Daily auricular stimulation with capsaicin ointment improved cough reflex sensitivity in elderly patients with dysphagia: a pilot study

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Running header: Capsaicin improved cough reflex.

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Abstract

Background: In our previous study, a single auricular application of capsaicin ointment, but not placebo improved cough reflex in elderly patients with dysphagia.

Aims/Objectives: In the present study, we examined whether daily auricular application of capsaicin ointment continued to improve cough reflex in similar patients.

Material and Methods: With a cotton swab, 0.025% capsaicin ointment was applied in each external auditory canal alternately once a day for two weeks. The cough reflex sensitivity was evaluated on videoendoscopy using a numerical score and inhalation cough challenge test using citric acid in elderly dysphagic inpatients.

Results: After daily auricular application of capsaicin ointment for two weeks, the endoscopic score of glottal closure and cough reflexes significantly improved, and the citric acid cough threshold significantly decreased. There was a significant correlation between the endoscopic score and the citric acid cough threshold before and after daily capsaicin application in the patients.

Conclusions: Daily auricular stimulation with capsaicin ointment for two weeks continued to improve the cough reflex sensitivity in elderly patients with dysphagia.

Significance: Daily auricular stimulation with capsaicin ointment would be a safe and effective intervention to prevent pneumonia in elderly with a risk of aspiration.

Keywords: capsaicin, auricular stimulation, Arnold's ear-cough reflex, cough reflex sensitivity.

Introduction

Cough reflex is an important airway protective mechanism against aspiration. However, the cough reflex sensitivity was reported to decrease in elderly subjects [1] and patients with aspiration pneumonia [2]. It was also reported that elderly patients with dysphagia who showed a week glottal closure reflex have a high risk of aspiration pneumonia [3].

The auricular branch of the vagus, called the Arnold's nerve, courses through the external auditory canal, and its stimulation triggers cough reflex [4]. The Arnold's ear-cough reflex is frequently encountered by otolaryngologists during manipulations of the external auditory canal, such as ear syringing [5]. Capsaicin, the main component of red pepper and an agonist of the transient receptor potential vanilloid 1 (TRPV1), activates peripheral sensory C-fibers [6]. Stimulation of the pharyngolaryngeal mucosa with capsaicin induces cough reflex through activation of the vagal sensory C-fibers with TRPV1 [7]. In our previous study, a single application of ointment containing 0.025 % capsaicin in the external auditory canal improved swallowing function in elderly patients with dysphagia [8]. Subsequently, we performed a randomized, placebo-controlled, double-blind, comparative study and found that topical auricular application of capsaicin ointment, but not placebo improved glottal closure and cough reflexes in elderly patients with dysphagia [9]. These findings suggested that TRPV1-mediated Arnold's ear-cough reflex induced by capsaicin, but not non-specific mechanical stimulation with a cotton swab, improved the cough reflex sensitivity.

In the endoscopic evaluation of cough reflex at bed-side, cough reflex is induced by touching the epiglottis or arytenoid with the tip of a flexible videoendoscope, and the cough reflex sensitivity is evaluated using a semiquantitative numerical score [9,10]. However, the pressure applied on the laryngeal mucosa highly varies in the touch method

[11]. On the other hand, the inhalation cough challenge test with citric acid enables a quantitative measurement of the cough reflex sensitivity, as citric acid can induce coughing in a dose-dependent and reproducible manner [12]. The reliability of endoscopic evaluation of cough reflex at bed-side has to be proved by showing the correlation of the cough reflex sensitivity between the endoscopic numerical score and the citric acid cough threshold.

In the present study, in order to clarify the improvement of cough reflex after repeated auricular application with capsaicin, we examined the effects of daily auricular stimulation with capsaicin ointment for 2 weeks on the cough reflex sensitivity using videoendoscopy and inhalation cough challenge test in elderly inpatients with dysphagia. Then, in order to clarify the reliability of endoscopic evaluation of cough reflex, we examined the correlation of the cough reflex sensitivity between the endoscopic numerical score and the citric acid cough threshold.

