

A study of the effectiveness of chemosurgery with trichloroacetic acid for Japanese cedar pollenosis in terms of the chemical mediator levels in the nasal discharge and results of nasal provocation testing[☆]

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Abstract

Objective: The purpose of the present study was to investigate the effectiveness of chemosurgery with 80 w/v% trichloroacetic acid (TCA) for the treatment of Japanese cedar pollenosis. The effectiveness of this treatment was evaluated in terms of the levels in the nasal washings of the chemical mediators histamine and eosinophil cationic protein, and the reactivity in the nasal provocation test.

Methods: Patients of cedar pollenosis were divided into two groups, the TCA-treated group ($n = 90$) and the group that was not treated with TCA (nonTCA-treated group) ($n = 79$), according to whether or not they received TCA treatment. In both the groups, the levels of the two aforementioned mediators in the nasal washings were measured during the pollen dispersal season. In addition, allergen provocation tests were performed using the disk method in volunteers from both the groups during the non-pollen dispersal season. The results of the above two determinations were compared statistically between the two groups.

Results: The results revealed significantly lower levels of the two mediators in the TCA-treated group than in the nonTCA-treated group ($p < 0.01$). There was also a greater tendency for the subjects in the TCA-treated group as compared to those in the nonTCA-treated group to show negative reactivity in the allergen provocation test ($p < 0.01$).

Conclusion: Regional suppression of the allergic reaction to Japanese cedar pollen appears to occur as a result of chemosurgery with TCA performed as a day surgery.

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Keywords: Trichloroacetic acid; Seasonal allergic rhinitis; Japanese cedar pollenosis; Histamine; Eosinophil cationic protein

1. Introduction

The number of patients with allergic rhinitis, particularly those with Japanese cedar pollenosis, has recently been on the increase, and the disease is now regarded as a contemporary disease causing social problems in Japan [1]. Although Japanese cedar pollenosis is mainly treated symptomatically with oral anti-allergic agents [2], these

drugs often have side effects, such as drowsiness and loss of concentration. At the present, there is little improvement in the frequency of these side effects. Furthermore, the use of these agents is contraindicated in the early stages of pregnancy. Thus, medical treatment is not completely satisfactory as a definitive treatment solution for cases with this condition. Furthermore, the nasal instillation of steroid preparations is prescribed for severe cases. It has been said that this form of treatment, in contrast to systemic administration, does not compromise the pituitary-adrenocortical function [3]. However, the fact remains that this is still a symptomatic treatment. With the progress in treatment in the area of internal medicine such as that described above,

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there will be an increasing tendency to prescribe medication casually without an accurate diagnosis.

Since 1986, we have treated patients of allergic rhinitis, including those with cedar pollenosis and perennial allergies caused by house dust, by the application, under topical anesthesia, of 80 w/v% trichloroacetic acid (TCA) (Kanto Chemical Co. Inc., Cat No. 40243-30, 25 g) to the inferior turbinates of both sides, using two cotton applicators; the procedure is performed as a day surgery [4,5].

In the case of seasonal allergic rhinitis due to Japanese cedar pollenosis, we usually wait until the pollen season is over and we perform TCA chemosurgery after ensuring that there are no allergic symptoms, especially watery nasal discharge [6]. The reason for administering this treatment after the end of the pollen dispersal season is that it is harder to use the cotton applicators in the presence of mucosal swelling; furthermore, it is difficult to fix the TCA to the nasal mucosal tissue in the presence of nasal discharge. In cases of perennial allergic rhinitis, the patient is treated with oral antihistamines until the symptoms are relieved before TCA chemosurgery is performed. In both patients with seasonal and perennial allergic rhinitis, TCA treatment is carried out only after obtaining informed consent of the patients.

We investigated the effects of TCA treatment, and found that the biological and pharmacological effects of TCA are probably based on its causing protein degeneration in the nasal mucosa [4,5,7–9]. A follow-up of randomly selected patients of allergic rhinitis for over 3 years after TCA treatment revealed good results of this treatment modality for this condition [4,10].

In the present study, patients with Japanese cedar pollenosis were divided into two groups, namely, the TCA-treated group and the group that was not treated with TCA (nonTCA-treated group), and the levels of the two chemical mediators, histamine and eosinophil cationic protein (ECP), in the nasal washings were measured in each group during the pollen dispersal season. In addition, the allergen provocation test for the protein Cry j I in the *Cryptomeria japonica* pollen was conducted using the disk method on volunteers from both the groups after obtaining their consent [11–13], in order to examine the degree of suppression of the nasal mucosal reactivity after TCA treatment.

