Noninvasive Brain Stimulation May Improve Stroke-Related Dysphagia

A Pilot Study

Sandeep Kumar, MD; Cynthia W. Wagner, MS, CCC-SLP; Colleen Frayne, MS, CCC-SLP; Lin Zhu, BS; Magdy Selim, MD, PhD; Wuwei Feng, MD, MS; Gottfried Schlaug, MD, PhD

Background and Purpose—Treatment options for stroke-related dysphagia are currently limited. In this study, we investigated whether noninvasive brain stimulation in combination with swallowing maneuvers facilitates swallowing recovery in dysphagic stroke patients during early stroke convalescence.

Methods—Fourteen patients with subacute unilateral hemispheric infarction were randomized to anodal transcranial direct current stimulation (tDCS) versus sham stimulation to the sensorimotor cortical representation of swallowing in the unaffected hemisphere over the course of 5 consecutive days with concurrent standardized swallowing maneuvers. Severity of dysphagia was measured using a validated swallowing scale, Dysphagia Outcome and Severity scale, before the first and after the last session of tDCS or sham. The effect of tDCS was analyzed in a multivariate linear regression model using changes in Dysphagia Outcome and Severity Scale as the outcome variable after adjusting for the effects of other potential confounding variables such as the National Institutes of Health Stroke Scale and Dysphagia Outcome and Severity scale scores at baseline, acute ischemic lesion volumes, patient age, and time from stroke onset to stimulation.

Results—Patients who received anodal tDCS gained 2.60 points of improvement in Dysphagia Outcome and Severity scale scores compared to patients in the sham stimulation group who showed an improvement of 1.25 points (P=0.019) after controlling for the effects of other aforementioned variables. Six out 7 (86%) patients in tDCS stimulation group gained at least 2 points of improvement compared with 3 out 7 (43%) patients in the sham group (P=0.107).

Conclusions—Because brain stem swallowing centers have bilateral cortical innervations, measures that enhance cortical input and sensorimotor control of brain stem swallowing may be beneficial for dysphagia recovery. (Stroke. 2011;42:1035-1040.)

Key Words: dysphagia ■ noninvasive brain stimulation ■ stroke recovery ■ swallowing recovery ■ transcranial direct current stimulation

Dysphagia is a potentially fatal complication of stroke. It affects numerous patients with hemispheric strokes and has high rates of complications, even after adjusting for stroke severity. Because hemispheric infarcts are the major subtype of ischemic stroke in the population, it can be assumed that the magnitude of dysphagia burden attributable to such strokes is large. Despite its frequent occurrence, treatment of stroke-related dysphagia remains limited. The usual practice is to provide nutritional support via alternative feeding methods, until swallowing functions recover; however, such methods fail to protect against complications of dysphagia such as aspiration pneumonia. Development of an effective intervention that improves swallowing in the early course of stroke recovery will be helpful in curtailing dysphagia-related complications and improving swallowing functions.

Swallowing functions are subserved by a distributed brain network, although involvement of the inferior peri-rolandic sensorimotor cortex appears consistent across studies. Disruption of projections from these cortical regions to the brain stem “swallowing centers” produces dysphagia with hemispheric strokes. Different lines of evidence suggest that recovery of swallowing functions occurs via expansion of the pharyngeal representation in the uninvolved hemisphere, possibly ensuring greater input to the brain stem swallowing centers. Cortical stimulation techniques may facilitate this process in patients with hemispheric lesions, in whom the brain stem and peripheral structures are intact but the upper echelons of the swallowing apparatus are dysfunctional. Repetitive transcranial magnetic stimulation over the swallowing motor cortex in healthy volunteers induces a long-term effect on the excitability of corticobulbar projections to...
the pharynx\textsuperscript{12} and may improve swallowing functions in dysphagic stroke patients.\textsuperscript{13}

Transcranial direct current stimulation (tDCS) is another noninvasive brain stimulation technique that utilizes weak direct current to produce shifts in neuronal excitability\textsuperscript{14,15} and can be combined with swallowing maneuvers or exercises. It has generated great interest recently for its ease of use, patient tolerability, and safety profile, which is of particular importance during the acute/subacute phases of a stroke. It has been shown to improve motor functions in chronic stroke patients.\textsuperscript{16,17} Moreover, presence of a sham mode makes it possible to examine its effects in a blinded trial paradigm.\textsuperscript{18} More recently, investigators have shown that application of anodal tDCS to the pharyngeal motor cortex in healthy human subjects increases pharyngeal excitability in an intensity-dependent manner.\textsuperscript{19} In this pilot study, we investigated the effects of anodal tDCS versus sham stimulation of the unaffected hemisphere for improving dysphagia in the acute–subacute stroke phase.