Materials and Methods

Subjects

In the present study, eleven elderly inpatients with non-obstructive dysphagia were enrolled (8 males and 3 females; age range: 70-95 years; mean age: 83.1 ± 8.5 years). They all received the endoscopic evaluation of cough reflex. Among them, six patients received the evaluation of the cough reflex with inhalation cough challenge test (4 males and 2 females; age range: 75-95 years; mean age: 84.5 ± 8.9 years).

The patients complained of occasional choking on water or food, but had no obstructive lesion in the pharyngolarynx on endoscopy. They suffered from old cerebrovascular disorders, but had no active ear diseases, such as otitis externa or myringitis. All patients received swallowing exercises twice a week under the

guidance of speech therapists using the standard protocol published by the Oto-Rhino-Laryngological Society of Japan [13]. This study was approved by the Committee for Medical Ethics of Tokushima University Hospital (UMIN000012055). This study was conducted Anan Kyoei Hospital, a branch of Tokushima University Hospital. The participants were recruited by the attending doctors in the hospital from April 2016 to March 2018. After oral and written information was given, written informed consent was obtained from all patients prior to the study.

Study design

With a cotton swab, 0.2 g of ointment containing 0.025% capsaicin was applied in each external auditory canal alternately once a day for two weeks by an otolaryngologist [14]. Before the start of the intervention, a baseline evaluation of the cough reflex sensitivity was performed with the endoscopic numerical score on Sensory-Motor-Reflex-Clearance (SMRC) scale [9,10]. Subsequently, the endoscopic evaluations were performed one and two weeks after daily auricular application of capsaicin ointment. Six patients also underwent the baseline and subsequent evaluations of the cough reflex sensitivity with the inhalation cough challenge test using citric acid one and two weeks after daily auricular application of capsaicin ointment [12,15,16]. The remaining five patients were bedridden, and therefore, could not undergo the inhalation cough challenge test in a sitting position.

Capsaicin ointment

Based on Japanese Pharmacopoeia (17th edition, 2016) published by Ministry of Health, Labor and Welfare of Japan, we prepared 0.025% capsaicin ointment in accordance with the protocol of Japanese Drug Preparation of Hospital Pharmacy (1st

edition, 2013) published by Japan Society of Hospital Pharmacists as follows: 25 mg of capsaicin (Sigma-Aldrich Co, St Louis, MO, USA) was dissolved in 500 μL of 100% ethanol (Wako Pure Chemical Industries, Ltd., Osaka, Japan) and the solution was then mixed with 100 g hydrophilic ointment [17].

Evaluation of the cough reflex sensitivity on videoendoscopy

The standard protocol of the videoendoscopic evaluation of swallowing proposed by the Oto-Rhino-Laryngological Society of Japan was used [13]. Accordingly, patients received it in a head-up position facing an otolaryngologist. Water was dyed with blue food coloring for ease of visualization and given to the patient in a bolus of 3 mL. Swallowing of the blue-dyed water was recorded by the video rhinolaryngoscope system with a flexible fiber optic endoscope of 3.1 mm diameter (VNL-100S, Pentax, Tokyo, Japan). The video images of swallowing were evaluated using SMRC scale by another otolaryngologist blinded to the clinical data and independent from the examiner.

The swallowing function consists of four subfunctions: 1) sensory initiation of swallowing reflex; 2) motion to hold a bolus in the oral cavity and to induce laryngeal elevation; 3) glottal closure and cough reflexes; and 4) pharyngeal clearance of a bolus into the esophagus [9]. Therefore, we used the SMRC scale to evaluate the four subfunctions of the swallowing function on videoendoscopy separately: 1) Sensory: initiation of swallowing reflex as assessed by endoscopic whiteout; 2) Motion: holding a bolus in the oral cavity and inducing laryngeal elevation according to instructions; 3) Reflex: glottal closure and cough reflexes induced by touching the epiglottis or arytenoids with endoscope in the touch methods [11]; and 4) Clearance: pharyngeal clearance of a bolus after swallowing (Table 1). Accordingly, we used the reflex score of the SMRC scale as an endoscopic semiquantitative numerical index of the cough reflex sensitivity

in the present study [9,10]. The increase of the endoscopic reflex score means the improvement of cough reflex.

