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Original Article

Capsaicin May Improve Swallowing Impairment in Patients with Amyotrophic Lateral Sclerosis: A Randomized Controlled Trial

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Patients with neurodegenerative diseases are at an increased risk of dysphagia and aspiration pneumonia. In this study, we examined whether ingestion of capsaicin prior to swallowing changes the temporal dynamics of swallowing in such patients. In a crossover, randomized controlled trial, 29 patients with neurodegenerative diseases were given a soluble wafer containing 1.5 μg capsaicin or an identical placebo 20 min prior to testing. For evaluation with video fluoroscopy (VF), patients consumed a barium-containing liquid plus thickening material. The durations of the latency, elevating and recovery periods of the hyoid were assessed from VF. Overall, no significant differences were observed in the duration of each period between capsaicin and placebo treatments. However, reductions in the latency and elevating periods were positively correlated with baseline durations. In subgroup analyses, that correlation was observed in patents with amyotrophic lateral sclerosis (ALS) but not in patients with Parkinson's disease. The consumption of wafer paper containing capsaicin before the intake of food may be effective in patients with dysphagia related with certain neurodegenerative diseases, particularly ALS patients. Further studies will be needed to validate this finding.

Key words: deglutition disorder, fluoroscopy, neurodegenerative diseases, amyotrophic lateral sclerosis, Parkinson disease

In conjunction with the health policy of the Japanese government, more than 300 designated intractable diseases have been defined. Among the intractable disease categorized as neurodegenerative are amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), myasthenia gravis and multiple sclerosis. A major common symptom of these diseases is dysphagia caused by motor function disorder. In patients with ALS, dysphagia progresses along with the time course [1], and in the terminal stage of ALS, bulbar palsy brings severe dysphagia [2]. In PD, the risk of dysphagia and aspiration pneumonia increases as the disease progresses [3], although many patients are not aware of that risk [4]. In patients with MSA, severe dysphagia is observed in MSA-parkinsonian variant [5]; likewise, progressive supranuclear palsy (PSP) is a Parkinsonian syndrome associated with the early onset of dysphagia [6].

In addition to the motor function disorder, previous studies have reported sensory dysfunctions in ALS

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[7,8] and degenerative changes in the somatosensory cortex of the brains of patients with MSA [9]. Previous findings obtained on the autopsied pharynges of patients with PD revealed that pharyngeal sensory nerves were directly affected by pathological processes in PD [10]. Therefore, disorders in pharyngeal sensory functions, which are crucial for the integration of swallowing, are considered to play important roles in dysphagia in patients with these neurodegenerative diseases.

Capsaicin increases the release of substance P from the dorsal root ganglia (DRG), thereby improving pharyngeal sensory functions in the elderly, and one of the mechanisms of the effect is considered to be a reduction in the latency time of the swallowing reflex [11,12]. In older patients with dysphagia, oral capsaicin treatment is reported to induce cortical changes in response to oropharyngeal sensory stimulation, which were correlated with improvements in swallowing biomechanics [13]. In addition, oral capsaicin has been shown to effectively prevent pneumonia in patients with dementia [14] or with dysphagia [15], maybe because of its function as a TRPV1 agonist [16]. We previously demonstrated that the latency time of the swallowing reflex in healthy adult volunteers was reduced by capsaicin [17].

In the clinical department of Special Needs Dentistry at Okayama University Hospital, patients with neurodegenerative diseases associated with dysphagia are introduced from the Department of Neurology specifically to evaluate their swallowing function and to re-train their swallowing if necessary. We designed a randomized double-blind crossover study to examine whether capsaicin reduces the durations of the latency, elevating and/or recovery periods of swallowing in these patients.

Methods

Study cohort. In a two-year period (Feb 2016-Feb 2018), all consecutive adult outpatients with neurodegenerative diseases, including ALS, MSA, PD, PSP, spinocerebellar ataxia, and Huntington's disease, from the Clinic of Neurology in Okayama University Hospital who visited the Special Needs Dentistry department of Okayama University Hospital for evaluations of swallowing function were considered for inclusion. Exclusion criteria were as follows: patients with a difficulty understanding the study, patients who showed aspiration during video fluoroscopy (VF) of swallowing, and patients with scores of less than 3 in the modified water swallowing test [18] and coughing test [19]. The present study was conducted at the Special Needs Dentistry department of Okayama University Hospital. The study protocol was approved by the Ethical Committee of Okayama University Hospital (reference no. 1506-001) and conformed to the Declaration of Helsinki guidelines. This study was also conducted according to the Consolidated Standards of Reporting Trials (CONSORT) recommendations concerning the reporting of RCT. Written informed consent was obtained from all participants or approved family members.

