Effects of capsaicin on swallowing function in stroke patients with dysphagia: A randomized controlled trial

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Background/Aims: Dysphagia is a common complication after acute stroke. While there are several innovative treatments being tested to improve the swallowing function of stroke patients with dysphagia, our aim is to explore the use of readily available natural capsaicin in stroke patients with dysphagia. *Study design:* A randomized, double-blind study. *Methods:* Sixty-nine hospitalized stroke patients were enrolled in this study. The capsaicin intervention group received thermal tactile stimulation with supplementation of natural capsaicin and additional nectar viscosity boluses. The control group received stimulation and boluses with placebo. Swallowing function was evaluated before and after the 3-week treatment, using Volume-Viscosity Swallow Test, Eating Assessment Tool, Standardized Swallowing Assessment, and Water Swallow Test. *Results:* The score decreases in the Eating Assessment Tool and Standardized Swallowing Assessment of the capsaicin intervention group were significantly greater than that of the placebo control group ($P < .01$). Among the 60 patients, the capsaicin intervention group exhibited effectiveness in a higher number of patients (n = 27, 90%) than the placebo group (n = 9, 30%, $P < .001$). *Conclusions:* Regular use of natural capsaicin could promote the recovery of swallow function in stroke patients with dysphagia. The ample availability of natural capsaicin could provide a low cost, easily accessible, and safe alternative method to address dysphagia in stoke patients.

Key Words: Stroke—deglutition disorders—capsaicin—dysphagia—TRPV1 agonist

Introduction

As the population is aging rapidly in China, stroke has gradually become the top leading cause of death. Dysphagia is a common complication after acute stroke, affecting between 37%-78% of stroke survivors, as assessed by multiple evaluation methods.[1,2] Dysphagia may cause not only oral phase problems such as decreases in bolus formation along with declines in masticatory function and manipulation, but also pharyngeal phase problems such as pharyngeal residues and aspiration".[3] Therefore, dysphagia is often associated with pulmonary complications,[4] poor functional

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outcomes,[5] dehydration, poor nutritional status,[6] readmissions, and even mortality,[7] resulting in social, and psychological burdens that significantly reduce the quality of life for both patients and caregivers.

Sensory input is significant for the initiation and modulation of swallowing, promoting changes in neuronal circuits.[8] Damage to sensory information reduces the sensory feedback and the cortical control of swallowing.[9] The disruption of the connection between the sensory afferents of the cortex and the brainstem may be the reason for swallowing dysfunction in stroke patients. There is evidence that therapeutic sensory stimuli on the oropharynx can compensate for the loss of oropharyngeal sensitivity in dysphagic patients.[10] An enhanced oropharyngeal stimuli might improve the afferent sensorial input to the central pattern generator in the swallowing center of the brainstem, achieving the required threshold to trigger the swallow response.[11] The threshold could also be reduced to decrease oral transit time and promote pharyngeal response, which may minimize the risks of aspiration and aspiration pneumonia.[12]

Several innovative treatments have been tested to examine the types of stimulation beneficial for promoting rehabilitation of swallowing dysfunction in these patients. One of these treatments is based on increasing the oropharyngeal sensory input through the afferent pathways using thermal,[13] chemical,[14] electrical,[15] or physical stimuli.[16] Chemical stimulation of the oropharynx is mainly based on the use of natural agonists of the polymodal sensory receptors TRPV1, TRPA1, and TRPM8.

Capsaicin, a readily available component of peppers responsible for the spicy taste, has long been known as a specific agonist to TRPV1. Some previous studies mentioned that capsaicin use can reduce swallowing time and improve swallowing function.[17,18] Capsaicin could also increase the amplitude and velocity of esophageal body peristalsis.[19] In addition, long-term stimulation with capsaicin may increase the sensory input from the laryngopharynx to the central pattern generator, influencing the plasticity of synapses.[20] Hence, we believe that capsaicin could be a safe and effective alternative method on patients with dysphagia.

