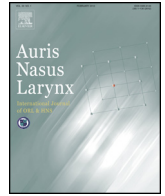




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Aural stimulation with capsaicin prevented pneumonia in dementia patients



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ABSTRACT

Objective: In the present study, we examined the effects of daily application of capsaicin ointment to the external auditory canal for 6 months on the development of pneumonia in elderly dementia patients at high risk of aspiration.

Methods: Twenty-nine oldest-old bedridden dementia inpatients at high risk of aspiration were enrolled in the present study. Ointment containing 0.025% capsaicin was applied to each external auditory canal with a cotton swab alternatively once a day for 6 months.

Results: The incidence of pneumonia during the 6 months before the intervention was 1.80 ± 0.37 in these patients. However, this incidence significantly decreased to 0.40 ± 0.29 ($p < 0.01$) during the 6 months of the alternative application of capsaicin ointment to each auditory canal. No adverse effect such as otalgia was observed.

Conclusion: These findings suggest that daily long-term aural stimulation with capsaicin ointment enhanced the cough reflex via Arnold's ear-cough reflex as a glottis protective measure, resulting in the reduction of incidence of pneumonia in elderly dementia patients at high risk of aspiration. The daily aural stimulation with capsaicin ointment may be a safe and promising intervention to prevent aspiration pneumonia in elderly people, especially those who cannot undergo swallowing exercise.

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1. Introduction

Pneumonia is still a major cause of death worldwide and is currently ranked as the 3rd leading cause of death in Japan. Particularly, an increased prevalence of dysphagia in the elderly

also rises their risk of developing aspiration pneumonia. Cough reflex plays an important role in protecting respiratory tract from the penetration of foreign bodies. However, the sensitivity of cough reflex appears to be reduced in the elderly subjects [1] and in those who suffer from aspiration pneumonia [2]. Besides, angiotensin converting enzyme inhibitors, which increase the sensitivity of cough reflex [3], have been shown to prevent pneumonia in elderly stroke patients [4,5]. However, most patients cannot take angiotensin converting enzyme inhibitors as an option for pneumonia prevention, because they can cause hypotension.

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Capsaicin is the main component of red pepper, and the stimulation of pharyngolaryngeal mucosa with capsaicin induces cough reflex by activating sensory C-fibers [6]. Accordingly, it was reported that the pharyngeal stimulation with pastille containing capsaicin improved the sensitivity of cough reflex in the elderly, suggesting that daily capsaicin pastille supplementation reduces a risk of pneumonia [7]. However, the oral administration with capsaicin pastille may increase a risk of aspiration conversely. In our previous study, we showed that the ectopic stimulation of the auricular branch of the vagus, the Arnold's nerve, with capsaicin ointment applied to the external auditory canal improves glottal closure and cough reflexes via the Arnold-cough reflex in elderly patients with dysphagia [8,9]. The findings suggest that daily aural stimulation with capsaicin ointment may prevent pneumonia in elderly at risk of aspiration.

In the present study, an attempt was made to examine the prophylactic effects of daily long-term aural stimulation with capsaicin ointment on the development of pneumonia in elderly dementia inpatients at high risk of aspiration. Because of their dementia, they could not receive swallowing exercise. In order to prevent pneumonia, we applied capsaicin ointment to each external auditory canal alternatively once a day for 6 months. The primary outcome was the reduction of the incidence of pneumonia during the 6 months of daily aural stimulation with capsaicin ointment, compared with that of the 6 months prior to the intervention.

2. Materials and methods

2.1. Patients

The present study was conducted in 3 branch hospitals of Tokushima University Hospital in Tokushima prefecture, Japan. Inclusion criteria for this study were as follows: (1) age between 65 and 100 years, (2) bedridden inpatients, (3) oral ingestion of a modified diet with the help of nurses or speech therapists, (4) dementia diagnosed with revised Hasegawa's dementia scale [10] and mini-mental state examination [11], (5) no swallowing exercises because of their dementia, (6) a history of cerebrovascular disorder and (7) a history of pneumonia within 6 months prior to the study. Patients with other serious complications were excluded from the study. Twenty-nine inpatients who fulfilled the inclusion criteria were consecutively enrolled in the present study (11 males and 18 females; 65–100 years old: mean age: 88.4 ± 8.4 years). Their physical and mental abilities were stable during the study. In addition, they all but one had been vaccinated with pneumococcal vaccine.