Randomization. In a randomized, double-blind, crossover design, we compared the efficacy of capsaicin with that of a placebo in patients with neurodegenerative disease. Patients were randomized to initially receive capsaicin or placebo, followed by the opposite treatment one week later. We used commercially available thin paper wafers containing 1.5 μg apsaicin (Capfilm®; Yamada Bee Farm, Okayama, Japan) and no capsaicin (Yamada Bee Farm) as the placebo. The reason why we used the wafers containing 1.5 μg apsaicin is that significant difference in latency time was brought in healthy volunteers in our previous study [17]. The wafers were identical in appearance, but the capsaicin wafers had a weak, distinctive pungency. Otherwise, clinical staff and patients were blinded to the types of wafers. Prior to experiments, VF was performed for screening purposes; patients with aspiration upon swallowing were excluded. In the first experiment, the assigned wafer was taken (written assignments were concealed in an opaque envelope), and VF was performed 20 min later. Patients with aspiration were excluded. After an interval of one week, the second experiment was performed; the other wafer was taken, and VF was performed again. Again, patients with aspiration were excluded.

The wafer with or without capsaicin was placed on the tongue of the patient 20 min before VF because of a previous result showing a significant reduction of the latency period 20 min after capsaicin wafer ingestion [17]. Regarding VF, patients sat on a stable chair and were administered exactly 3 ml of barium-containing liquid consisting of 40% barium sulfate (Baricon Meal, Horii Pharmacy, Japan) mixed with 2% thickening material (Toromi-up perfect, Nisshin Oilio, Japan) [20]

to achieve a honey-like viscosity. After the barium liquid was applied under the tongue using a syringe, patients were allowed to swallow it in their own time [21]; this was repeated 2 more times. All three sets of intakes were recorded laterally with a digital X-ray TV system (Xinscope 4000 DBX-4000A, Toshiba, Japan).

Measurements. The hyoid movement in the swallowing reflex can be divided into three periods: the latency, elevating and recovery periods. The swallowing reflex starts as the food bolus is transported to the back of the tongue. In VF, the start of the swallowing reflex can be observed as the beginning of the displacement of the tongue tip. In this study the latency period was defined as the beginning of the displacement of the tongue tip to the beginning of the hyoid movement. The elevating period was from the end of the latency period to the time point when the hyoid reached its highest position. The recovery period was the time from the hyoid reaching its highest position to its return to its original position. The durations of each period were obtained from an analysis of still pictures from VF, which were taken at intervals of $3/100^{ths}$ of a second using movie processing software (Windows Live Movie Maker Ver 2011; Microsoft, Redmond, WA, USA). The average of three durations was used for each period in statistical analyses. Measurements and statistical analyses were performed by a person blinded to randomization.

Statistical methods. The durations of each period after consumption of capsaicin and placebo were compared using the Wilcoxon matched-pairs signed rank test. As an index of the effects of capsaicin, reductions in the durations of each period induced by capsaicin were calculated by subtracting the durations after capsaicin from those after the placebo in each patient. The relationships between these reductions and the durations of each period after the placebo were examined using Spearman's rank correlation coefficient. Significance was set at $p < 0.05$. We used Prism ver. 4R (GraphPad, San Diego, CA, USA) for all calculations.

Sample size. The sample size was selected based on our preliminary research, in which the effects of wafers containing capsaicin on the duration of the latency period of swallowing were assessed in healthy adult volunteers in a double-blind crossover study. In the present study, Student's paired *t*-test with two-sided $\alpha = 0.05$ revealed 80% power with a sample size of 32 patients using a crossover design. To compensate for the loss of patients and potentially large variations in each period, we estimated that 40 patients with complete datasets needed to be included.

Subgroup analysis. As a subgroup analysis, the relationships between the reductions and the durations of latency, elevating and recovery period after the placebo were examined in each group of patients with ALS and PD, using Spearman's rank correlation coefficient.