Evaluation of the cough reflex sensitivity with inhalation cough challenge test

The patients were seated in an upright position on a chair. A nebulized saline solution (control) and subsequently citric acid solution delivered using a supersonic wave nebulizer (Omron, Japan). They tidally breathed a citric acid isotonic sodium chloride solution orally from the nebulizer for 1 min at incremental concentration of 1%, 2%, 5% and 10 % at 3-minute intervals. The number of induced coughing was counted, and the cough threshold was defined as the minimum citric acid concentration when coughing was induced five times or more during the 1 min-breathing [2,15,16].

Statistics

Changes in the endoscopic reflex score and the citric acid cough threshold over time were analyzed by Wilcoxon signed-rank test and Friedman test with Shirley-Williams post hoc test were used for statistical analysis. The correlation between the endoscopic R score and the citric acid cough threshold was evaluated using Spearman's rank correlation coefficient. $p \leq 0.05$ was considered significant. The statistical analysis was performed using Microsoft Excel 2016 Japanese version (Microsoft Japan, Tokyo, Japan) and Statcel version 4 (OMS Publishing Inc., Saitama, Japan).

Results

The median endoscopic score of glottal closure and cough reflexes were 1.0 (95% confidence interval (CI) = 0.75−1.44) in eleven elderly patients with dysphagia. After repeated applications of ointment containing 0.025% capsaicin in each external auditory

canal alternately once a day for one week, the median endoscopic reflex score significantly increased to 2.0 (95% confidence interval (CI) = 1.32–2.15) (p=0.002 in Friedman test; p=0.05 with Shirley-Williams post hoc test). After repeated applications of capsaicin ointment in each external auditory canal alternately once a day for two weeks, the median endoscopic reflex score significantly increased to 2.0 (95% confidence interval (CI) = 1.50–2.50) (p=0.002 in Friedman test; p=0.01 with Shirley-Williams post hoc test) (Fig. 1).

Five patients cannot undergo the inhalation cough challenge test, as they were bedridden. In the remaining six elderly patients with dysphagia, the median threshold of inhaled citric acid concentration to induce five series of coughing was 5.0 (95% confidence interval (CI) = 3.11−9.23)%. After repeated applications of capsaicin ointment in each external auditory canal alternately once a day for one week, the median citric acid cough threshold significantly decreased to 1.5 (95% confidence interval (CI) = 0.52−3.48)% (p=0.002 in Friedman test; p=0.05 with Shirley-Williams post hoc test). After repeated applications of capsaicin ointment in each external auditory canal alternately once a day for two weeks, the median citric acid cough threshold significantly decreased to 2.0 (95% confidence interval (CI) = 0.76–3.58)% (p=0.002 in Friedman test; p=0.05 with Shirley-Williams post hoc test) (Fig. 2).

There was a significant correlation between the endoscopic score of glottal closure and cough reflexes and the threshold of inhaled citric acid concentration to induce five series of coughing before and after repeated daily applications of capsaicin ointment for one and two weeks in six elderly patients with dysphagia ($p<0.01$ in Spearman's correlation coefficient by rank test) (Fig. 3).

No adverse effects, including otalgia and otitis externa were induced in the present study. No patients felt discomfort with the repeated exposures of capsaicin to the

external auditory canal for 2 weeks.

Discussion

In our previous randomized, placebo-controlled, double-blind, comparative study, we showed that a single auricular application of capsaicin ointment specifically increased the endoscopic score of glottal closure and cough reflexes in elderly patients with dysphagia [9]. In the present study, we showed that repeated daily auricular stimulation with capsaicin ointment for two weeks increased the endoscopic score of glottal closure and cough reflexes in elderly patients with dysphagia. This finding suggests that daily auricular capsaicin stimulation continued to improve the cough reflex sensitivity, which was evaluated on the numerical score after touching the epiglottis or arytenoid with a videoendoscope.