This study was approved by the Committee for Medical Ethics of Tokushima University Hospital, and a written informed consent was obtained from each participant or conservator prior to the study (UMIN12055).

2.2. Intervention

With a cotton swab, 0.2 g of ointment containing 0.025% capsaicin was applied to each external auditory canal

alternatively once a day for 6 months (Fig. 1). The intervention period started in January for 2 patients, March for 4, April for 4, May for 5, June for 2, July for 1, August for 5, September for 2, October for 2, November for 1 and December for 1. Similarly, the observation period 6 months before the intervention started in January for 1 patient, February for 5, March for 2, April for 2, May for 1, June for 1, July for 2, September for 4, October for 4, November for 5 and December for 2.

2.3. Endpoint and primary outcome

In the present study, the endpoint was defined as the incidence of pneumonia. The primary outcome was the reduction of the incidence of pneumonia for the intervention period of 6 months, compared with that for the observation periods of 6 months before the intervention. The diagnosis of pneumonia was based on clinical symptoms, such as fever and cough, followed by C-reactive protein elevation, and/or analysis of chest radiograph.

2.4. 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 according to 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 μ L of 100% ethanol (Wako Pure Chemical Industries, Ltd., Osaka, Japan) and the solution was then mixed with 100 g hydrophilic ointment.

2.5. Statistical analysis

Comparison of the incidence of pneumonia was carried out by Wilcoxon signed-rank test. Distribution of the starting month between observation and intervention periods was compared by Mann–Whitney's U test. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using Statcel version 4 (OMS Publishing Inc, Saitama, Japan).



Fig. 1. A photograph showing capsaicin ointment applied to right external auditory canal using a cotton swab.

3. Results

The incidence of pneumonia for 6 months before the intervention (observation period) was 1.80 ± 0.37 (95% confidence interval (CI) = 1.43–2.17) in 29 elderly dementia patients at high risk of aspiration. However, after the alternative application of 0.025% capsaicin ointment to each auditory canal was conducted once a day for 6 months, the incidence of pneumonia during the 6 months of the intervention (intervention period) was significantly decreased to 0.40 ± 0.29 (95% CI = 0.11–0.69) ($p < 0.01$) (Fig. 2). No adverse effect such as otalgia was observed. No significant differences were found in the distribution of the starting month between intervention and observation periods ($p = 0.28$).

4. Discussion

In the present study, elderly dementia inpatients at high risk of aspiration were enrolled. They were oldest-old and bedridden with a history of cerebrovascular disease, and were able to ingest food orally without swallowing exercise. Their incidence of pneumonia was significantly reduced during the 6 months of daily alternative applications of capsaicin ointment to each external auditory canal, compared with that of the 6 months before the intervention. This finding indicates that daily long-term aural stimulation with capsaicin ointment prevented the development of pneumonia in the elderly dementia patients. Cough reflex is an important airway protective mechanism against aspiration, however, elderly patients with a history of pneumonia show weak cough reflexes [2]. Besides, angiotensin converting enzyme inhibitors were reported to prevent pneumonia in post-stroke patients [4,5] by enhancing cough

reflex [3]. In our previous study, daily aural stimulation with capsaicin ointment for a week improved glottal closure and cough reflexes in elderly patients with dysphagia [8]. Taken together, we suggest that daily long-term aural stimulation with capsaicin ointment enhanced the cough reflex as a glottis protective measure, resulting in the reduction of pneumonia development in elderly dementia patients at high risk of aspiration.

The stimulation of Arnold's auricular branches of the vagus triggers the cough reflex [12]. The Arnold's ear-cough reflex is frequently encountered by otolaryngologists during manipulation of the external auditory canal, such as ear syringing [13]. Furthermore, capsaicin is an agonist of transient receptor potential vanilloid 1 (TRPV1). Because TRPV1 are found in unmyelinated vagal afferents [14], capsaicin activates vagal sensory C-fibers including the Arnold's nerve through TRPV1. Recently, we have conducted a randomized placebo-controlled, double-blinded, comparative study regarding the aural stimulation with capsaicin ointment for dysphagia. The results showed that TRPV1-mediated stimulation of the external auditory canal with capsaicin improved glottal closure and cough reflexes in elderly patients with dysphagia, whereas non-specific mechanical aural stimulation with a cotton swab had no significant effect [9]. Therefore, the present findings suggest that the stimulation of TRPV1 on the Arnold's nerve of the external auditory canal with capsaicin ointment enhanced cough reflex to prevent pneumonia in the elderly dementia patients. The daily long-term aural stimulation with capsaicin ointment may be a new safe and effective option for prevention of pneumonia in elderly dementia people, who are at high risk of aspiration pneumonia, but cannot undergo swallowing exercises.