Results

Patients. Forty patients met the inclusion criteria and provided informed consent. Aspiration was observed in 7 patients; it was not possible to obtain clear VF movies in 3 patients; and 1 patient withdrew consent. Therefore, 29 patients were ultimately included (Fig. 1). The cohort, consisting of 13 males and 16 females, included 10 patients with ALS, 9 with PD, 5 with MSA, 3 with PSP, 1 with spinocerebellar degeneration, and 1 with Huntington's disease. The average age of patients was 71.5 ± 6.0 years (Table 1). No adverse side effects were associated with the consumption of

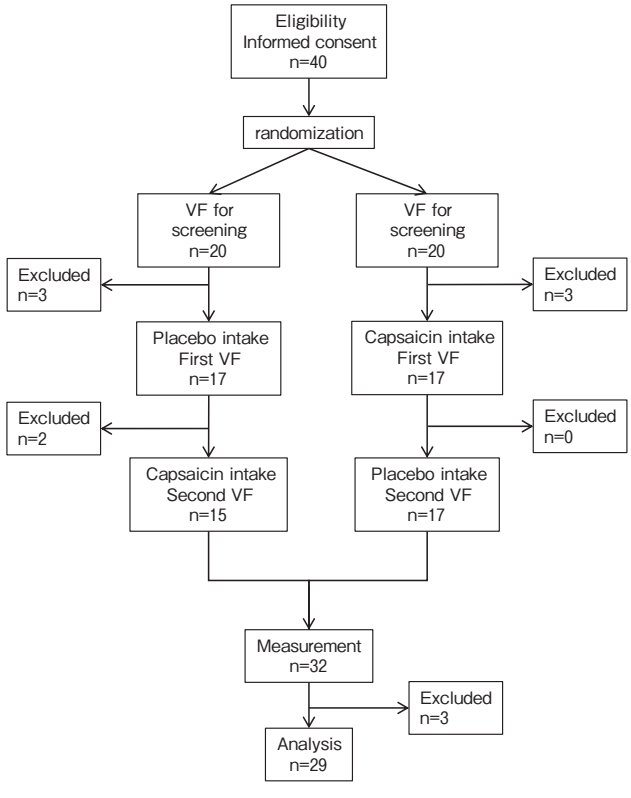

Fig. 1 CONSORT flow diagram of patients enrolled in the present study. VF, video fluoroscopy.

wafers containing capsaicin.

Durations of each period of hyoid movement. The durations of the latency period were 0.73 (0.42, 2.21) sec (median, IQR) after the placebo and 0.65 (0.33, 1.42) sec after capsaicin. The durations of the elevating period were 0.74 (0.60, 0.98) sec after the placebo and 0.73 (0.57, 0.95) sec after capsaicin. The durations of the recovery period were 1.11 (0.72, 2.32) sec after the placebo and 1.04 (0.76, 2.24) sec after capsaicin. The median values were shortened by capsaicin, but no significant differences between the placebo and capsaicin treatments were observed in the durations of any of the periods (Table 2).

Correlations between capsaicin-induced reductions in period durations and placebo-associated period durations. Reductions in the latency period by capsaicin were positively correlated with the baseline latency period duration, defined as that in the placebo setting ($R^2 = 0.52$, $p < 0.0001$) (Fig. 2A). On the other hand, in 1 patient with MSA, the latency period was 0.8 sec after the placebo and was prolonged by more than 2 sec by capsaicin. Reductions in the elevating period by capsaicin were also positively correlated with the post-placebo duration of this period ($R^2 = 0.28$, $p = 0.003$) (Fig. 2B). Reductions in the recovery period were not significantly correlated with the post-placebo duration of the recovery period ($R^2 = 0.01$, $p = 0.700$) (Fig. 2C). In 1 patient with PD, the elevating period was prolonged by more than 1 sec by capsaicin.

Subgroup analysis. In a group of patients with ALS, reductions in the latency period ($R^2 = 0.86$, $p < 0.0001$) and elevating periods ($R^2 = 0.76$, $p < 0.0011$) were positively correlated with baseline duration

