

Submucous turbinectomy decreases not only nasal stiffness but also sneezing and rhinorrhea in patients with perennial allergic rhinitis

S. MORI, S. FUJIEDA, M. IGARASHI, G. K. FAN and H. SAITO

Department of Otorhinolaryngology, Fukui Medical University, Fukui, Japan

Summary

Background Turbinate surgery, in which mucous epithelium is resected, has often been used for patients with perennial allergic rhinitis, since the mucous epithelium is the principal site for immunoglobulin (Ig)E-mediated allergic reactions and chronic inflammation.

Objective To assess the effect of submucous turbinectomy on allergic rhinitis.

Methods Sixty patients with severe perennial allergic rhinitis underwent submucous turbinectomy and were followed-up for 1 year. Nasal symptoms were evaluated with a standard symptom score. Rhinometry was used to evaluate nasal congestion, and nasal provocation tests *in vivo* were performed to evaluate allergic reactions. In 16 cases, biopsies from the nose were also available for immunohistochemical analysis. These examinations were performed before and after submucous turbinectomy.

Results The mean total nasal symptom score (7.2 ± 1.7 , mean $\pm$ SD before surgery) was significantly reduced after surgery (1.2 ± 1.4 , $P < 0.0001$), and the effect of the surgery on nasal symptoms continued for at least 12 months (1.9 ± 1.8 , $P < 0.0001$). Submucous turbinectomy reduced both nasal discharge and sneezing, as well as nasal stiffness. Histopathological examination following surgery revealed that the lamina propria was occupied by fibrous tissues, and that the number of vessels, nasal glands, eosinophils and infiltrating IgE⁺ cells decreased in the turbinate. There were no significant differences in the levels of either house dust mite-specific or non-specific IgE in the serum between before and after surgery.

Conclusion Submucous turbinectomy preserving the ciliary epithelium is a powerful strategy for improving nasal symptoms induced by allergic reaction via the reduction in the number of allergy-related cells in the nose.

Keywords: airflow, allergic rhinitis, immunoglobulin E, mast cell, provocation test, rhinometry, submucous turbinectomy, surgery, symptom score

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Introduction

Turbinate surgery is a useful treatment for chronic nasal stiffness induced by perennial allergic rhinitis [1]. Since a large proportion of nasal allergic reactions occur in the superficial layer of the inferior turbinate, it has been recommended that the nasal mucosa, including the epithelial layer, be extensively resected. For that purpose, various

methods, including lasers (CO₂ [2–5], Nd:YAG [6], potassium-titanyl phosphate [7,8]) and a chemical agent (trichloroacetic acid [9]) have been employed to resect the mucosa in allergic nasal disease.

Another form of turbinate surgery, submucous turbinectomy (ST), has been performed to reduce nasal congestion, but this method is not expected to improve the nasal symptoms caused by nasal allergy because it preserves the nasal mucosa. Thus, until now, ST has been only performed in patients with nonallergic, hypertrophic rhinitis [10,11].

Correspondence: S. Mori, Department of Otorhinolaryngology, Fukui Medical University, 23 Shimoaizuki, Matsuoka, Fukui, 910–1193, Japan.

However, we have observed many cases of improved perennial allergic rhinitis after ST. The improvements occurred not only in nasal stiffness, but also in sneezing and rhinorrhea.

The purpose of this study was to determine the effectiveness of ST in the treatment of severe perennial allergic rhinitis and to investigate why ST is effective in relieving allergic symptoms.

Methods

Clinical cases and ST procedures

A total of 60 patients (41 men and 19 women, mean 25.9 years) with perennial allergic rhinitis caused by house dust mite (HDM) underwent ST and were followed-up for 12 months postoperatively. All patients with perennial allergic rhinitis had a high titre of anti-*Dermatophagoides pteronyssinus*-specific immunoglobulin (Ig) E antibodies. They also had positive skin tests and positive provocation tests on the nasal mucosa using HDM. They had a history of perennial nasal allergic symptoms that were resistant to various medications and to inhalation therapy in the nose. None had a history of HDM-specific immunotherapy. The control consisted of 29 patients with nonallergic hypertrophic rhinitis (23 men and six women, mean 39.8 years) who underwent ST. This study was conducted at Fukui Red Cross Hospital between 1992 and 1994, and at Fukui Medical University between 1994 and 1997. Informed consent was obtained from all patients.