The numerical endoscopic reflex score with the touch method is a semiquantitative evaluation of the cough reflex sensitivity, as the pressure applied to the larynx was highly varies [11]. In the present study, we used the inhalation cough challenge test to evaluate quantitatively the cough reflex sensitivity [12]. It was reported that in the inhalation cough challenge test, the citric acid cough threshold increased in patients with a history of aspiration pneumonia [2]. In the present study, daily auricular stimulation with capsaicin ointment for two weeks decreased the threshold of inhaled citric acid concentration to induce a series of coughing in elderly patients with dysphagia. All these findings suggest that after daily auricular stimulation with capsaicin ointment for two weeks, the capsaicin-TRPV1-mediated Arnold's ear-cough reflex continued to improve the cough reflex sensitivity in elderly patients with dysphagia.

In the present study, the cough reflex sensitivity was initially improved after daily auricular stimulation with capsaicin ointment for a week and the improvement was

sustained for the next week. Because the cough reflex was improved 60 min after a single auricular application of capsaicin ointment in elderly patients with dysphagia [9], but not within 24 hours (unpublished data). Therefore, daily auricular stimulation with capsaicin ointment would be needed to keep the improvement of cough reflex.

The finding of the inhalation cough challenge test reinforces the endoscopic evaluation of improvement of the cough reflex sensitivity after repeated auricular stimulation with capsaicin ointment. There was a significant correlation between the endoscopic score of glottal closure and cough reflexes and the threshold of inhaled citric acid concentration to induce a series of coughing. Thus, it is also suggested that the numerical endoscopic score of glottal closure and cough reflexes with the touch method is a reliable bed-side test to evaluate the cough reflex sensitivity in substitution for the inhalation cough challenge test.

Capsaicin initially stimulates the unmyelinated sensory nerves in the pharyngolaryngeal mucosa to induce coughing through TRPV1 [7]. But, chronic exposure to high-doses of capsaicin causes long-term functional impairment of the sensory nerves through desensitization of TRPV1 and depletion of neuropeptides, such as substance P (SP), which is called capsaicin defunctionalization [18]. Thus, repeated auricular stimulation with capsaicin might induce capsaicin defunctionalization, resulting in decreased improvement of the cough reflex sensitivity that is induced through the capsaicin-TRPV1-mediated Arnold's ear-cough reflex. However, it is unlikely, as in the present study, repeated applications of capsaicin ointment at a low dose (0.025%) in each external auditory canal alternately once a day up until two weeks continued to improve the cough reflex sensitivity in elderly patients with dysphagia. It was reported that pharyngeal stimulation with pastille containing capsaicin improved the cough reflex sensitivity in the elderly, suggesting that daily capsaicin pastille supplementation reduces

a risk of pneumonia [19]. However, the oral administration of the capsaicin pastille might increase a risk of aspiration conversely.

There are some limitations of the present study. The sample size was small. There was no control group and gender bias. Capsaicin challenge is a more common cough challenge test than citric acid [20]. However, we cannot use the inhalation cough challenge test with capsaicin in the present study, because of the possibility that pharyngeal stimulation with capsaicin improves the cough reflex [19].

In conclusion, the present findings suggest that daily auricular stimulation with capsaicin ointment may be a safe and effective intervention to prevent pneumonia in elderly who have a risk of aspiration. Recently, we reported that daily auricular stimulation with capsaicin ointment for 6 months decreased the incidence of pneumonia in elderly dementia patients at high risk of aspiration in the uncontrolled before-after study [14]. Further randomized, placebo-controlled, double-blinded, comparative studies are required.

Disclosure statement

The authors declare no conflicts of interest in this study.

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Figure Legends

Fig. 1

Effects of repeated auricular stimulation with capsaicin ointment once a day for two weeks on the endoscopic score of glottal closure and cough reflexes in elderly patients with dysphagia. The box plot shows the median and spread of the data. n=11, *p=0.002 in Friedman test; p=0.05 with Shirley-Williams post hoc test, **p=0.002 in Friedman test; p=0.01 with Shirley-Williams post hoc test.

Fig. 2

Effects of repeated auricular stimulation with capsaicin ointment once a day for two weeks on the threshold of inhaled citric acid concentration to induce five series of coughing in elderly patients with dysphagia. The box plot shows the median and spread of the data. n=6, *p=0.02 in Friedman test; p=0.05 with Shirley-Williams post hoc test.

