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NEUROLOGY | RESEARCH ARTICLE

Efficacy of transdermal scopolamine for sialorrhea in patients with amyotrophic lateral sclerosis

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Abstract: *Background*: Sialorrhea, the excessive flow of saliva from the mouth, causes distress in about half of patients with amyotrophic lateral sclerosis (ALS). Treatments of sialorrhea in ALS include systemic anticholinergic drugs, amitriptyline, botulinum toxin injection, and salivary gland radiotherapy, although each has limitations. Scopolamine transdermal patches have been used to prevent motion sickness since the 1980s but have also been used to treat sialorrhea in oropharyngeal disease, cerebral palsy, and Parkinson's disease. To date, no blinded, controlled studies of sialorrhea in ALS have been reported. *Methods*: A crossover, double-blind comparative study was conducted by randomly assigning patients to receive scopolamine or placebo patches for 1 week. *Results*: A total of 10 patients (three males and seven females; mean age 71.6 years) were enrolled. The mean volume of daily oral suction was decreased with scopolamine treatment. However, there were no significant differences between scopolamine and placebo in terms of a visual analogue scale of sialorrhea severity and difficulty, and the saliva item of the ALS Functional Rating Scale-Revised (ALSFRS-R). *Conclusions*: Our findings suggest that scopolamine patches might decrease saliva production and relieve sialorrhea in some patients with ALS. However, these findings were not statistically significant for all patients.

ABOUT THE AUTHORS

Our team is based at three hospitals, Mie University Hospital, National Mie Hospital, and Matsusaka Central General Hospital. Each hospital provides treatments and care for the patients in the hospitals and at the patients' home. We thank the patients who participated in our study, their care providers, visiting nurses, and the ward nurses.

PUBLIC INTEREST STATEMENT

Sialorrhea is mentally and socially stressful for patients with amyotrophic lateral sclerosis (ALS), not only in early stage disease but also in advanced stages with ventilator and tube feeding. Several treatments are available to control sialorrhea but none are without limitations. Some studies have previously indicated the efficacy of scopolamine patches for preventing motion sickness in reducing sialorrhea without severe side effects in patients following otorhinolaryngology/oral surgery, with cerebral palsy, and with Parkinson's disease, although the numbers of patients were small. To date, no blinded controlled studies of scopolamine in ALS have been reported. We conducted a double-blind, crossover study in 10 patients with ALS to evaluate the efficacy and safety of scopolamine patches. The daily oral suction volume of saliva appeared to decrease with scopolamine treatment, although the effect was not statistically significant. Our findings suggest that scopolamine patches represent an optional treatment for sialorrhea.

Subjects: Palliative and Supportive Care; Neurology; Palliative Medicine; Palliative Care Nursing

Keywords: ALS; sialorrhea; scopolamine; transdermal patch

1. Introduction

Sialorrhea, or excess saliva, is mentally and socially stressful for patients with amyotrophic lateral sclerosis (ALS) and their care providers, influencing daily living and quality of life. According to the ALS care database, approximately 50% of patients with ALS complain of sialorrhea (Bradley et al., 2001). Sialorrhea may cause aspiration pneumonia. In the guidelines for the management of ALS by the European Federation of Neurological Societies, amitriptyline, systemic anticholinergic drugs, injection of botulinum toxin (BTX) into salivary glands, irradiation of salivary glands, and transdermal scopolamine (class IV) are recommended to control sialorrhea (Andersen et al., 2011).

In the 1960s, scopolamine was introduced in several countries for motion sickness, antiemesis, and preanesthesia (Brand & Perry, 1966). Scopolamine structurally resembles acetylcholine, and because it competitively blocks muscarinic acetylcholine receptors, it induces mydriasis and exerts secretory, sedative and antispasmodic effects. In the 1980s, scopolamine transdermal patches became commercially available to prevent motion sickness. Dry mouth has been reported as an adverse reaction to scopolamine patches and is related to decreased salivary volume, suggesting the usefulness of scopolamine patches in sialorrhea treatment (Gordon, Ben-Aryeh, Attias, Szargel, & Gutman, 1985). Subsequently, several studies indicated the efficacy of scopolamine patches for sialorrhea, without severe side effects, following otorhinolaryngology/oral surgery (Gordon et al., 1985; Talmi, Zohar, Finkelstein, & Laurian, 1988) and in cerebral palsy (Brodtkorb et al., 1988; Mato et al., 2010; Talmi, Finkelstein, & Zohar, 1990; Talmi et al., 1988) and Parkinson's disease (Brodtkorb et al., 1988), although the numbers of patients were small. In Japan, scopolamine patches are not commercially available, although an ointment can be used as an in-hospital preparation (Shimoda, Hoshino, Sugiyama, Morisaki, & Shiotsu, 2011) and has been considered empirically effective and safe.