Shin et al. explored the effect of regular ingestion of capsaicin containing food on the latency of the swallowing response and reported that swallowing function was improved. However, only young adult participants were recruited in the research.[21] Some other studies limited their study demographics to elderly patients, with a mixed population of cerebrovascular disorder and neurodegenerative disease.[22-25] Nakato et al also examined the therapeutic effects of Capsaicin Plus (Sanwa Kagaku Kenkyusho Co., Ltd., Nagoya, Japan), containing capsaicin. While they concluded that the safety and efficacy of swallowing improved with shortened swallow response time,[26] regular use of this form of capsaicin might be hard for Chinese patients due to high cost or poor availability.

To address these limitations, the aim of this study was designed with a specific focus on the effects of readily available natural capsaicin in stroke patients with dysphagia, in order to address its clinical applications.

Methods

This study is a double-blind, randomized controlled study. It was conducted at Yancheng City No.1 People's Hospital from January to September 2018. It was approved by the Committee for Medical Ethics of Yancheng City No.1 People's Hospital, and a written informed consent was obtained from each patient prior to the study. The Clinical Trial registration number of this study is [2018]-(K015).

Subjects

Hemorrhagic or ischemic stroke patients within 1-week of admission were included with the following selection criteria. Patients must be clinically assessed with the Volume-Viscosity Swallowing Test (V-VST), presenting clinical signs of dysphagia, older than 55 years of age, scoring above a 7 on the Abbreviated mental test scale, and able to give informed consent and follow study procedures. Exclusion criteria were unstable health conditions such as pyrexia or heart and respiratory disease, history of previous other diseases that might be associated with the presence of dysphagia, refusal to participate, and bronchial asthma or chronic coughs.

Sixty-nine stroke patients met the entry criteria. Thirty-four patients were assigned to the intervention group, with 35 patients in the control group. Nine total patients met the exclusion criteria during the experiment phase. Five patients were discharged from hospital in less than three weeks. Two patients had a history of bronchial asthma, and 2 patients had a history of pyrexia.

Intervention

By adding 1 g of Sichuan red pepper powder to 50 mL of mineral water, a capsaicin concentration of bg150 μM/L was obtained, based on the Chinese Pharmacopoeia. A cotton swab soaked in the capsaicin solution at cold (4°C) temperature was used to dab the oropharyngeal mucosa region in the thermal tactile stimulation. A soft, fast touch no longer than 5 minutes was performed to minimize the mechanical effect of the stimulus. In addition, a 1mL nectar bolus of 150 μM/L capsaicin was administered to patients before each meal, as previous researches demonstrated that 150 μM/L was the most effective concentration for natural capsaicinoids.[22] Nectar viscosity was obtained by adding 3.5 g of thickener Resource ThickenUp (Nestlé Nutrition, Barcelona, Spain) to 100 mL of mineral water. Treatment was administered to patients three times per day before each meal for 3 weeks. The capsaicin and placebo solutions were prepared once weekly and preserved under refrigeration (4°C). In the control group, the solution and the nectar bolus were made to be identical to that in the intervention group, except for capsaicin. The randomization and supply of capsaicin were performed by a blinded pharmacist who was not involved in the study. Both groups received the same conventional dysphagia treatments such as orofacial muscle exercises, thickeners, postures, and therapeutic or compensatory maneuvers.

Swallowing Evaluation Measurements

Volume-Viscosity Swallow Test (V-VST)

V-VST was used to clinically assess the safety of impaired swallowing. This test uses three volumes and 3 viscosities together with a pulse oximeter to assess clinical signs of dysphagia.[27] It was administered daily to the patients during the treatment.

Eating Assessment Tool (EAT-10)

The Eating Assessment Tool was created by Belafsky et al to assess dysphagia symptom severity, quality of life, and treatment efficacy.[28] This assessment tool has been validated in Italian, Spanish, and Chinese translations. Higher score indicates higher self-perception of dysphagia while a score equal to or greater than 3 is considered abnormal. It was administered to the patients before and after the 3-week treatment.