Fig. 3

The correlation between the endoscopic score of glottal closure and cough reflexes and the threshold of inhaled citric acid concentration to induce five series of coughing before and after repeated applications of capsaicin ointment for one and two weeks in elderly patients with dysphagia. n=6, ○: baseline, ▲: after one week, ■: after two weeks, r=-0.63, $p<0.01$ in Spearman's correlation coefficient by rank test. r: Spearman's correlation coefficient.

Table 1 SMRC scale

1) Sensory: Initiation of swallowing reflex as assessed by endoscopic white-out

3: Bolus at vallecula

2: Bolus at pyriform sinuses

1: Bolus retention at bottom of pyriform sinuses

0: No swallowing initiation

2) Motion: holding a bolus in oral cavity and inducing laryngeal elevation according to instructions

2: Both holding a bolus in oral cavity and inducing laryngeal elevation

1: Either holding a bolus in oral cavity or inducing laryngeal elevation

0: Neither of them

3) Reflex: glottal closure and cough reflexes induced by touching the epiglottis or arytenoids with endoscope

3: Brisk cough reflex

2: Brisk glottal closure reflex with weak or delayed cough reflex

1: Weak or delayed glottal closure and cough reflexes

0: Neither of them

4) Clearance: pharyngeal clearance of a bolus after swallowing

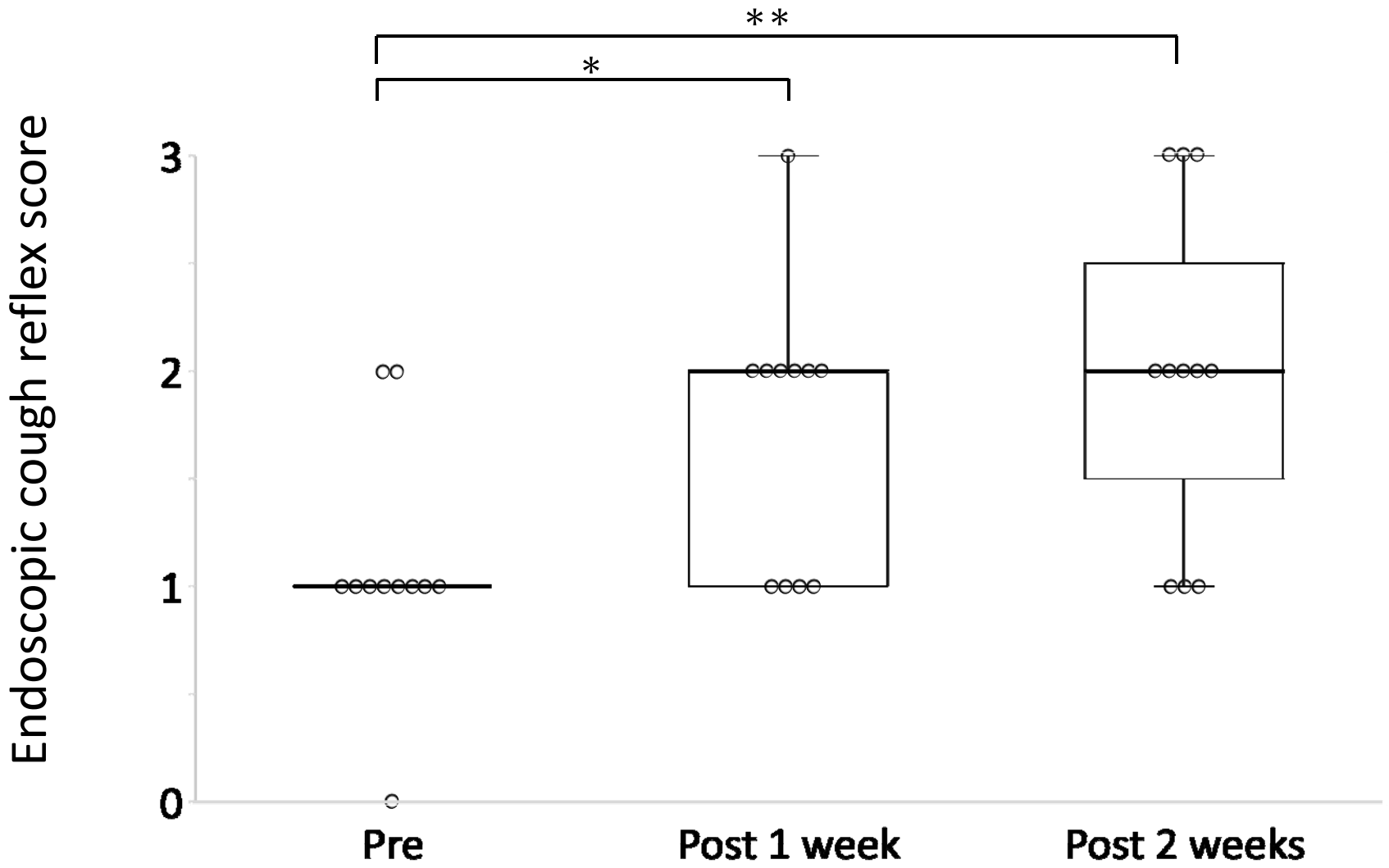
3: No bolus and saliva residues after swallowing once or twice