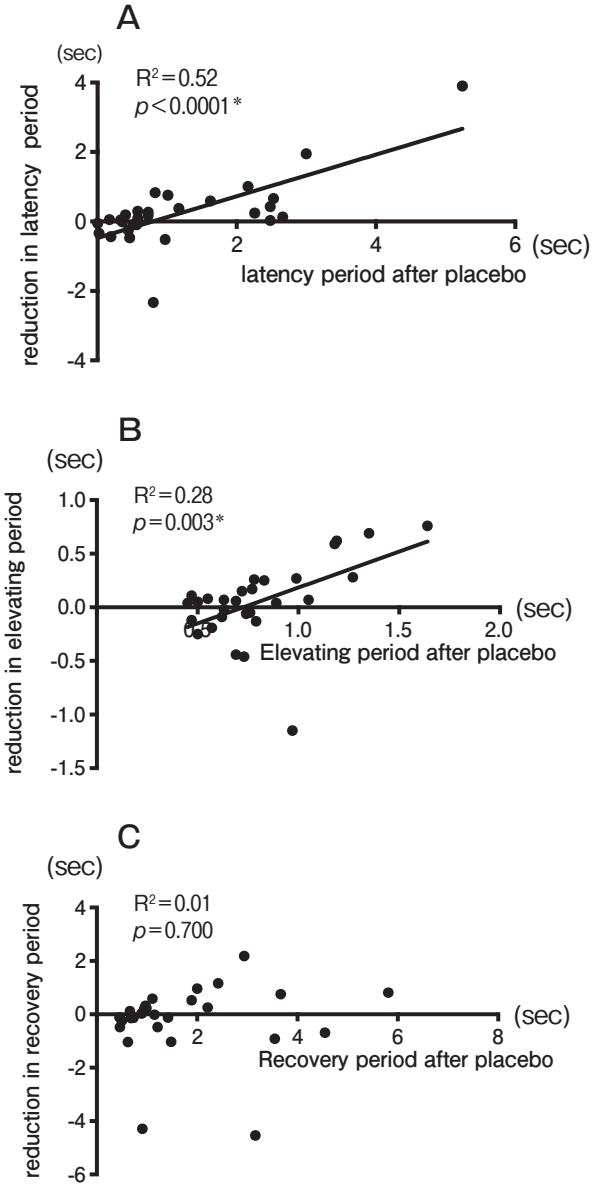

Fig. 2 Relationship between capsaicin-induced reduction in the latency period and "baseline" duration, *i.e.*, that in the placebo setting (**A**). Relationship between capsaicin-induced and placebo-associated reduction in the elevating period (**B**). Relationship between capsaicin-induced and placebo-associated reduction in the recovery period (**C**).

Table 1 Background of participants

age (average ± SD) (years)	71.4 ± 5.8
Male/female (n)	13/16
Amyotrophic lateral sclerosis (n)	10
Parkinson disease (n)	9
multiple system atrophy (n)	5
Others (n)	5

Table 2 Durations of each period after intake film of placebo or capsaicin

	Placebo	Capsaicin	Significance
Latency period (s, IQR)	0.73 (0.42, 2.21)	0.65 (0.33, 1.42)	n.s.
Elevating period (s, IQR)	0.74 (0.60, 0.98)	0.73 (0.57, 0.95)	n.s.
Recovery period (s, IQR)	1.11 (0.72, 2.32)	1.04 (0.76, 2.24)	n.s.

(Fig. 3A, 3C). In the group of patients with PD, no significant correlation was observed in either the latency period or the elevating period (Fig. 3B, 3D). There was no significant correlation between reduction in the recovery period and duration after placebo in either group of patients (Fig. 3F, 3F).

Discussion

The durations of the latency and elevating periods were not significantly different between the placebo and capsaicin treatments in this study. In the preliminary experiments, patients with aspiration were excluded to avoid harm caused by the experiment, and this exclusion may have affected the results of this study. However,