Standardized Swallowing Assessment (SSA)

The Standardized Swallowing Assessment demonstrated strong feasibility with excellent sensitivity and specificity. It consists of 3 steps. The patients were clinically examined first, followed by administration of three 5 mL water boluses. The assessment is terminated if any abnormal conditions are met. Patients who passed the first assessment were given 60 mL water boluses in a beaker. Higher score indicates a decreased swallowing ability.[29] The test was administered to the patients before and after the 3-week treatment.

Water Swallow Test

The Water Swallow Test was a screening tool to identify individuals at risk of dysphagia,[30] which requires individuals to drink 30 mL of water without interruption. Those who stop, choke, cough, or show a wet-hoarse vocal quality during the test or for 1-minute afterwards are considered to have failed. The score is divided into 5 grades, with a higher grade indicating a decreased swallowing function. The treatment efficacy is considered effective only if the grade improves to less than or equal to 2. It was administered to the patients before and after the 3-week treatment.

Statistical Analysis

Continuous data are presented as mean ± standard deviation (SD) and compared with the unpaired *t* tests (between-group differences) or paired *t* tests (differences between baseline and the 3-week follow-up assessment). Categorical variables were described as counts and percentages, compared by chi-square test or Fisher's exact test. To adjust for baseline swallowing function measurements, ANCOVA was used as an additional analysis of changes in Eating Assessment Tool and Standardized Swallowing Assessment. *P* less than 0.01 was considered statistically significant. Statistical analysis was performed using GRAPHPAD PRISM and SPSS version 17.0.

Results

Baseline clinical characteristics are shown in Table 1. There were no statistical differences in age, sex, history of

Table 1. *Baseline characteristics*

	Capsaicin intervention group (n = 30)	Sham control group (n = 30)	*P* value
Age, y	63.77 (12.18)	66.23 (11.91)	.43
Men	16 (53.4%)	20 (66.7%)	.29
Hypertension	25 (83.3%)	27 (90%)	.32
Abbreviated mental test scale	8.67 (1.06)	8.47 (1.31)	.518
Stroke type			
Ischemic	19 (63.3%)	23 (76.7%)	.26
Hemorrhagic	11 (36.7%)	7 (23.3%)	
Stroke side			
Left	16 (53.3%)	10 (33.3%)	.29
Right	6 (20.0%)	9 (30.0%)	
Bilateral	8 (26.7%)	11 (36.7%)	
Stroke site			
Cortical	5 (16.7%)	5 (16.7%)	.80
Subcortical	18 (60.0%)	20 (66.7%)	
Brain stem/cerebellar	7 (23.3%)	5 (16.7%)	
Eating Assessment Tool (EAT-10)	24.00 (2.18)	23.97 (2.82)	.96
Standardized swallowing assessment(SSA)	30.63 (1.87)	30.27 (2.70)	.54

Data are mean (SD) and frequency (%), unless stated otherwise.

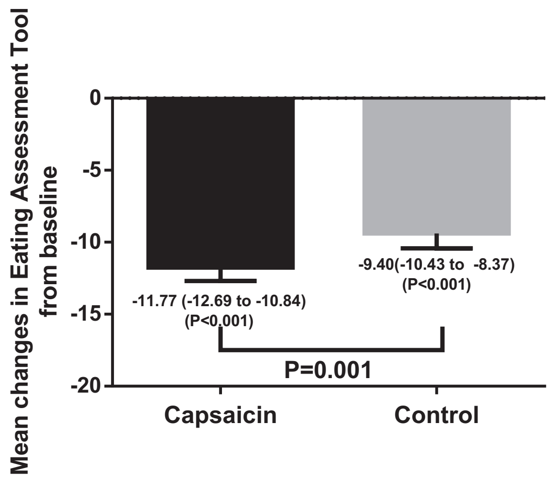

Figure 1. *Mean changes in Eating Assessment Tool from baseline in capsaicin and control groups.*

Notes: Data shown as mean. 95% CIs and *p* values are given for each comparison.

hypertension, pathology, Abbreviated Mental Test Scale, Eating Assessment Tool, or Standardized Swallowing Assessment.