2: No bolus residue after swallowing once or twice, but saliva residue

1: No bolus residue after swallowing three times or more

0: Bolus residue even after swallowing three times or more

Figure 1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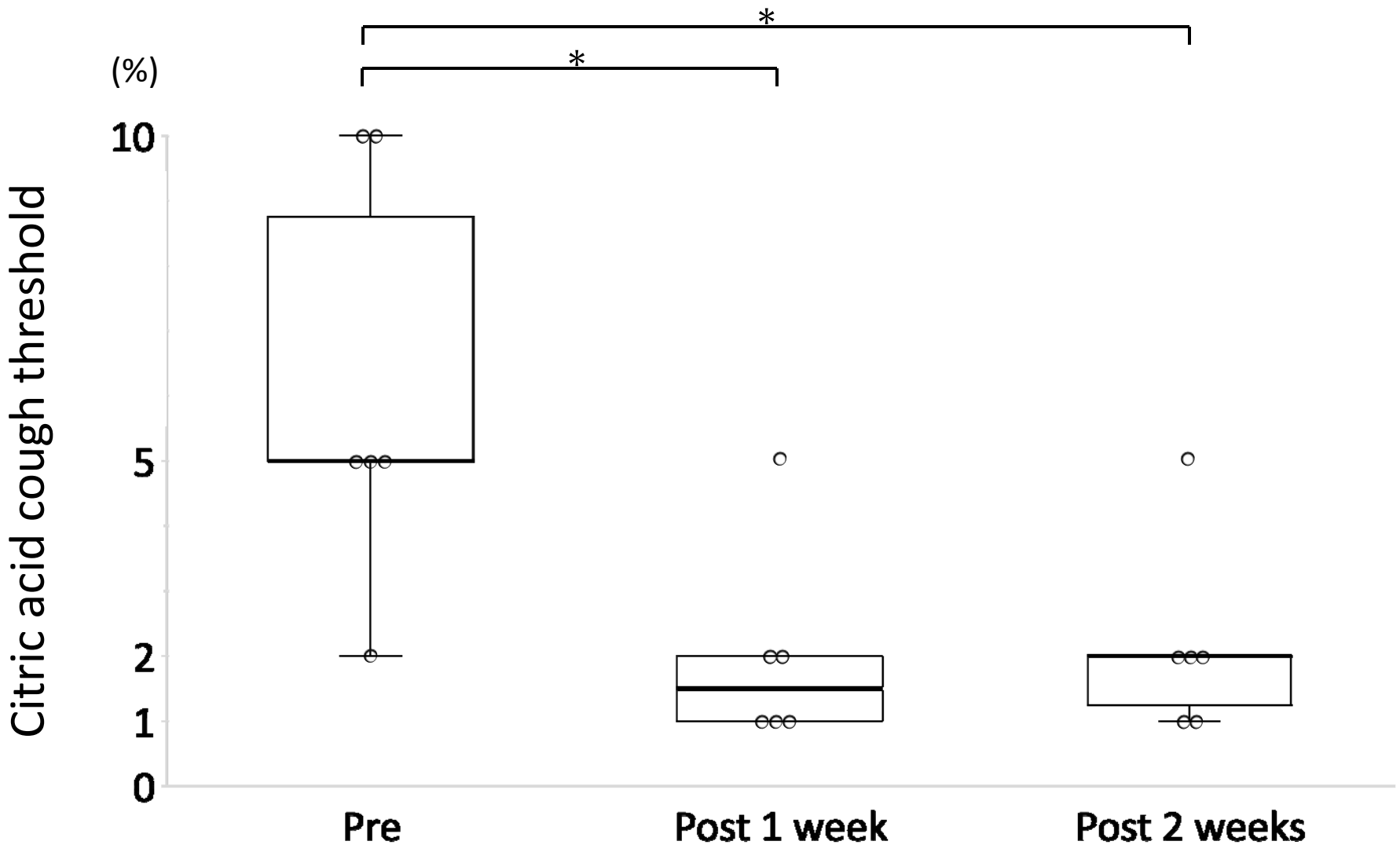
Endoscopic cough reflex score
3
2
1
0
Pre
Post 1 week
Post 2 weeks