ST was performed under local anaesthesia by injection with 0.5% lidocaine and 1 : 10000 adrenaline. Incision of the nasal mucosa was performed along the edge of the aperture

piriformis, and the turbinate bone was isolated and removed (Fig. 1a). In 30 of 60 cases, mucosa of the inferior turbinate was too thick to form a sufficient nasal airway by resecting the turbinate bone. In these cases, we added wedge-shaped mucous turbinotomy (WST) and formed turbinate without the lacking site in the epithelium (Fig. 1b). In addition, traditional septoplasty was performed in 54 cases with nasal septum deviation.

Timeline for the evaluation

All patients were referred to our clinic 2 and 12 months after surgery. The daily grade of nasal congestion and the frequency both of sneezing and nasal blowing were recorded for 2 weeks prior to their presentation at the clinic. All patients were free from postoperative medication for nasal allergy in principle. When patients had complained of nasal allergic reaction, we permitted them to use an intranasal inhalation of beclomethasone dipropionate. In such cases, the inhalation was stopped at least 2 weeks before the evaluation period.

Evaluation of sneezing, rhinorrhea, subjective nasal stiffness grade and total nasal symptom score

Means of the daily frequency of sneezing and nasal blowing and a subjective grade measuring nasal stiffness were evaluated using a numerical scoring system, as follows: for both sneezing and nasal blowing, grade 0 (none), grade 1 (one to four times per day), grade 2 (five to nine times per day) and grade 3 (more than 10 times per day); for nasal stiffness, grade 0 (none), grade 1 (mild), grade 2 (moderate) and grade 3 (severe) [12]. Total nasal symptom score was

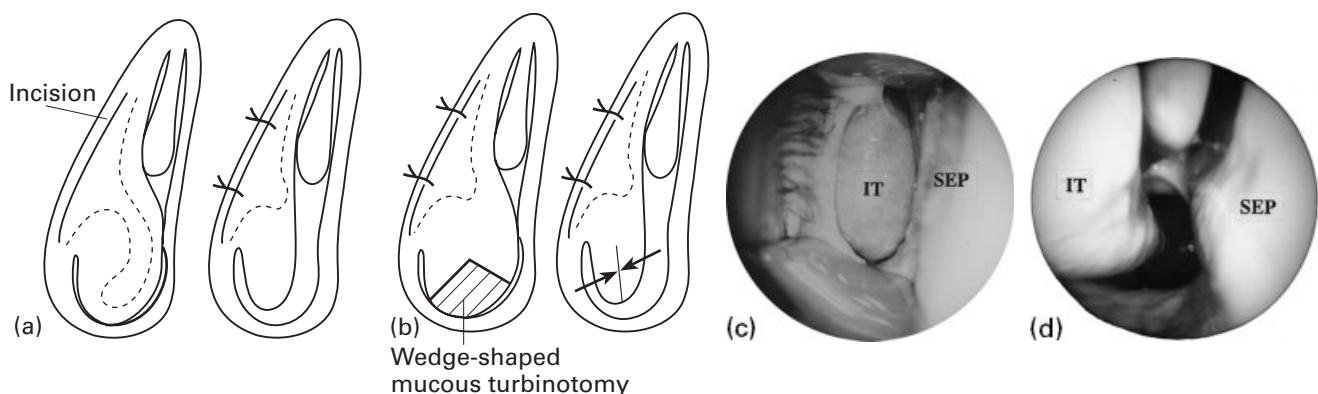


Fig. 1. ST operative procedures (a, b) and rhinoscopic findings of right side nose before (c) and 2 months after ST (d). (a) An incision was made along the edge of the aperture piriformis. The turbinate bone was isolated and removed. (b) In the 30 patients whose turbinate mucosa was too thick to create a sufficient nasal airway, wedge-shaped turbinotomy was added. (c) The inferior turbinate in a patient with nasal allergy before ST. (d) ST reduced the volume of the inferior turbinate and created a sufficient space in the nose. Little crust formation was detected. (IT: inferior turbinate, SEP: nasal septum)

expressed as the sum of the three scores. The maximum possible score was 9.