Mean changes in Eating Assessment Tool from baseline in the capsaicin intervention group and the placebo control group are shown in Fig 1. A reduction in score of Eating Assessment Tool in both capsaicin and control group was seen. However, the decrease in Eating Assessment Tool of the capsaicin intervention group was significantly greater than that of the placebo control group ($P < .01$).

Standardized Swallowing Assessment scores before and after administration of capsaicin and placebo are shown in Fig 2. A reduction in score of Standardized Swallowing Assessment in both capsaicin and control group was observed. However, the decrease in Standardized Swallowing Assessment score of the capsaicin intervention group was significantly greater than that of the placebo control group ($P < .001$).

Comparison of the 3-week change between the groups, adjusted for baseline measures by use of ANCOVA, showed similar mean differences for Eating Assessment Tool and Standardized Swallowing Assessment (Table 2). These results were consistent with unadjusted analyses.

Treatment efficacy in Water Swallow Test after administration of capsaicin or placebo are shown in Table 3 and Fig 3. Among the 60 patients, the capsaicin intervention was effective in a higher number of patients (n = 27, 90%) than the placebo group (n = 9, 30%, $P < .001$).

Safety of the Treatment

During the study, we had two adverse events due to respiratory infection, 1 in the capsaicin intervention group and 1 in the placebo control group. Neither adverse events were caused by the study treatments. We believe that our treatment is safe for stroke patients with dysphagia.

Discussion

Both groups were found to be effective in improving swallow function based on results from Eating Assessment Tool and Standardized Swallowing Assessment. However, the number of patient improved in the capsaicin intervention group was significantly greater than that of the placebo control group. Our results suggest that regular use of natural capsaicin could promote the recovery of swallow function in stroke patients with dysphagia.

This is the first study to explore the effects of regular use of natural capsaicin easily available in stroke patients with dysphagia. The conventional strategies used in the treatment of dysphagia in the stroke typically consist of modification of food textures for solids and liquids, behavioral treatments with postures, orofacial muscle

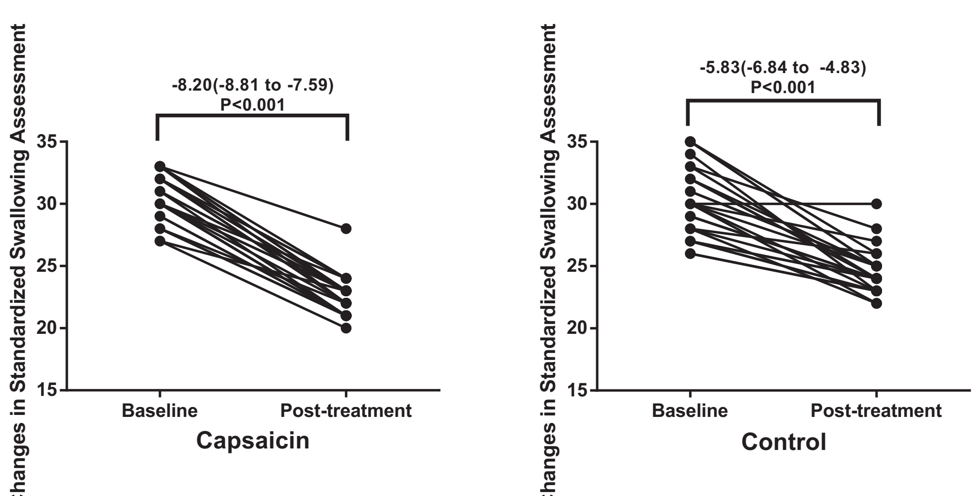

Figure 2. *Changes in Standardized Swallowing Assessment in capsaicin and control groups.*

Notes: Data shown as mean. 95% CIs and p values are given for each comparison.