Repeated exposure to high-dose of capsaicin causes their long-term functional impairment due to desensitization of TRPV1 and depletion of substance P (SP), called capsaicin defunctionalization [15]. However, in our previous study, repeated alternative application with ointment containing 0.025% capsaicin to each external auditory canal once a day for 7 days still improved glottal closure and cough reflexes in elderly patients with dysphagia [8]. In the present study, daily long-term alternative application with 0.025% capsaicin ointment to each external auditory canal for 6 months reduced the incidence of pneumonia in the elderly dementia patients at high risk of aspiration. Therefore, once-a-day alternative application to each external auditory canal with low dose of capsaicin may be a useful method to avoid capsaicin defunctionalization.

Because influenza become epidemic during winter season [16], the incident of influenza pneumonia may increase at the same period. However, the starting month of observation period for 6 months before the intervention was similar to that after intervention. Therefore, we expect no seasonal bias in the present study.

The present study has several limitations including uncontrolled before-after study design and its small sample size. Further randomized, placebo-controlled, double-blinded, comparative studies are required. It is also still uncertain how the stimulation of the Arnold's nerve of the external auditory canal with capsaicin ointment enhanced the cough reflex. The central

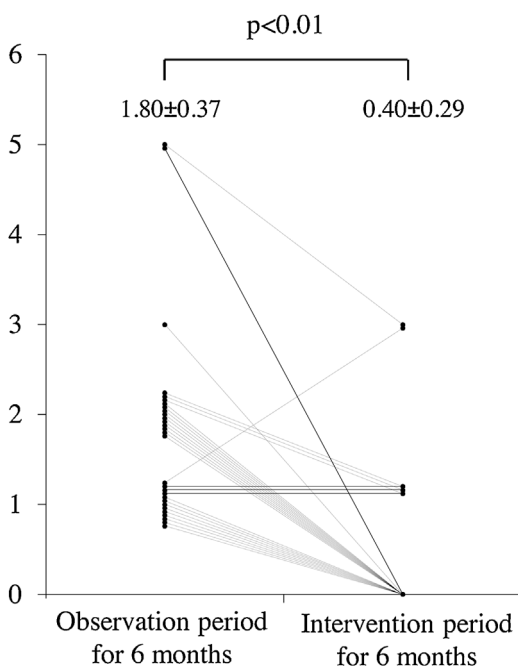


Fig. 2. The effects of daily aural stimulation with capsaicin ointment on the incidence of pneumonia in elderly dementia patients at high risk of aspiration. The observation period: 6 months before the intervention, the intervention period: 6 months during the intervention. * $p < 0.01$, $n = 29$.

pattern generator (CPG) of coughing is located in the brainstem and activated by sensory afferent inputs from the larynx or trachea to drive the cough reflex [17]. In our preliminary study, the aural stimulation of capsaicin ointment increased the concentration of SP in the sputum of healthy volunteers, suggesting that the aural capsaicin stimulation induced the retrograde release of SP in the pharyngolarynx or trachea. The finding further suggests that the aural stimulation of capsaicin also induced the anterograde release of SP in the brainstem including CPG of coughing. The capsaicin-induced increased level of SP at the CPG of coughing may be a possible central mechanism that the aural capsaicin stimulation enhances the cough reflex.

5. Conclusions

In conclusion, the present study showed that daily long-term alternative application of ointment containing 0.025% capsaicin to each external auditory canal reduced the incidence of pneumonia without the induction of capsaicin defunctionalization in elderly dementia inpatients at high risk of aspiration. Because capsaicin ointment applied to the external auditory canal induces cough reflex via Arnold's ear-cough reflex, the daily aural stimulation with capsaicin ointment may be a safe and promising intervention to prevent aspiration pneumonia in elderly people, especially those who cannot undergo swallowing exercise.

Conflict of interest

The authors declare no conflicts of interest in this study.

Acknowledgments

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