Evaluation of nasal airflow value

Total nasal airflow was measured using a rhinomanometer (MPR-2100, Nihon Koden, Tokyo, Japan) by the anterior method with the patient in a sitting position. The value of expiration per second at the pressure of 100 Pa in the nasopharynx [9] was evaluated.

Provocation test

A provocation test was performed using a disk that contained HDM (TORII, Tokyo, Japan) on the mucosa of the anterior site of the inferior turbinate. When provocation tests were performed after surgery, the challenged site was apart from the incision scar and the site of the linear scar of the inferior turbinate for the cases who had the added WST. The provocation test results were graded as follows: grade 0 (none or one allergic symptom out of three allergic symptoms, local oedema of the mucosa, sneezing and rhinorrhea occurred within 15 min after challenge), grade 1 (two allergic symptoms), grade 2 (all three allergic symptoms) and grade 3 (all three allergic symptoms with more than six sneezes).

Histopathological or immunohistochemical study

In 16 cases, we were able to obtain informed consent for histopathological and immunohistochemical studies, which we performed before and after surgery. The nasal mucosa was biopsied at the anterior site of the inferior turbinate with the infiltration anaesthesia with 4% lidocaine. Specimens were immediately fixed into 4% paraformaldehyde in 0.1 mol/L phosphate buffer (pH 7.4) for over 24 h. After fixation, samples were embedded in paraffin and sectioned at 4 µm thickness. They were deparaffinated and treated with ethanol, then rinsed with pH 7.4 phosphate-buffered saline (PBS). Histopathological changes were detected by Mayer haematoxylin and eosin staining.

Immunohistochemical staining was performed to detect IgE-positive cells, eosinophils (major basic protein [MBP]-positive cells), B cells (CD20⁺ cells) and plasma cells (CD38⁺ cells) migrating in the preoperative and postoperative nasal mucosa by the traditional Avidin-Biotin-Complex technique. Specimens were washed in distilled water and rinsed with pH 7.4 PBS, then incubated in 0.3% H₂O₂ solution dissolved in absolute methanol at room temperature for 15 min to inhibit endogenous peroxidase activity. After washing in distilled water and rinsing with PBS, they were incubated with mouse antihuman IgE (ε-chain Fc region specific) mAb diluted at 1:1000 [13] (a kind gift of

Dr Andrew Saxon, University of California, Los Angeles, CA, USA), mouse antihuman MBP (specific granule with eosinophils) mAb diluted at 1:50 (Harlan Sera-Lab, Loughborough, UK), mouse antihuman CD20 (expressed in unstimulated and activated B cells) mAb diluted at 1:50 (Dako A/S, Glostrup, Denmark) or mouse antihuman CD38 (expressed in Langerhans' cells and B cells/plasma cells) mAb diluted at 1:50 (Dako A/S) at 4°C for 24 h. All specimens were treated with biotinylated-anti mouse IgG (Dako A/S LSAB kit) for 1 h, rinsed with PBS, and reacted with an avidin-biotin-peroxidase complex for 1 h at room temperature. After rinsing with pH 7.4 TRIS-HCl buffer, peroxidase colour visualization was carried out with 15 mg of 3–3'-diaminobenzidine tetrahydrochloride (DAB, Wako, Tokyo, Japan) dissolved in 100 mL TRIS-HCl buffer with 8 µL of 30% H₂O₂ for 5 min. Nuclear counter-staining was carried out with Mayers haematoxylin for 30 s before mounting. Mean numbers per field of stained cells were counted at a magnification of ×400 in the lamina propria below the basement membrane in more than 10 fields.

Evaluation of IgE level in the serum

In 20 cases, we obtained informed consent and the values both of non-specific and *D. pteronyssinus*-specific IgE in the serum were also measured by ELISA both preoperatively and 3 months postoperatively.