Although the usefulness of scopolamine for sialorrhea in patients with ALS has been described, based on the experience of a single patient (Talmi, Finkelstein, & Zohar, 1989), no blinded, controlled study in ALS has been reported to date.

The incidence of tracheostomy invasive ventilation (TPPV) has increased in Asian countries, especially in Japan, where approximately 29% of ALS patient undergo this procedure (Atsuta et al., 2009). Sialorrhea can be stressful not only for patients with early-stage disease but also for those with TPPV and receiving tube feeding. Patients with TPPV require prolonged periods of low-pressure continuous suction. Although patients' activities are restricted, any strategy to reduce their sialorrhea is meaningful, even for ALS patients with TPPV. Although patient numbers in this study were limited, we considered that the outcomes would be beneficial in the treatment of ALS patients. If the efficacy and safety of scopolamine for sialorrhea in ALS are demonstrated, scopolamine patches may represent a novel therapeutic option.

2. Methods

2.1. Patients

Ten ALS patients with sialorrhea were recruited to this study. Patients were diagnosed based on clinical findings, according to the El Escorial-revised Airlie House diagnostic criteria (Brooks, Miller, Swash, & Munsat, 2000).

2.2. Trial design

A crossover, double-blind comparative study was designed. Patients were randomly assigned into two groups: one group initially attached scopolamine patches and the other initially attached placebo patches for 1 week (Figure 1). After a 1 week washout period, the opposite patches were

attached. Transcop® scopolamine patches (Recardati, Inc., Italy) and placebo patches using siliconic fixation tape (Mepitac®, Molnlycke Health Care Inc., Sweden) of the same size and shape as scopolamine patches were prepared and were replaced every three days by medical staff, except for attending doctors, and were covered with fixation tape. In previous crossover studies in healthy control or disabled patients, the washout period was fixed at 4 (Brodtkorb et al., 1988) or 7 (Mato et al., 2010) days; therefore, we used a 1-week washout period before the next test. Volume of saliva was assessed by the weight of oral cotton roll (placed at the oral vestibule and bilateral second molar area for 5 min) and volume of daily oral suction. The severity of sialorrhea and sialorrhea-related difficulty was evaluated using a 10 cm visual analogue scale (VAS). Furthermore, we evaluated the "saliva" item of the ALS Functional Rating Scale-Revised (ALSFRS-R) ((0): always use a piece of tissue paper or handkerchief; (1): the saliva volume is marked, showing leakage; (2): the saliva volume is moderate, showing slight leakage; (3): oral saliva retention results in leakage at night; and (4): normal).

Considering the influence of diet, evaluation was performed at the same time: 1 h after meals. Furthermore, blood pressure, heart rate, and biochemistry (serum protein, albumin, lactate dehydrogenase, creatine phosphokinase, blood urea nitrogen, creatinine, sodium, potassium, chloride, and C-reactive protein) were evaluated before and after patch attachment. Patients or their care providers were questioned regarding adverse events.

Because the first recruited patient developed aspiration pneumonia with the retention of carbon dioxide 2 days after scopolamine patch attachment and subsequently died, our institutional safety review committee assessed that the patient's death was associated with worsening of ALS and suggested that narrower eligibility and strict exclusion criteria should be implemented. Subsequently, we excluded patients with rapid progression rate (ΔFS), calculated as (48-ALSFRS-R at time of diagnosis/duration [months] from onset to diagnosis) ≥0.67) (this did not apply to respirator-wearing patients) and those with marked respiratory hypofunction (%vital capacity [VC]: ≤30%, or $PaCO_2$: ≥45 mmH_2O) where the attachment of a respirator was not planned. At the beginning of the study, we planned to include patients still able to eat unaided, but after adjusting the exclusion criteria, we could not include these patients.

