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Vagus nerve magnetic modulation facilitates dysphagia recovery in patients with stroke involving the brainstem - A proof of concept study

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ABSTRACT

Background & aims: Stroke involving the brainstem (SBS) causes severe oropharyngeal dysphagia (OD). Research on the therapeutic efficacy of vagus nerve modulation (VNM) by using repetitive transcranial magnetic stimulation (rTMS) in SBS patients with OD has been limited thus far. We aimed to assess the effect of VNM by using rTMS in improving swallowing function after SBS.
Method: We conducted a sham-controlled, double-blinded, parallel pilot study in 28 SBS patients with OD randomly allocated to a real rTMS group (n = 13; TMS_{real}) or a sham group (n = 15; TMS_{sham}). For VNM, 5-Hz rTMS was applied to the left mastoid in 10 sessions. We evaluated all patients for swallowing function before and after rTMS conditioning, assessed on the 8-point Penetration–Aspiration Scale (PAS) through videofluoroscopy and the Australian Therapy Outcome Measures–Swallowing scale (AusTOMs). We measured the amplitude and latency of cricopharyngeal motor evoked potentials (CP-MEPs) as the neurophysiological parameters.
Results: TMS_{real} exhibited significant improvement in all swallowing outcomes—neurophysiological, radiological, and functional—compared with TMS_{sham}: We noted higher CP-MEP amplitude ($p = 0.004$), shorter CP-MEP latency ($p = 0.004$), a lower PAS score ($p = 0.001$), and a higher AusTOMs score ($p < 0.001$) following rTMS in TMS_{real}. Moreover, the neurophysiological improvements were significantly correlated with the functional outcomes ($p < 0.05$).
Conclusions: Our results encourage the application of VNM by using rTMS for improving swallowing function after SBS. The immediate therapeutic effects suggest that this novel intervention can be an effective complementary therapy to traditional oropharyngeal rehabilitation.
Clinical trial registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02893033.

Introduction

Stroke involving the brainstem (SBS) causes a wide spectrum of neurologic deficits, particularly oropharyngeal dysphagia (OD), which may compromise nutrition and respiratory function [1,2]. SBS patients with chronic OD have the worst recovery because the center for the initiation and integration of swallowing sequences, located in the brainstem, is affected [1–5]. Prognosis remains poor among these patients; therefore, further research focusing on SBS with OD is warranted. The current therapies for OD, largely involving compensatory strategies or restorative training, have yielded limited efficacy in recovering swallowing function [6].

Abbreviations: AusTOMs, Australian Therapy Outcome Measures–Swallowing scale; CP-MEPs, cricopharyngeal motor evoked potentials; EMG, electromyographic; OD, oropharyngeal dysphagia; PAS, 8-point Penetration–Aspiration Scale; rTMS, repetitive transcranial magnetic stimulation; SBS, stroke involving the brainstem; tDCS, transcranial direct current stimulation; VNM, vagus nerve modulation; VNS, vagus nerve stimulation.

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Clearly, additional therapeutic approaches are required to enhance the recovery of swallowing function following SBS.

Noninvasive brain stimulation can be administered to enhance the recovery of swallowing function by modifying the excitability of the corticobulbar motor system in controlling deglutition muscles; the two most commonly used techniques are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Preliminary studies have used either high-frequency [7] or low-frequency [8] daily rTMS regimens to improve swallowing function. Although the rationale underlying target selection for rTMS application differed among studies, the majority of the results demonstrated a significantly greater improvement in functional outcome measures as well as a higher amplitude of motor evoked potentials in swallowing muscles bilaterally after intervention [9].

Recent studies on left vagus nerve modulation (VNM) using an implanted electrode have demonstrated that VNM paired with limb rehabilitation can efficiently facilitate motor function in rat stroke models [10–12], or in hemiplegic humans [13]. VNM causes the nucleus tractus solitarius to release plasticity-enhancing neurotransmitters, including acetylcholine, norepinephrine, and serotonin [10,12]. Thus far, little is known about the application of VNM for facilitating OD recovery of stroke survivors. The results of a series of experiments performed on healthy individuals indicated that extracranial vagus nerve excitation before cortical stimulation facilitates esophageal motor evoked potential (MEP) responses [14,15]. This phenomenon can be predicted on the basis of the extensive brainstem convergence from the afferent fibers of vagal nerves, which terminates within the nucleus tractus solitarius of the dorsal brainstem, and the efferent interneurons, which synapse with nucleus ambiguous and other swallowing motor nuclei. When the motor neurons in the brainstem are activated by the afferent electric current or the Valsalva maneuver [16], the primed motor nuclei reach an excited status close to their firing threshold, thus facilitating the subsequent esophageal MEPs. On the basis of this observation, the rationale of the present study design is that extracranial vagus stimulation using rTMS promotes swallowing recovery in stroke patients.