Statistical analysis

All data were analysed with the Wilcoxon's test.

Results

Nasal stiffness

A comparison of the intranasal findings before and 2 months after ST is shown in Fig. 1(c,d). ST reduced the volume of inferior turbinate and made enough space for an airway in the nose. Little crust formation was detectable on the turbinate mucosa. Before ST, mean nasal airflow value in the nasal allergy group was $266.8 \pm 252.6 \text{ cm}^3/\text{s}$ (mean $\pm$ SD, Fig. 2). There were no significant differences between the mean value of the nasal allergy group and that of the nonallergic hypertrophic rhinitis group ($289.9 \pm 251.3 \text{ cm}^3/\text{s}$) before ST. The nasal airflow value 2 months after surgery was significantly improved by ST in the nasal allergy group ($666.4 \pm 392.3 \text{ cm}^3/\text{s}$, $P < 0.0001$). Also, significant improvement of nasal airflow was obtained in the nonallergic hypertrophic rhinitis group after ST ($728.8 \pm 259.6 \text{ cm}^3/\text{s}$, $P < 0.0001$). Improvement in nasal airflow was found at 12 months after ST in both the nasal allergy group ($476.9 \pm 237.0 \text{ cm}^3/\text{s}$, $P < 0.0005$) and the

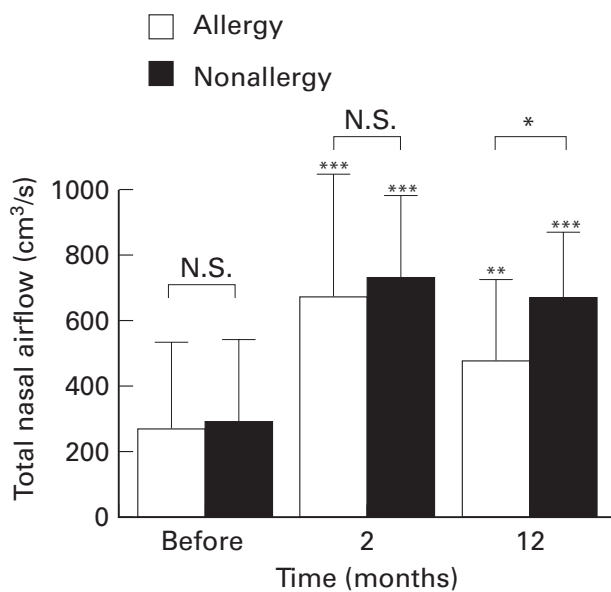


Fig. 2. Comparison between pre- and postoperative total nasal airflow. Significant improvement of total nasal airflow values was obtained and maintained at least 12 months after ST in both groups. * $P < 0.05$, ** $P < 0.0005$, *** $P < 0.0001$.

nonallergic hypertrophic rhinitis group ($666.4 \pm 192.2 \text{ cm}^3/\text{s}$, $P < 0.0001$) (Fig. 2). Fifty-four of the 60 patients with nasal allergy underwent septal surgery. There were no significant differences both in the preoperative background and the postoperative outcome between the two groups with and without septoplasty (Table 2).

Sneezing, nasal discharge and total nasal symptom score

The mean total nasal symptom score was 7.2 ± 1.7 before ST in the nasal allergy group. The mean total nasal symptom score was significantly reduced to low levels after ST (1.2 ± 1.4), and this low score continued 12 months after ST (1.9 ± 1.8) (Table 1). The proportion of patients who were free from all symptoms for 2 months and 12 months was 50.0% (29 patients) and 33.3% (20 patients), respectively.