Materials and Methods

This was an investigator-initiated, prospective, single-center, blinded pilot trial. All participants were recruited from our inpatient stroke service, were between 24 to 168 hours after their first ischemic stroke at time of enrollment, and had dysphagia secondary to a new unilateral hemispheric infarction. They were all evaluated by speech and language pathologists specializing in dysphagia (C.W. and C.F.) who were blinded to study allocation and rated swallowing impairments using a validated dysphagia scale, Dysphagia Outcome and Severity scale (DOSS).\textsuperscript{20} DOSS scores range from 1 to 7, with 7 representing normal swallowing and 1 representing severe dysphagia. DOSS rates the functional severity of dysphagia and recommends a dietary level, independence level, and type of nutrition representing normal swallowing and 1 representing severe dysphagia. DOSS demonstrates it to be centered over the caudal end of the primary motor cortex in a healthy volunteer.

We recorded patient age, gender, lesion site, time in hours from stroke onset (time when patient was last seen normal if precise time of onset was unknown) to stimulation, lesion volume, and NIHSS scores as measures of stroke severity before stimulation. Acute ischemic lesion volumes were computed on diffusion-weighted imaging sequences on patient’s brain MRI using customized software routines. The details of specific MRI sequence parameters, imaging processing, and volumetric analysis are described elsewhere.\textsuperscript{21} Two patients, unable to undergo an MRI, had their ischemic lesion volumes computed on a subacute head CT (obtained within 48–96 hours after symptoms onset). Patients were randomized to receive either anodal tDCS or sham stimulation to the unaffected hemisphere using simple randomization and were blinded to their stimulation allocations. Using the international 10- to 20-EEG electrode system for guidance,\textsuperscript{22} a saline-soaked anodal electrode was placed over the undamaged hemisphere, mid-distance between C3 and T3 on the left or C4 and T4 on the right, with a reference electrode over the contralateral supraorbital region. This montage was expected to generate maximal current density over the inferior sensorimotor cortex and the neighboring premotor brain regions critical for reorganization of the swallowing motor cortex after a dysphagic stroke.\textsuperscript{10,11,23} We confirmed the location of the stimulating electrode and its proximity to the targeted regions by coregistering it with high-resolution T1-weighted brain MRI scans (Figure). A DOSS score was obtained immediately before stimulation sessions (DOSS-pre) and after the fifth session (DOSS-post).

The tDCS/sham was applied in conjunction with standardized swallowing maneuvers to provide adequate sensory and motor activation of the swallowing cortex.\textsuperscript{24} All participants sucked on a lemon-flavored lollipop during these sessions. Patients reporting dryness of mouth were provided with 1 to 2 small ice chips intermittently. Patients were instructed to “swallow hard” every 30 seconds, thereby generating approximately 60 effortful swallows during each session. We used gesticulations to encourage aphasic patients to swallow at regular intervals. Occurrence of a swallow response was assessed by observing the movement of the thyroid cartilage or by palpating its excursion in patients with thicker necks. All subjects were able to follow study swallowing instructions appropriately. Anodal tDCS (2 mA for 30 minutes) or sham was
applied daily to the nonlesional hemisphere for 5 consecutive days. The tDCS was delivered through a battery-driven constant current stimulator (Phoresor; Iomed, Salt Lake City, UT), with the following electrode dimensions: 3\( \times \)5 cm for the anode and 5\( \times \)6 cm for the reference electrode.

The study was approved by our Institutional Review Board. A written informed consent was obtained from the patients or their legal representative before enrollment.

Statistical Analysis

We analyzed the effect of stimulation (tDCS or sham, entered as a binary variable) on improvement in dysphagia scores after adjusting for the potential confounding effects of other important variables, ie, stroke severity as assessed by baseline NIHSS score, ischemic lesion volume, baseline DOSS score, patient age, and time from stroke onset to stimulation. A correlation analysis and collinearity assessment among all independent variables were checked before the final model. A responder variable (yes or no) was defined as at least 2 points of improvement on DOSS. A logistic regression was applied with the same covariates from the general linear regression model as a secondary outcome analysis. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Fourteen patients were recruited and randomized to anodal tDCS or sham stimulation group in a 1:1 fashion. The important characteristic of our patient sample is tabulated in Table 1. All patients who consented to participate in this study tolerated the sessions well; stimulation was not curtailed in anyone because of discomfort or fatigue. No adverse events, such as seizures, headaches, visual disturbances, or significant skin irritation, were observed. Two patients in the sham group but none in the tDCS group underwent percutaneous endoscopic gastrostomy placement after their trial participation.