The study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research of the Japanese Ministry of Health, Labour and Welfare. All participants provided written informed consent. The ethical committee for each site approved the protocol and any modifications (No. 2,589 of the institutional review board [IRB] at Mie University, No. 103 and 123 of the IRB at Matsusaka Central General Hospital, and No. 27–53 of the IRB at National Mie Hospital). Trial registration: The University Hospital Medical Information Network, Japan: UMIN 000011494.

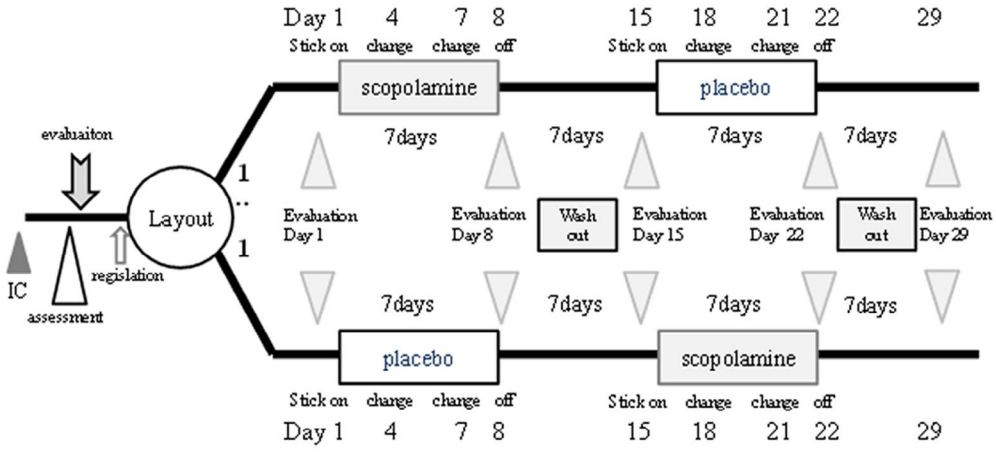

Figure 1. Trial design.

Note: IC: informed consent.

2.3. Statistical analysis

The primary endpoint was efficacy of scopolamine for treating sialorrhea using VAS and secondary endpoints were the saliva item of ALSFRS-R, volume of saliva, and adverse events. Changes in VAS score and volume of saliva were analyzed using the paired t-test or Wilcoxon's signed rank test. Changes in ALSFRS-R scores were examined using the McNemar test. We used SPSS software, version 22 (SPSS Inc., Chicago, IL, USA).

Initially, we estimated that 20 patients were required to assess the efficacy of scopolamine by more than one point score difference of VAS between scopolamine and placebo if the standard deviation of difference was 1.5, level of significance was 5%, and power was 80%. However, we adjusted the design according to the new exclusion criteria and ultimately included 10 patients. The threshold for significance was $p < 0.05$.

3. Results

3.1. Clinical characteristics of patients

From September 2013 to March 2016, 10 patients were enrolled (three males and seven females) with a mean age of 71.6 years. One patient had bulbar paralysis-type and the others had classical-type. The mean duration of disease was 112.3 months. In nine patients, a positive pressure ventilator was attached through tracheotomy and all patients required tubal feeding through a gastric fistula. No patient had previously received any medication for sialorrhea. The patients' profiles are shown in Table 1. Eight patients were statistically analyzed to assess endpoints, as two discontinued because of pneumonia.

3.2. Changes in sialorrhea

Self-assessment of sialorrhea using the VAS was based on the severity of sialorrhea and sialorrhea-related difficulty. In the scopolamine group, the mean severity of sialorrhea before and after use was 54.4 ± 2.0 mm and 43.7 ± 18.7 mm, respectively. In the placebo group, it was 60.0 ± 32.1 mm and 55.6 ± 29.0 mm. Concerning sialorrhea-related difficulty, the values before and after using scopolamine were 60.0 ± 28.8 and 46.3 ± 29.2 mm, respectively. In the placebo group, they were 58.8 ± 31.8 and 55.6 ± 29.0 mm. There were no significant differences between the two groups (severity: $p = 0.384$, difficulty: $p = 0.388$; paired *t*-test). However, in the scopolamine group, all patients showed "no change" or "improvement", whereas some patients in the placebo group showed "deterioration" (severity: $p = 0.392$, difficulty: $p = 0.172$; McNemar test) (Figure 2(a)).