Table 2. *Changes in eating assessment tool and standardized swallowing assessment at 3 weeks for capsaicin and control groups*

	Capsaicin intervention group		Sham control group		Mean difference: capsaicin vs control	
	Unadjusted*	Baseline adjusted†	Unadjusted*	Baseline adjusted†	Unadjusted*	Baseline adjusted†
Changes in EAT-10	−11.77 (−12.69 −10.84) ($P < .001$)	−11.75(−12.25−11.26)	−9.40(−10.43 −8.37) ($P < .001$)	−9.42 (−9.91 −8.92)	−2.37(−3.72 −1.02) ($P = .001$)	−2.34(−3.04 to −1.64) ($P < .001$)
Changes in SSA	−8.20(−8.81 −7.59) ($P < .001$)	−8.07(−8.62 −7.52)	−5.83(−6.84 −4.83) ($P < .001$)	−5.96 (−6.51 −5.42)	−2.37(−3.52 −1.22) ($P < .001$)	−2.11(−2.88 - −1.33) ($P < .001$)

Notes: Data shown as mean. 95% CIs and *p* values are given for each comparison.

exercises, thermal tactile stimulation, and compensatory maneuvers. The benefit of these strategies was confirmed in our study, as it has been shown in previous studies,[31,32] even though modification of food textures or behavioral treatments are recognized to be compensatory strategies that do not change the impaired swallow physiology in patients with dysphagia.[33] Our patients were able to reach 30% of effective treatments in the placebo control group using such strategies. Addition of capsaicin raised the effectiveness to 90%, as shown in our intervention group.

Our study showed that scores of Eating Assessment Tool and Standardized Swallowing Assessment were significantly higher in the capsaicin intervention group than the placebo control group. This is similar to the results seen in a double-blind, placebo-controlled, crossover study in older patients based on EAT-10 scores.[26] Rofes et al found both penetrations and pharyngeal residue were reduced, and the time of laryngeal vestibule closure, upper esophageal sphincter opening, and maximal hyoid and laryngeal displacement was shortened through treatment with capsaicinoids.[34]

Swallowing is triggered by the swallowing center, an interneuronal network located at the brain stem, receiving both peripheral sensory inputs from the pharynx and larynx, and central inputs from the cortex.[14] Damage to cerebral cortex, the ipsilateral subcortical tissues, peripheral sensory inputs, and other brain regions such as the brainstem and cerebellum often lead to dysphagia in stroke patients.[35,36] The TRP channels are a family of polymodal sensory receptors expressed in the epithelial cells and sensory neurons of the human oropharynx and larynx, acting directly via second messengers. Capsaicin, a pungent extract of red pepper, is a specific agonist to TRPV1. Therefore, we speculate that capsaicin, a TRP channel thermoreceptor agonists, has dual effects on the swallowing function.[37] Firstly, it could induce a direct effect on peripheral sensory neurons that improve sensory input from regions of the oropharynx and hypopharynx, promoting the pharyngeal phase of swallowing, as decreased oropharyngeal sensitivity often occur in stroke patients.[38] In addition, oral administration of capsaicin stimulates the sensory C-fibers of the trigeminal, glossopharyngeal, and vagal nerves in the oral and pharyngolaryngeal mucosa, while sensory nerve branches are vital for carrying afferent inputs from the oropharynx and hypopharynx to the sensory cortex. Secondly, it could induce an indirect effect through repetitive sensory stimuli to the cortex.[39] Afferent neuronal pathways provide for discriminative sensation, where the lamina-I neurons carry signals to the final insular cortex with 1 or 2 relays.[40] Due to the brains of post stroke patients having greater neuroplasticity, repeated sensory stimulation, activating the feedback loops and the brainstem swallowing center, may restore the function of the insular cortex and induce cortical neuroplasticity, resulting in restoration of swallowing function.[16,37] Neuroplasticity re-organization may also

Table 3. *Treatment efficacy in Water Swallow Test at 3 weeks for capsaicin and control groups*

	Capsaicin intervention group	Sham control group	*P* value
Water swallow test			
Effective	27 (90.0%)	9 (30.0%)	< .001
Invalid	3 (10%)	21 (70%)	