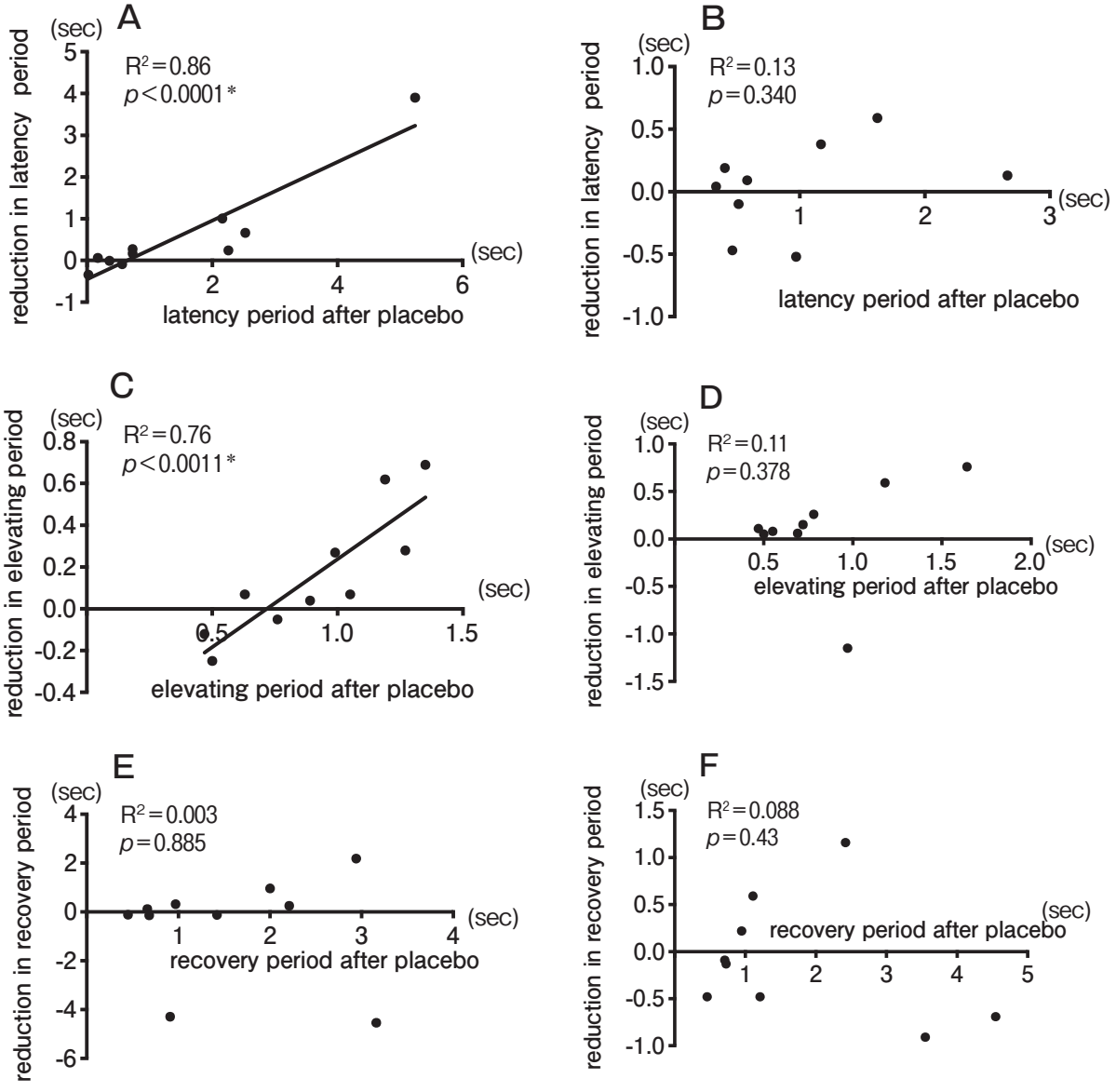

Fig. 3 Relationship between capsaicin-induced reductions in the latency period and baseline duration, *i.e.*, that in the placebo setting, in groups of patients with ALS (**A**) and PD (**B**). Relationship between capsaicin-induced and placebo-associated reduction in the elevating period in groups of patients with ALS (**C**) and PD (**D**). Relationship between capsaicin-induced and placebo-associated reduction in the recovery period in groups of patients with ALS (**E**) and PD (**F**).

a correlation was observed between reductions by capsaicin and baseline durations in both the latency and elevating periods. Furthermore, we enrolled patients at risk of dysphagia; previous studies [12,15] showing significant improvement in the swallowing reflex by capsaicin enrolled patients diagnosed with dysphagia. Therefore, it is suggested that the effects of capsaicin in patients excluded from the present study should be investigated. In addition, previous studies have used a larger quantity of barium-containing liquid, and have used a nectar-like consistency; however, we sought to avoid aspiration and used a honey-like consistency in the experiments in this study [15,22]. This difference in consistency may be one of the reasons why significant difference was not obtained in this experiment.

Reductions in the durations of the latency and elevating periods by capsaicin were correlated with the post-placebo durations of these periods in patients with motor function disorders in this study. Since the latency and elevating periods were previously reported to be longer in older patients with dysphagia than in younger controls [23], the longer durations observed in the present study are tentatively attributed to an impaired swallowing reflex. The effects of capsaicin in the present study are consistent with previous findings showing that capsaicin effectively improved the swallowing reflex and hyoid movement in patients with dysphagia [12,15,24]. Thus, the present results indicate that capsaicin may also be effective in patients with dysphagia related to neurodegenerative diseases.