The number of patients with severe sneezing (more than five times per day) was 44 (73.3%) before ST. This number was strikingly reduced to four (6.9%) and six (10.0%) 2 months and 12 months after ST, respectively. Twenty-nine patients (48.3%) were free from sneezing for at least 12 months after ST. The number of patients with severe nasal blowing (more than five times per day) was 48 (80.0%) before ST. This number decreased to eight (13.8%) and 12 (20.0%) 2 months and 12 months after ST. Twenty-six patients (43.3%) were free from rhinorrhea for at least 12 months. Septoplasty had not influenced on the

Table 1. Improvements in nasal symptom scores and provocation test scores after ST

	Number	Score (mean $\pm$ sd)	P-value
<i>Total symptom score</i>			
Before	60	7.2 ± 1.7	
2 months After	58	1.2 ± 1.4	$P < 0.0001^*$
12 months After	60	1.9 ± 1.8	$P < 0.0001^\dagger$
<i>Nasal stiffness</i>			
Before	60	2.8 ± 0.5	
2 months After	58	0.2 ± 0.4	$P < 0.0001^*$
12 months After	60	0.4 ± 0.6	$P < 0.0001^\dagger$
<i>Sneezing</i>			
Before	60	2.1 ± 1.0	
2 months After	58	0.5 ± 0.6	$P < 0.0001^*$
12 months After	60	0.7 ± 0.8	$P < 0.0001^\dagger$
<i>Rhinorrhea</i>			
Before	60	2.3 ± 0.9	
2 months After	58	0.6 ± 0.8	$P < 0.0001^*$
12 months After	60	0.9 ± 0.9	$P < 0.0001^\dagger$
<i>Provocation test score</i>			
Before	60	2.1 ± 0.9	
2 months After	55	0.8 ± 0.7	$P < 0.0001^*$
12 months After	55	0.5 ± 0.7	$P < 0.0001^\dagger$

*2 months after vs before. † 12 months after vs before

improvement of total symptom score after the surgery in allergic patients (Table 2).

Provocation test

To evaluate *in vivo* allergic reaction in the patients, provocation tests using a disk containing house dust were performed both before and after ST. A positive reaction occurred in 57 of 60 cases (95.0%) before ST. Especially strong reactions (grade 3) occurred in 38.3% of the patients (23 cases) before ST. After ST, 72.7% (40 of 55 cases, 2 months) and 61.8% (34 of 55 cases, 12 months) of the patients were shown to be free from nasal allergic reactions by nasal allergen challenge. No patients had stronger reactions 12 months after ST than before ST (Table 1).

Histopathological and immunohistochemical findings

Before ST, numerous eosinophils had infiltrated the noses of the patients in the allergy group (Fig. 3a). After ST, almost all the lamina propria was occupied by collagen fibre nets and was infiltrated by few nasal glands, eosinophils or venous plexus (Fig. 3b).

Immunohistochemical study showed that migration of IgE⁺ cells at the lamina propria was easily observed

	Without septoplasty <i>n</i> = 6	With septoplasty <i>n</i> = 54	<i>P</i> -value*
Total nasal airflow			
Before	85.2 ± 103.8†	284.0 ± 256.2	NS
2 months After	727.6 ± 369.9	659.9 ± 397.8	NS
12 months After	497.6 ± 417.2	474.5 ± 214.4	NS
Total symptom score			
Before	7.2 ± 1.7	7.6 ± 2.6	NS
2 months After	1.2 ± 1.4	1.2 ± 1.1	NS
12 months After	2.6 ± 1.8	1.9 ± 1.9	NS
Provocation test score			
Before	2.6 ± 0.5	2.0 ± 0.9	NS
2 months After	0.5 ± 0.6	0.4 ± 0.7	NS
12 months After	1.0 ± 1.0	0.4 ± 0.6	NS

*Simple ST vs ST with WST, †Nasal airflow was evaluated by a rhinomanometry. The volume represents cm³/s.

before ST, but was only found with difficulty after ST (data not shown). When the number of IgE⁺ cells was counted under the microscope, the mean number of IgE⁺ cells per field was significantly reduced after ST. Also, a reduction in MBP⁺, CD20⁺ and CD38⁺ cells infiltrating the nose was found after ST (Table 3).