Table 1. Baseline clinical characteristics of patients

Patient no.	Age (y)	Sex	Weight (kg)	Height (cm)	Time since diagnosis (months)	ALSFRS-R (total)	ALSFRS-R (saliva)	Nutrtion	Respirator	Episode of Pneumonia	Result
1	72	F	32.6	148.5	30	24	0	Tube	no	–	Withdrew
2	68	M	58.2	170.0	111	5	0	Tube	TPPV	+	Completed
3	69	F	40.9	158.0	85	4	0	Tube	TPPV	+	Completed
4	77	F	40.8	147.0	132	4	0	Tube	TPPV	+	Withdrew
5	77	F	30.1	152.0	204	4	0	Tube	TPPV	–	Completed
6	79	F	38.0	144.0	72	8	2	Tube	TPPV	–	Completed
7	46	F	45.1	161.0	62	3	2	Tube	TPPV	–	Completed
8	79	F	39.8	147.0	133	1	0	Tube	TPPV	–	Completed
9	82	M	42.6	162.0	94	2	1	Tube	TPPV	+	Completed
10	67	M	48.6	160.0	139	2	2	Tube	TPPV	+	Completed

Notes: Tube: tube feeding via gastric fistula, TPPV: tracheostomy positive pressure ventilation.

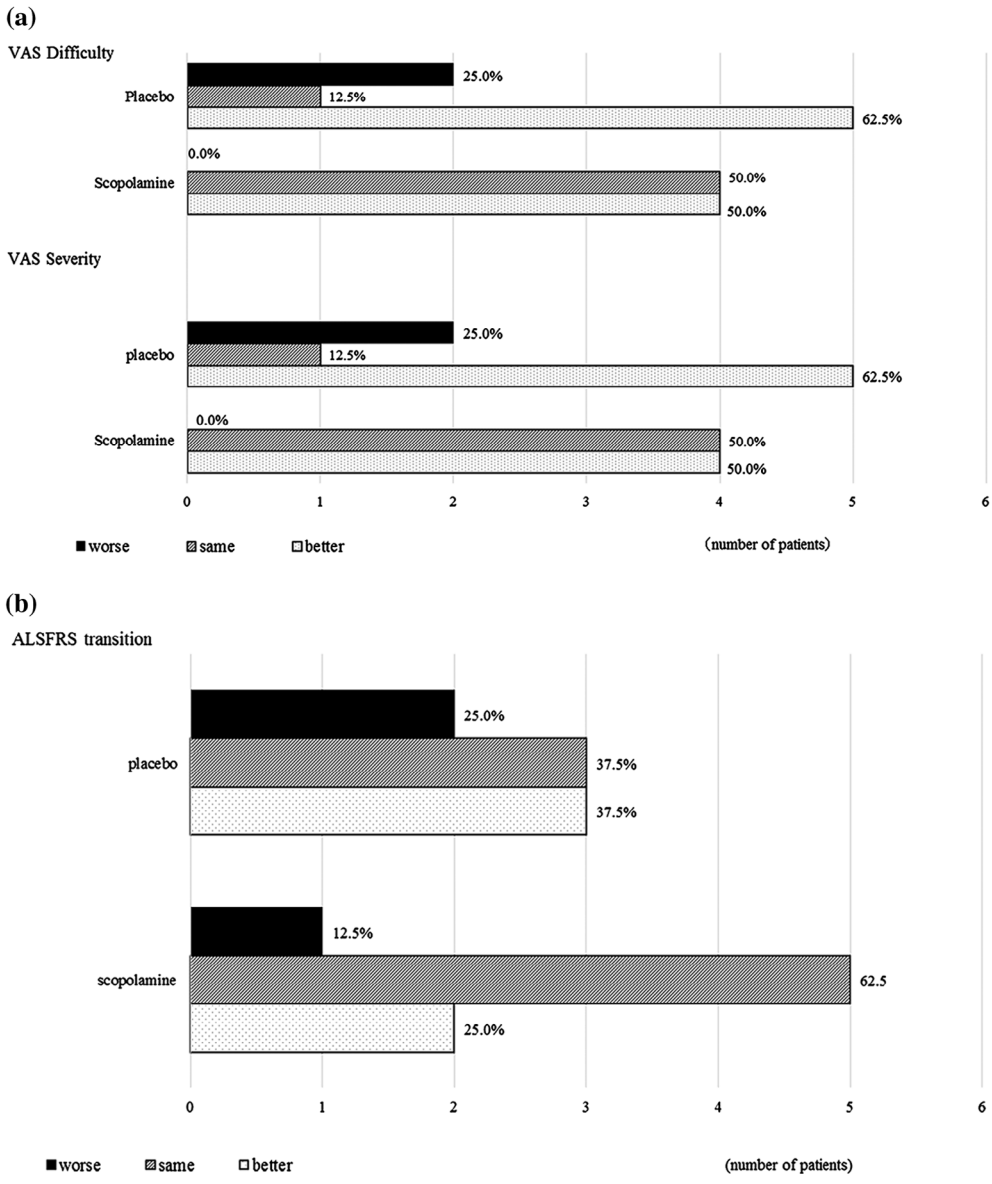

Figure 2. Transition of assessment of sialorrhea. (a) VAS on the severity of sialorrhea and sialorrhea-related difficulty. In 25% of patients assessed, sialorrhea worsened with placebo compared with scopolamine. (b) Saliva item of ALSFRS-R assessment.

Note: VAS: visual analogue scale.

For assessment with the "saliva" item of the ALSFRS-R, changes after intervention were classified into three grades (better, same, and worse). In both the scopolamine and placebo groups, an improvement was reported for some patients, although there was no significant difference ($p = 0.572$, McNemar test) (Figure 2(b)).