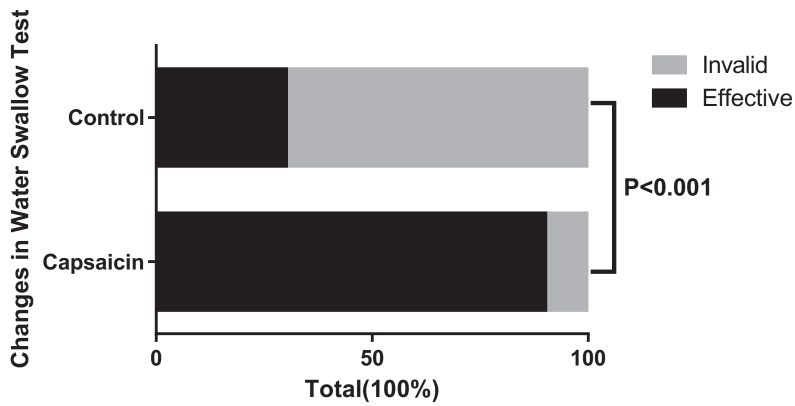

Figure 3. *Treatment efficacy in Water Swallow Test at 3 weeks in capsaicin and control groups.*

occur in cortical undamaged swallowing areas through enhancement of pharyngeal cortical representation, compensating for swallowing dysfunction.

Alvarez-Berdugo assessed the therapeutic effect of stimulating oropharyngeal sensory afferents with TRPV1, TRPA1, or TRPM8 agonists, and discovered that only capsaicin (TRPV1) had a powerful effect on swallow efficacy, while the other TRP agonists such as piperine (TRPV1/A1) and menthol(TRPM8) had a neutral effect on swallow efficacy.[22] It is hypothesized that the mildly acidic pH of the capsaicinoid sauce could sensitize the TRPV1 channels and triggers other sensory receptors expressed in the oropharynx, thus increasing its effect. However, a study from Király et al indicated that capsaicin-containing red pepper sauce suspension failed to induce esophageal motility response in patients with Barrett's esophagus.[41] It could be attributed to the impaired functions of mucosal chemosensory afferents, impaired peristaltic functions of the distal esophagus, and the absence of lower esophageal sphincter response to capsaicin,[42,43] which are less common in stroke patients.[35]

We used a strategy of supplementation of natural capsaicin in thermal tactile stimulation and additional nectar viscosity boluses to evaluate the possibility of improving swallowing function in stroke patients. Capsaicin can be used without causing adverse reactions, as no attributable adverse reactions occurred in our study. The capsaicin concentration was also designed to be low, making it almost indistinguishable in taste from the placebo. In this study, we used Sichuan red pepper powder, which is readily available in everyday life and cheap in China. The pepper source allowed us to maintain a constant amount of capsaicin, providing an easy and cheap strategy that does not require specific equipment or trained staff for patients at home. As seen in a previous study that utilized Japanese pickled Napa cabbage to encourage continued and repeated stimulation, the source of capsaicin can vary.[21] Further studies are needed to normalize the capsaicin concentration in each pepper source, which can be measured by high-performance chromatography, standardizing it for worldwide use. The duration of the intervention was similar to that in the study of Ebihara et al,[17] as repeated stimulation over twenty days is thought to have an influence on the plasticity of synapses.

Limitation

Our study has several limitations. The main drawback is lack of objective instrumental evaluation of swallowing, even though Water Swallow Test and V-VST are reliable methods for dysphagia screening by various studies.[30,44] Large controlled randomized clinical trials objectively evaluating the swallowing function with videofluoroscopy, should be performed in the future. In addition, future neuroimages or neurophysiologic studies should explore the mechanism of action, confirming the effects at the neurological level. It would also be interesting to discover whether repeated stimulation with capsaicin in such a way could prevent capsaicin defunctionalization.

Conclusion

In summary, supplementation of natural capsaicin in thermal tactile stimulation and additional nectar viscosity boluses improves swallowing function in stroke patients with dysphagia. In light of these findings, it is conceivable that regular use of natural capsaicin might become a strategy to treat dysphagia in stroke. This study may also provide the basis for further randomized trials of regular use of capsaicin in home care stroke patients suffering from dysphagia.

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