Serum IgE level

The mean value of the preoperative index of specific IgE against *D. pteronyssinus* in the serum was 4.9 ± 1.5 units in the allergy group. The post surgical value was unchanged (4.8 ± 1.5 units). The mean value of preoperative non-specific IgE in the serum was 1060.4 ± 1497.2 IU/mL. Also, non-specific IgE titre in the serum was not reduced after ST (953.7 ± 1412.9 IU/mL) (Table 3).

Discussion

ST has been widely performed for chronic hypertrophic rhinitis [10,11], but not for allergic rhinitis. This is because the mucous epithelium has been regarded as the central site for IgE-mediated allergic reaction and inflammation characterized by nasal eosinophilia, and therefore was resected for the treatment of allergic rhinitis. Since the epithelial layer is preserved in ST, nobody has performed ST to reduce nasal symptoms in patients with allergic rhinitis. In this study, we showed that ST is as effective as other surgeries for allergic rhinitis, suggesting that resection of the epithelial layer is not necessary for improvement of allergic symptoms.

After ST, fibrous tissue occupied the lamina propria of the nose, but normal mucous epithelium, including cilia, was

Table 2. Comparison of the efficacy between two groups with and without septoplasty

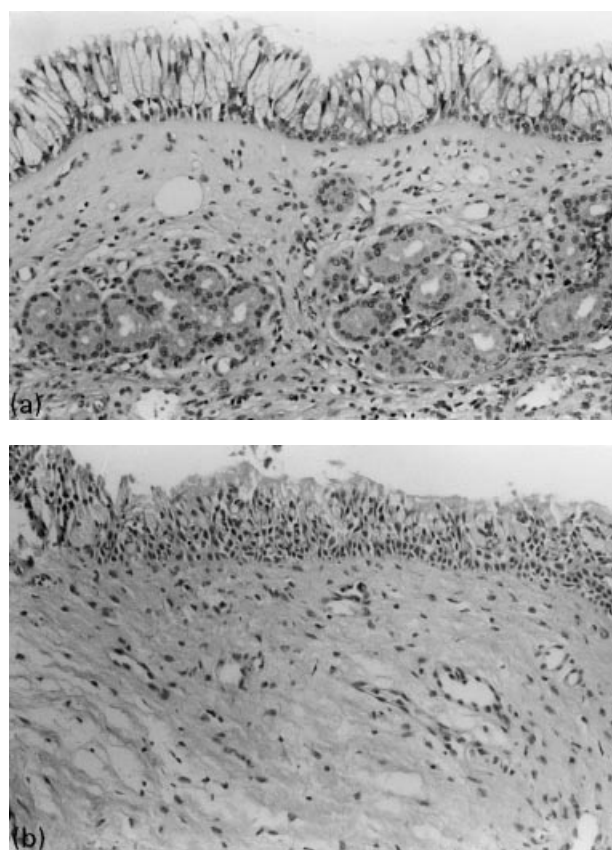


Fig. 3. Changes in histopathological findings and cell migration in the lamina propria after ST. Mayer haematoxylin and eosin staining before (a) and after (b) ST (×200). The lamina propria was occupied by the collagen fibre nets and infiltrated by few inflammatory cells after ST.

preserved intact. Standard turbinectomy, laser surgery or chemosurgery also made a scar formation at the site of lamina propria [4,5,9], with the loss of the mucous epithelium. However, regeneration of the epithelium in the inferior turbinate occurred at least 1–2 months after standard turbinectomy, laser surgery or chemosurgery [2,5,7,8] with a decrease in the effectiveness on nasal stiffness. Thus, the efficacy of standard turbinate surgery seems to depend on the regeneration of the mucous epithelium. On the other hand, ST preserves the epithelial layer. Preservation of the nasal ciliary epithelium is clinically important in preventing problems caused by bacteria, fungus or allergens and in maintaining normal physiological activity in the upper respiratory tract [14]. Usually, a crust is formed over the surgical layer after standard turbinate surgery resecting the epithelial layer. Patients complain of nasal blockage due to crust formation, have a high risk level of bacterial infection, and must be treated frequently during this period. In our experience, ST has been accompanied by little crust formation and has required few postoperative treatments. All of our patients were free from local infections. In addition, when we evaluated nasal clearance in five cases, saccharin transport times were maintained at 10–20 min (reaching the

mesopharynx within 35 min in normal individuals [15]) a month after surgery (data not shown). We believe that our good clinical outcome was due to preservation of the epithelium and scar formation on the lamina propria, and the loss of the turbinate bone is thought to get the good result in nasal airflow.

