of dysphagia (DD) (Ertekin et al., 2000). The National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989), Barthel Index (BI) (Mahoney and Barthel, 1965), and modified Rankin Scale (mRS) were used to assess the severity of stroke and functional disability.

2.3. Randomization

The patients enrolled were randomized as high-frequency (3-Hz), low-frequency (1-Hz), and sham (control) rTMS groups. Treatment allocations were kept in sequentially numbered sealed opaque envelopes and opened only at the time of enrollment. This study was approved by the Jinling Hospital Ethical Committee.

2.4. Determining cortical excitability

2.4.1. Preparation

Each subject was seated comfortably in a quiet room and was asked to relax as much as possible. Electromyography (EMG) recordings from mylohyoid muscles (representing oral swallowing musculature) were detected using two pairs of silver–silver chloride surface electrodes (Alpine biomed ApS, Skovlunde, Denmark). Each pair had an inter-electrode distance of 1 cm, with each electrode positioned submentally, 2 cm lateral to the midline, one over the left mylohyoid muscle and the other over the right (Hamdy et al., 1996). The EMG recording system (Danteckeypiont, Skovlunde, Denmark) consisted of filters set at 20 Hz to 10 kHz, with a sensitivity of 50 μV/division and a recording time window of 50 ms. All magnetic stimulations were carried out using a MagPro X100 stimulator (MagVenture Company, Farum, Denmark) with a figure-of-eight coil (outer diameter of one wing: 9 cm).

2.4.2. Determination of resting motor threshold and motor evoked potential

Single-pulse TMS was applied to both hemispheres separately in order to measure cortical excitability (resting motor threshold (rMT) and the motor evoked potential (MEP)) for each patient. The coil was first located at the vertex of cranium, then positioned 2–4 cm anteriorly and 4–6 cm laterally, and moved around in this region to obtain the highest MEP recording to locate the mylohyoid cortical area of hemisphere (Hamdy et al., 1996). The location yielding the highest MEP recording was termed "hot spot," and we delivered magnetic stimulation to that point. Then, single-pulse TMS was delivered to the "hot spot," decreasing in steps of 2% of the stimulator output.

The rMT is defined as the minimal stimulus intensity capable of inducing MEP of >100-μV amplitude in three of five consecutive trials on mylohyoid muscles. The amplitude of MEP to cortical stimulation was measured as the peak-to-peak voltage (μV) of the EMG response. The latency of MEP was determined as the interval between the onset of the stimulation and the onset of the EMG response (ms). If MEPs were absent upon stimulation of the stroke-affected hemisphere, the "hot spot" was defined as being symmetrical to the unaffected hemisphere.

2.5. Treatments

Each patient received rTMS daily for 5 consecutive days. Patients in the high-frequency stimulation group received 3-Hz rTMS for 10 s, with an inter-train interval of 10 s, and 40 trains with a total of 1200 pulses at 90% rMT on the affected hemisphere. For low-frequency stimulation, patients received 1-Hz rTMS for 30 s, with an inter-train interval of 2 s, and 40 trains with a total of 1200 pulses at 100% rMT on the unaffected hemisphere. The coil