VNM has several extracranial stimulation targets. Rather than the anterior sternocleidomastoid approach, in which a smaller coil (50-mm diameter) is placed 2 cm below the angle of the jaw [14], we preferred the mastoid approach [17–19], because of its anatomic accessibility and recruited neural structure. We used a larger figure-eight coil (95-mm outer diameter), which cannot fit into the neck properly and remain close to the target area during the modulation period. Furthermore, compared with neck stimulation, proximal mastoid stimulation may recruit more nervous structures, such as intracisternal roots at the level of the medulla [20] and auricular branches of the vagus nerve [21,22]. Considering the promising effects of implanted vagus nerve stimulation (VNS) on poststroke motor recovery and cortical rTMS modulation on patients with dysphagia, we hypothesize that repetitive VNM facilitates recovery from dysphagia in SBS survivors.

In this study, we investigated the immediate effect of a long-term rTMS conditioning protocol on the vagus nerve for restoring swallowing function in SBS patients with chronic OD and identifying whether this innovative method could be applied as an effective therapy complementary to traditional oropharyngeal rehabilitation.

Methods

Patients

We included 55 patients with ischemic or hemorrhagic stroke with chronic bulbar manifestation. In total, 55 consecutive patients were assessed for eligibility. Among them, 5 declined to participate and 20 were excluded. The remaining 30 patients satisfied the following inclusion criteria: (1) a diagnosis of stroke-related dysphagia resulting from a first ever brainstem infarction or hemorrhage, which was confirmed through magnetic resonance imaging and presented clinically with bulbar signs, including a flaccid tone of the palate and tongue, bulbar muscle weakness and fasciculations, and a decreased gag reflex; 2) at least 3 months since the first stroke and a stable medical and cognitive condition. Exclusion criteria included unstable cardiac dysrhythmia, fever, infection, hyperglycemia, epilepsy, and prior administration of tranquilizers. We excluded patients with intracranial metallic devices, pacemakers, or any other devices. The study was approved by the local institutional review board of Taipei Veterans General Hospital. In total, 30 patients were recruited, and their written informed consent was obtained before participation. The trial was registered on clinicaltrials.gov (NCT02893033). Two patients in the experimental group (TMS_{real}) dropped out at subsequent intervention. Table 1 lists the biographical data of the enrolled patients.

Experimental design

We conducted a sham-controlled, double-blinded parallel study. A researcher blinded to the assessment assigned the patients to either TMS_{real} or the control group (TMS_{sham}). TMS_{real} comprised 13 patients, each of whom underwent 5-Hz rTMS. TMS_{sham}

Table 1
Demographic and clinical characteristics of all patients.

	Experiment Group(n = 13)	Sham group(n = 15)	p
Number	13	15	
Male/Female	12/1	9/6	0.053
Age	68.5 ± 12.8	72.9 ± 12.2	0.319
Months post stroke	25.2 ± 42.2	21.6 ± 19.5	0.633
Feeding route (NG/Oral)	11/2	11/4	0.464
SBS characteristics			
Etiology (Infarction/Hemorrhage/Both)	11/1/1	10/4/1	0.425
Lesion side (Right/Left/Bilateral)	2/7/4	1/8/6	0.690
Location (Midbrain/Pons/Medulla/Cerebellum/Multiple)	0/6/1/1/5	0/9/1/0/5	0.711
Clinical characteristics			
Hypertension (%)	90.9%	93.3%	0.916
Diabetes mellitus (%)	27.3%	40.0%	0.339

* Significant difference in intergroup comparisons ($p < 0.05$).
Abbreviations: NG, nasogastric tube.