2. Materials and methods

2.1. Histamine and ECP levels in the nasal washings

All the patients who voluntarily visited our clinic with cedar pollenosis examined during the pollen season between January 19 and April 16 in the year 2000 were divided into two groups, the TCA-treated group and the nonTCA-treated group. During this period, the daily dispersal of cedar pollen into the environment in Kanagawa Prefecture was estimated using a Durham-type pollen collector placed at the Clinical Research Division of Sagami-hara National Hospital.

Eventually, 90 TCA-treated patients and 79 nonTCA-treated patients were enrolled in the present study. The TCA-treated group ($n = 90$) was composed of 64 patients who did not desire to receive anti-allergic drugs and 26 patients who did not receive anti-allergic drugs during this period despite wanting to take these drugs because of anxiety regarding the development of symptoms. Besides these 90 patients, there were 31 other TCA-treated patients who were excluded from the study because of the following reasons: (1) they had received anti-allergic drugs at other hospitals; (2) they had received anti-allergic drugs because of anxiety regarding the possible development of symptoms, even though they had no, or only mild, symptoms of pollenosis.

The 90 TCA-treated cases consisted of 19 males and 71 females aged 44.1 ± 11.9 years (mean $\pm$ S.D.). The average duration of follow-up after the treatment was 48.9 ± 38.0 months (mean $\pm$ S.D.). Before TCA treatment, the symptom severity was rated, according to Okuda's classification of symptom severity, as moderate to severe during the cedar pollen dispersal season [14]. All these patients were categorized as being over class 2 (0.7 kU/L and over) in the radio-allergoabsorbent test (CAP-RAST, Pharmacia Inc.) for Japanese cedar pollen-specific IgE. However, after the TCA treatment, 78 of the 90 cases showed only mild symptoms and the remaining 12 patients showed no symptoms, according to Okuda's classification of symptom severity [14], even during the month of March in the year 2000, when pollen dispersal was at its peak. We confirmed that none of these 90 patients had received any anti-allergic drugs during this period.

The nonTCA-treated/control group consisted of 79 cases (14 males and 65 females) with an average age of 32.0 ± 13.4 years (mean $\pm$ S.D.). All the 79 patients underwent medical examination during the cedar pollen dispersal season, and were scheduled to receive TCA treatment. All of them provided their consent for undergoing TCA treatment after the pollen dispersal season according to the above-mentioned reasons [6]. The symptom severity was rated as severe in 71 cases and moderate in eight cases. There were 48 cases that needed anti-allergic drugs and 29 cases that needed both anti-allergic drugs and steroid nasal drops. There were two cases that needed only steroid nasal drops. All the patients were categorized as being over class 2 (0.7 kU/L and over) in the CAP-RAST test.

Nasal lavage was performed in each subject. A 5-mL sterile saline solution was flushed into each nasal cavity and the irrigated samples were collected by suction using a bottle provided with double tubes, in accordance with Proud et al.'s method [15].

After the sample was centrifuged (2000 rpm for 20 min at 4 °C), 1000 μ L of the processed sample was used for determining the level of histamine; another 270 μ L of the sample was separated for ECP determination, and 30 μ L of protamine sulfate treated by 0.01N HCl was added to this sample to make up a volume of 300 μ L, with the object of preventing adhesion of the ECP to the bottle [16]. Both the sample portions were immediately stored at -77 °C. The

histamine level was measured by enzyme-linked immunosorbent assay (ELISA: Immunosorbent Inc.), and the ECP level was determined by radioimmunoassay (RIA: Pharmacia Inc.). When the results obtained by the above procedure were below the detection limit, the histamine level was regarded as 0.11 ng/mL and the ECP was taken as $2 (\times 0.9) \mu\text{g/L}$.

The levels of histamine and ECP were statistically compared between the two groups using the *t*-test. Comparison was also made of the histamine levels between the two groups with reference to the daily variations in the degree of dispersal of the pollen.