Multivariate Analysis

NIHSS scores and DOSS scores at baseline, acute ischemic lesion volume, time to stimulation, and age were initially
Table 2. Results of Anodal tDCS Versus Sham Stimulation in Multivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>Anodal tDCS</th>
<th>Sham</th>
<th>P</th>
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<tbody>
<tr>
<td>Change in DOSS scores</td>
<td>2.6‡ (1.91–3.29)</td>
<td>1.26† (0.57, 1.95)</td>
<td>0.019‡</td>
</tr>
<tr>
<td>≥2-point improvement</td>
<td>6/7 (86%)</td>
<td>3/7 (43%)</td>
<td>0.107*</td>
</tr>
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<td>in DOSS score</td>
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*P is based on a logistic regression model with baseline DOSS, NIHSS, age, time to treatment, and stimulation group as covariates.
†P based on a general linear regression model with baseline DOSS, NIHSS, age, time to treatment, and stimulation group as covariates.
‡Least square mean and 95% confidence interval estimated from the general linear model.

Also included for a generalized linear model; however, NIHSS and lesion volume were highly correlated (r=0.84 and P=0.0002), and further collinearity diagnostics revealed a significant collinearity (tolerance >0.1; variance inflation factor <10) between the 2 variables. Thus, the latter was eliminated from the model. In summary (Table 2), our results show that patients who received anodal tDCS gained 2.60 (95% CI, 1.91–3.29) points on DOSS, whereas patients in the sham stimulation group improved by 1.25 (95% CI, 0.57–1.95); the difference between 2 groups reached a statistical significance with P=0.019. DOSS at baseline (P=0.045) and NIHSS at baseline (P=0.049) were significantly associated with improvement on DOSS scores. Age (P=0.228) was not a good predictor for improvement based on our model analysis. Our secondary outcome included a logistic regression analysis that was based on at least 2 points of improvement with DOSS. Six out of 7 patients (86%) in the tDCS group had ≥2 points of improvement on their DOSS scores versus 3 out 7 patients (43%) in the sham stimulation group (P=0.107).

Discussion

The findings of this pilot study show that repeated application of anodal tDCS to the unaffected swallowing cortex in combination with timed effortful swallowing is associated with significant swallowing improvement over sham after adjusting for the effects of baseline stroke and dysphagia severity, age, and time to stimulation in patients with acute–subacute unilateral hemispheric infarction. Our results also attest to the feasibility and tolerability of tDCS in this stroke subpopulation during early phases of stroke recovery.

The brain stimulation effect might be explained by an augmentation effect of the naturally occurring changes in the unaffected swallowing cortex.10,11 Combining the sensorimotor effects of swallowing maneuvers with simultaneous brain stimulation of the unaffected hemisphere may have been an important component of the effect. Sensory input from the pharynx is known to increase excitability of the swallowing sensorimotor cortex through convergent afferent activity,12 and pharyngeal sensory stimulation in dysphagic stroke patients produces an increase in the excitability of the swallowing motor cortex of the unaffected hemisphere.24 However, studies investigating induction of plasticity in the human motor cortex using paired associative paradigm have shown that cortical stimulation, if paired with peripheral stimulation of the somatosensory afferents, leads to greater increases in cortical excitability than produced by stimulation alone and induces topographically specific plastic changes.25 This increase in excitability was prevented by using dextromethorphan, which is known to block development of long-term potentiation.26 In animal studies, motor skill learning has been shown to produce long-term potentiation and long-term depression, leading to changes in synaptic strength in the primary motor cortex.27 Cortical stimulation studies in experimental stroke models have shown stronger effects when peripheral sensorimotor activities were combined with central stimulation.28 More recently, investigators29 have shown that training in humans or low-frequency stimulation in mouse M1 slices produces release of brain-derived neurotrophic factor, which is necessary to induce long-term synaptic plasticity from direct current stimulation. In chronic stroke patients, combining peripheral nerve stimulation or peripheral sensorimotor activities with tDCS facilitates the beneficial effects of training on motor performance beyond levels reached by each intervention alone.30,31 Thus, data from diverse sources indicate that combining repetitive peripheral sensorimotor stimulation with noninvasive brain stimulation can potentiate relearning and consolidation of motor skills to a level unattainable by any of these interventions alone in subacute or chronic stroke patients and appears to have benefitted our subjects.