Figure 2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(%)
10
5
2
1
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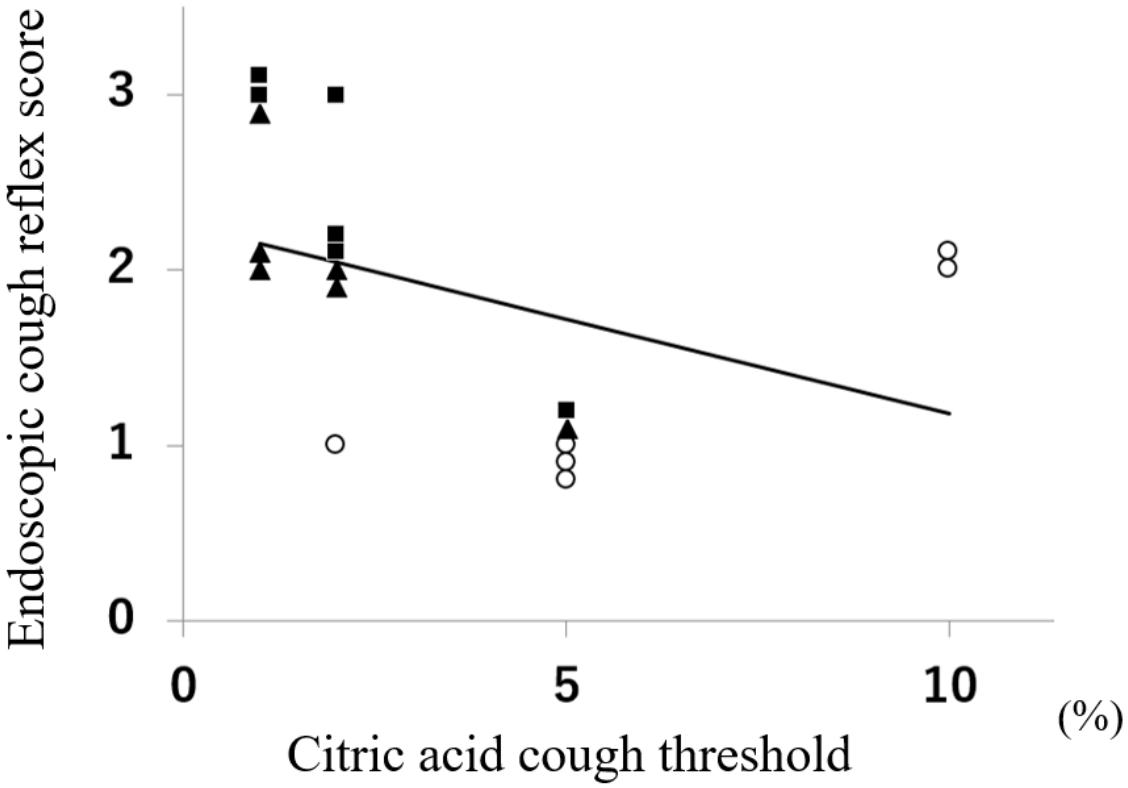
Citric acid cough threshold
Pre
Post 1 week
Post 2 weeks

Figure 3


Endoscopic cough reflex score
3
2
1
0
0
5
10
(%)
Citric acid cough threshold