The fibrous change in the lamina propria led the nasal glands and the number of vessels in the inferior turbinate to decrease. The reduction of the nasal glands may have an immediate effect on the decrease of rhinorrhea. The reduction of vessels may have improved the local oedema of the inferior turbinate mucosa.

In the typical type I allergic pathogenesis of allergic rhinitis, mast cells and eosinophils have been established as the allergic inflammation effector cells [16–18]. The reduced infiltration of these cells was expected to weaken allergic reaction and inflammation immediately. Cytokines released from these cells are important factors in the differentiation and accumulation of themselves [19]. Thus, the reduction of infiltrated immunocompetent cells may inhibit allergic inflammation in the orchestrated manner exhibited by the cytokine network. Recently, it was reported that IgE isotype switching is also induced in the local mucosa of the nose and the trachea [20,21]. While IgE isotype switching occurred in the presence of IL-4 or IL-13 [20,22–24], inflammatory cytokine IL-8 and interferon- γ inhibited IgE production by human B cells [25]. Major sources of IL-4 and IL-13 include mast cells [18,20], and the source of IL-8 and interferon- γ is fibroblasts [26]. The reduction of such immunocompetent cell infiltration and the increase of fibroblasts in the lamina propria may inhibit IgE production in the nasal mucosa locally.

In nasal mucosa, autonomic and sensory nerve fibres are distributed around the vessels and nasal glands and inside the epithelial layer [27,28]. Nerves control the physiological functions of the nasal mucosa, microvascular circulation, secretion of nasal discharge [29] and immunoglobulin production [30,31]. These nerve fibres pass through the sphenopalatine foramen and branch into the inferior turbinate mucosa. Surgically induced injury at the submucous or periosteal area may broadly cut off these peripheral nerve fibres. The reduction of nerve fibres in the nasal mucosa after ST might be a cause of the decrease in allergic symptoms after ST.

We obtained short-term improvement in nasal symptoms through ST. However, the effect of surgical treatments for allergic rhinitis seems to gradually lessen [4,5,9]. In particular, while the airflow value of the allergic group 12 months after ST was significantly lower than the value 2 months after ST ($P < 0.05$). We hypothesize that the collagen fibrous tissue is gradually broken down by collagenases such as matrix metalloproteinases, and regeneration of the vessels and innervations continues to increase in the normal process

Table 3. Changes in infiltrated cells in the lamina propria and serum IgE level

	Number	Cells/field (mean $\pm$ SD)	P-value*
<i>IgE⁺ cells</i>			
Before	16	8.7 $\pm$ 3.4	0.0007
After	16	1.1 $\pm$ 1.1	
<i>MBP⁺ cells</i>			
Before	16	11.3 $\pm$ 14.5	0.0342
After	16	2.1 $\pm$ 4.4	
<i>CD20⁺ cells</i>			
Before	16	4.3 $\pm$ 3.3	0.0015
After	16	0.7 $\pm$ 1.1	
<i>CD38⁺ cells</i>			
Before	16	4.7 $\pm$ 4.3	0.0037
After	16	1.2 $\pm$ 2.2	

	Number	Value (mean $\pm$ SD)	P-value*
<i>Non-specific IgE in the serum</i>			
Before	30	1060.4 $\pm$ 1497.2†	NS
After	30	953.7 $\pm$ 1412.9†	
<i>Specific IgE index against D. pteronyssinus</i>			
Before	30	4.9 $\pm$ 1.5‡	NS
After	30	4.8 $\pm$ 1.5‡	

*After vs before, †IU/mL, ‡Units

of wound healing [32]. Our study shows that, for at least 12 months, ST is useful for inhibiting allergic reactions and improving nasal congestion. Further evaluation regarding the long-term results after more than 12 months is required.

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