3.3. Changes in the volume of saliva

In the scopolamine group, the mean cotton roll weight before and after use was 2.35 ± 1.95 and 2.19 ± 1.46 g, respectively. In the placebo group, it was 2.77 ± 2.31 and 2.49 ± 1.99 g. There were no significant differences observed between the two groups ($p = 0.674$, Wilcoxon's signed rank test). We also measured the volume of daily oral suction. The box plot of the mean volume during each week of the attachment and washout periods is shown in Figure 3. Patients who received scopolamine showed a greater decrease in volume of daily saliva suction than placebo, but the difference was not statistically significant ($p = 0.069$, Wilcoxon's signed rank test).

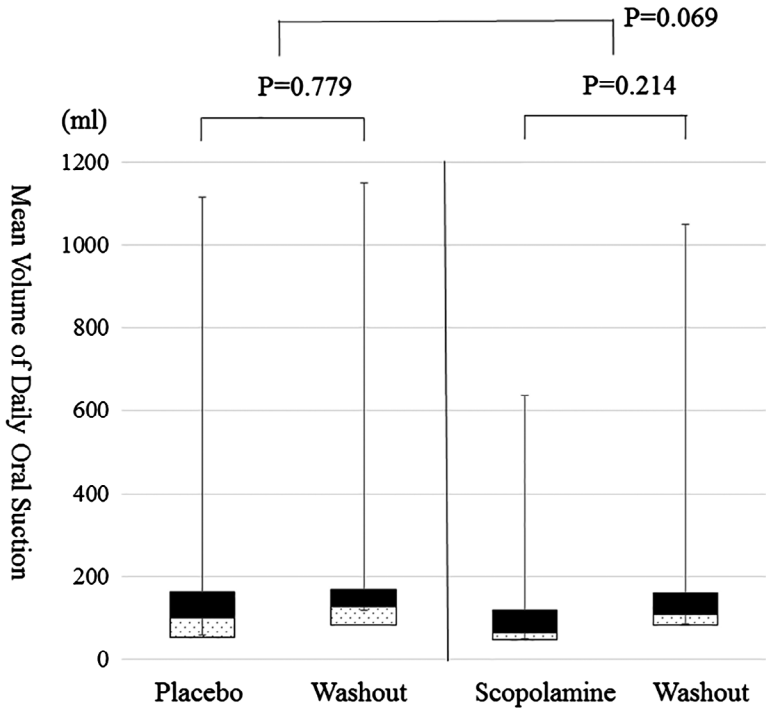

Figure 3. Box plot of mean volume of daily saliva suction.

Note: Each bar indicates median volume.

3.4. Adverse events

Patient no.1 developed aspiration pneumonia and discontinued the study as described previously. Furthermore, patient no. 4 used a respirator with a tracheotomy but the respirator connection was accidently detached for several minutes on day 18 of the study. Subsequent management caused pneumonia and pneumothorax to develop, so the patient was discontinued the study. Associations between the development of pneumonia and the test drug in the two cases were considered unlikely.