Our statistical methods were designed to control for discrepancies of important predictors of dysphagia recovery between groups that the randomization procedures may have failed to correct in our small sample. Although there is little data published on predictors of dysphagia recovery in stroke patients, baseline NIHSS score,32 stroke lesion volume,33 and age34 have been found to be important factors influencing functional recovery in stroke patients and were included in the analysis. Because swallowing functions in our patients were expected to recover over time, time to stimulation was also included in our analysis. Our model shows that baseline NIHSS, DOSS scores, and anodal tDCS were associated with improvement. Introduction of all these variables could have overfitted our model and exhausted degrees of freedom for estimation with a small sample size. However, the intent of this analysis was to gain an understanding about the important covariates influencing swallowing recovery and adjust for their effects on experimental treatment and not to try to build a predictive model.

It is possible that in a minority of patients, especially in those with more circumscribed lesions, the ipsilesional hemisphere may have played a role in swallowing recovery and accounted for some variability in responses to stimulation. This poses an important question whether uniform application of anodal tDCS to the uninvolved hemisphere will benefit all such patients. However, because brain stem swallowing centers have bilateral innervations with little evidence for transcortical inhibition,35 we hypothesized that stimulation of either hemisphere would produce an increase in pharyngeal excitability. Furthermore, stimulation of the uninvolved hemisphere was less likely to be affected by neuronal loss or tissue damage and responses would be more
uniform; stimulating the nonlesioned hemisphere was also expected to be safer with respect to any potential seizures risk or tissue damage in the acute stroke phase. The optimal dose for stimulating the pharyngeal motor cortex has not been established. A recent report suggests that doses higher than that used for stimulating the primary motor cortex are necessary to produce comparable responses from the swallowing cortex.19 Our protocol predates the publication of this report and alternative doses can be tried in future studies to assess their superiority. We chose our dose based on previous study protocols that have shown that application of 2 mA to the dorsolateral frontal lobes is effective and well-tolerated.36 Our decision to perform 5 sessions of stimulation was based on recent reports showing an additive effect of repeated session of tDCS37 and taking logistical considerations such as duration of hospitalization in mind. It is possible that more sessions may have produced a stronger effect. Other study limitations include nonroutine use of video-fluoroscopic swallowing evaluations in all subjects, which were performed based on clinical judgment of evaluating speech and language swallowing evaluations in all subjects, which were performed based on clinical judgment of evaluating speech and language physiologists. Although DOSS has excellent inter-rater reliability, it cannot capture pertinent details about changes in swallowing physiology in these subjects. In future studies, additional dysphagia assessment scoring tools should be obtained to tests the robustness of any treatment effect.

Conclusions

In conclusion, the results from this pilot study show a promising efficacy of anodal tDCS application with the swallowing cortex of the unaffected hemisphere combined with effortful swallowing maneuvers for improving dysphagia in stroke patients. Further studies are warranted to refine this promising intervention by exploring effects of stimulation parameters, frequency of stimulation, and timing of the intervention in improving swallowing functions in dysphagic stroke patients.

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Disclosures

None.

References


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无创性脑电刺激改善卒中相关性吞咽困难的预研究

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背景与目的：目前治疗卒中相关性吞咽困难的措施有限。本研究中，我们观察了无创性脑电刺激结合吞咽动作训练是否有助于改善康复早期卒中相关吞咽困难患者的吞咽功能。

方法：14 例急性卒中相关性吞咽困难患者随机分入治疗组和对照组。治疗组接受 5 天经颅直流电刺激 (tDCS)，刺激区域为病变侧大脑半球的感知触觉/运动皮层代表区。对照组接受假刺激，两组同时接受标准化吞咽动作训练。吞咽困难的严重程度采用已经证实有效的“吞咽困难总分和严重程度量表 (DOSS)”来评价。在 tDCS 或假刺激首次治疗前、末次治疗后进行评估。在校正了诸如基线水平的美国国立卫生研究院卒中量表评分、DOSS 评分、急性期失语症基础、患者年龄、以及从卒中发生到接受刺激的时间等其他潜在的混杂变量影响后，以 DOSS 量表的变化为终点变量，采用多元线性回归模型分析 tDCS 的疗效。

结果：在调整前述其它变量的影响后，接受 tDCS 治疗患者的 DOSS 评分增加 2.60 分，高于假刺激组 DOSS 评分增加的 1.25 分 (P=0.019)。以 DOSS 提高至少 2 分为临床显著改善，tDCS 组的 7 例中有 6 例，而假刺激组 7 例患者中只有 3 例 (P=0.107)。

结论：由于无创性脑电刺激有助于卒中相关性吞咽困难的改善，可能有助于卒中相关性吞咽困难的恢复。

关键词：吞咽困难，无创性脑电刺激，卒中恢复，吞咽功能恢复，经颅直流电刺激

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