Capsaicin activates sensory nerve terminals [25] and participates in laryngeal sensory innervation with the mediation of TRPV1 receptors [26]. Substance P is released from neurons in the DRG after the activation of TRPV1 receptors by capsaicin [27]. Since substance P is a sensory neurotransmitter, its release by capsaicin is considered to have contributed to the reductions in the durations of both the latency and elevating periods observed in the present study. In a previous study [15], wafer paper containing 0.75 μg capsaicin effectively shortened the duration of cervical esophageal wall opening in patients with dysphagia. Since cervical esophageal wall opening synchronizes with the elevation of the hyoid [28], these findings are consistent with the present results. Therefore, we conjecture that capsaicin in the wafers bound to TRPV1 receptors and released substance P from DRG, thereby improving the swallowing reflex in participants with prolonged latency and elevating periods in this study.

Our subgroup analysis indicated that the capsaicin-associated reductions in the durations of both the latency and elevating periods were highly correlated with the baseline durations in the group of patients with ALS. In this study, the latency period was from the beginning of tongue movement to the beginning of the hyoid movement. Since tongue movement is for transport of the food bolus into the larynx, a decline in tongue function is considered to lead to abnormal food transport and disturbance in the latency period. Clinical hallmarks of ALS are progressive muscle atrophy and weakness [29], and the early stage of dysphagia in ALS is mainly caused by oral dysfunction. The oral phase disorders have been shown to begin with a decrease in either the bolus-transport function at the anterior part of the tongue, or the bolus-holding function at the posterior part of the tongue [30]. Therefore, it is possible that the decline in tongue function in patients with ALS is improved by substance P released by capsaicin's activation of the TRPV1 receptor. Since the elevating period reflects movements of the suprahyoid muscles, dysfunction of those muscles may also be improved by the same mechanism. However, the sample size of this subgroup analysis is so small that an additional experiment is necessary to validate the effect of capsaicin on dysphagia in patients with ALS.

Patients in the present study had ALS, MSA, PD, and PSP. An overall decrease in the senrory nerve signals senf the pharyngeal and supraglottic areas has been reported in the elderly [31-33] and also in stroke patients with oropharyngeal dysphagia, and this decrease is more prominent in those with aspiration [34]. A lack of afferent myelinated nerve fibers in the superior laryngeal nerve has also been found in the elderly, and may be related to age-related sensory dysfunctions in the upper aerodigestive tract [35]. These sensory deficits are involved in the pathophysiology of the impaired swallowing reflex in patients with dysphagia [36], and predispose them to aspiration. Since the average age in the present study was 71.5 ± 6.0 years, most of our patients were elderly. Collectively, the results obtained herein not only reflect the characteristics of neurodegenerative diseases, but are likely also influenced by age.

There are some limitations in this study. First, although we performed a simple crossover test using a placebo wafer, VF prior to wafer ingestion might have

been performed before each trial to obtain a more accurate baseline. Second, the level of salivary substance P could have been measured, since substance P is a key factor to improving swallowing function by capsaicin, and is measurable [15]. Third, the distinctive pungency of the capsaicin-containing wafers may have indirectly affected the results by potentially allowing articipants to distinguish between the experimental and placebo treatments. Fourth, we did not collect the medical history of the patients or clinically evaluate their current disease condition. In order to clarify the difference in the effect of capsaicin in each disease, careful classification of patients by patient condition is necessary. Fifth, since we only analysed timing of each period of swallowing, it remains unclear how the holistic swallowing holistic swallowing kinematics of subjects' swallowing function was affected by capsaicin administration.

In conclusions, the average durations of the latency and elevating periods were not significantly different between the placebo and capsaicin treatments in this study, but consumption of wafers containing capsaicin before the intake of food might be effective in patients with signs of dysphagia related with neurodegenerative diseases. In subgroup analysis, the correlation of reduction in duration with baseline duration was clearly observed in patients with ALS, but not in those with PD. Further studies are needed to examine the effects of capsaicin on severe dysphagia caused by neurodegenerative diseases. In particular, the effect on patients with ALS will need to be confirmed.

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