One patient complained of dry mouth but continued in the study. In this patient, the cotton roll weight and daily oral suction were markedly decreased and the VAS (severity) was improved by scopolamine. No other patient complained of any other symptom. No remarkable differences were observed in blood pressure, pulse, SpO2, or hematological/biochemical parameters.

4. Discussion

To our knowledge, this is the first prospective double-blind comparative study of scopolamine use for reduction of sialorrhea in patients with ALS. There were no statistically significant differences in VAS for severity of sialorrhea and sialorrhea-related difficulty between scopolamine and placebo, however a marked difference in the mean "sialorrhea-related difficulty" score was observed between the two groups. In addition, scopolamine appeared more likely to reduce the volume of daily oral suction than placebo. Scopolamine patches can reduce saliva production in ALS patients but the clinical applicability is likely limited to patients with TPPV suffering from sialorrhea.

When investigating the treatment of sialorrhea in ALS, there are two important issues. One is the difficulty in enrolling patients because ALS progression varies. In addition, respiratory disorders or dysphagia may lead to rapid changes in ALS. The other issue is the difficulty in evaluating sialorrhea. In many studies, VAS has been adopted. Because of the small number of patients and the high degree of variance in the VAS, a statistically significant outcome was difficult to achieve. In addition, it may be difficult to accurately evaluate symptoms in patients using a ventilator. For this reason, we evaluated symptoms and adverse reactions through speech therapists using a communication device, but such conditions led to a perceived low incidence of adverse events. This trend warrants further investigation with a larger sample size and revised evaluation of sialorrhea.

As adverse events related to scopolamine patches, dry mouth (Brodtkorb et al., 1988; Clissold & Heel, 1985; Mato et al., 2010; Talmi et al., 1988, 1990; Tassinari, Poggi, Fantini, Tamburini, & Sartori, 2005; Tysnes, 2008), skin reactions (Mato et al., 2010), photophobia (Brodtkorb et al., 1988; Talmi et al., 1988, 1990), frequent urination (Mato et al., 2010; Talmi et al., 1990), sleepiness (Brodtkorb et al., 1988), hallucination (Clissold & Heel, 1985; Tysnes, 2008), and confusion (Tassinari et al., 2005; Tysnes, 2008) have been reported. In previous studies, the incidence of dry mouth was markedly high, whereas the incidence of other adverse events was very low. These observations may be of considerable merit when comparing scopolamine patches with other treatments. However, the use of scopolamine patches should be avoided in patients where the consciousness level or respiratory state is unstable, with hypercapnia. Similar precautions are also needed for BTX therapy or radiotherapy. Moreover, adverse events related to BTX include xerostomia (Jackson et al., 2009; Mato et al., 2010), topical pain (Costa et al., 2008), masticatory disorder involving the facial muscle, jaw dislocation (Tan, Lo, Seah, & Auchus, 2001), respiratory tract infection, and an increase in the viscosity of saliva (Costa et al., 2008; Jackson et al., 2009). Concerning radiotherapy, buccal pain (Andersen, Grönberg, Franzen, & Funegård, 2001), xerostomia (Andersen et al., 2001), and edema (Guy et al., 2011) have been reported. Thereby, the safety of BTX or radiotherapy for sialorrhea in patients with ALS requires consideration. Our results may indicate a limited benefit compared with BTX. A statistically significant effect of BTX type B in use of VAS of saliva problem and volume of saliva has been demonstrated (Jackson et al., 2009). However, a trend for decreased volume of daily oral suction suggests the potential of scopolamine. Our findings suggest that scopolamine patches may decrease sialorrhea in patients with ALS using TPPV or stable respiration.

To date, scopolamine patches have been used in the field of palliative care based on experience. In Japan, they are not commercially available and in some institutions, scopolamine ointment is dispensed for application to the papillary process site. Clinically, the effects of this procedure on sialorrhea have been confirmed, and the incidence of adverse reactions was low, suggesting its usefulness. However, it is necessary to apply the ointment daily. We expect that scopolamine patches will become available for ALS patients with sialorrhea in the future.

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Competing Interests
The authors declare no competing interest.

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