2.2. Provocation test using allergen disks

The provocation test [11,12] using allergen disks containing 50–100 ng Cry j I which was the protein in the *Cryptomeria japonica* pollen (provided by the Clinical Research Division of Sagami-hara National Hospital), recommended by Okuda [12], was performed after the end of the pollen-dispersal season, from May 24 to July 26 of the same year, in volunteers from both the TCA- and nonTCA-treated groups, after obtaining their informed consent. There were 42 cases from the TCA-treated group, consisting of 7 men and 35 women with an average age of 42.2 ± 12.1 years (mean $\pm$ S.D.). They underwent the provocation test 52.1 ± 38.6 months, on average, after the TCA treatment. On the other hand, 33 of the 79 cases from the nonTCA-treated group volunteered to undergo the provocation test, and this group was composed of 8 men and 25 women with a mean age of 36.3 ± 12.5 years (mean $\pm$ S.D.).

2.3. Ethical considerations

Prior to the present study, we obtained permission from each subject for each procedure and for using the obtained specimens for study purposes. The study was conducted in accordance with the guidelines of the Ethical Committee of Kitasato University Hospital.

3. Results

The total cedar pollen count for 2000 was $13,350/\text{cm}^2$, while the mean airborne pollen count per year during the past 10 years was $4615.8/\text{cm}^2$ (the minimum, $502/\text{cm}^2$ in 1994 and maximum, $15,387/\text{cm}^2$ for 1995).

The average volume of the nasal washings collected was 9.39 ± 0.89 mL in the TCA-treated group and 9.42 ± 0.72 mL in nonTCA-treated group. The difference between the two groups was not significant. This result was also consistent with that reported by Proud et al. [15].

3.1. Histamine levels in the nasal washings

Fig. 1 shows the degree of pollen dispersal into the environment during the period from January 19 to April 26

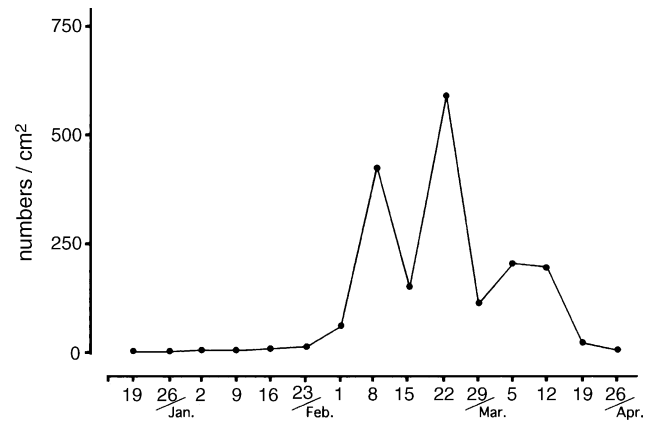


Fig. 1. Weekly variations in the average amount of Japanese cedar pollen dispersed during the pollen dispersing season from January 19 to April 26, 2000, in the Kanagawa Prefecture (data provided by the Clinical Research Division of Sagami-hara National Hospital).

in the year 2000, and the daily average amount of pollen collected weekly during this period was plotted. Fig. 2 illustrates the temporal distribution of the histamine levels during the above period in the TCA-treated group (top) and nonTCA-treated group (bottom). Each dot represents the histamine level in the sample obtained from each subject. In the TCA-treated group, the histamine level was close to the detectable limit in most cases, whereas in the nonTCA-treated group, higher values were detected. Overall, as shown in Fig. 3, the mean histamine level in the TCA-treated group was 0.57 ± 1.60 (mean $\pm$ S.D.) ng/mL, while that in the nonTCA-treated group was 0.96 ± 2.06 ng/mL. The value in the TCA-treated group was significantly lower than that in the nonTCA-treated group ($p < 0.01$).

3.2. ECP levels in the nasal washings

Fig. 4 shows the temporal distribution of the ECP levels in the TCA-treated group (top in the figure) and nonTCA-treated group (bottom) during the same period, from January 19 to April 26, 2000. During the month of March, when the pollen dispersal was at its peak, only four patients showed an ECP level higher than $10 (\times 0.9) \mu\text{g/L}$ in the TCA-treated group, whereas in the nonTCA-treated group, very high levels were observed. Overall, the level of ECP in the TCA-treated group was $3.17 \pm 3.98 (\times 0.9) \mu\text{g/L}$, whereas that in the nonTCA-treated group was $21.55 \pm 101.25 (\times 0.9) \mu\text{g/L}$. The value in the TCA-treated group was significantly lower ($p < 0.01$; Fig. 5).

3.3. Provocation test

Table 1 presents the results of the provocation test. The number of patients showing a positive reactivity in the provocation test was significantly smaller in the TCA-treated group than in the nonTCA-treated group ($\chi^2 = 39.97$, $p < 0.01$). In other words, there were many more cases that

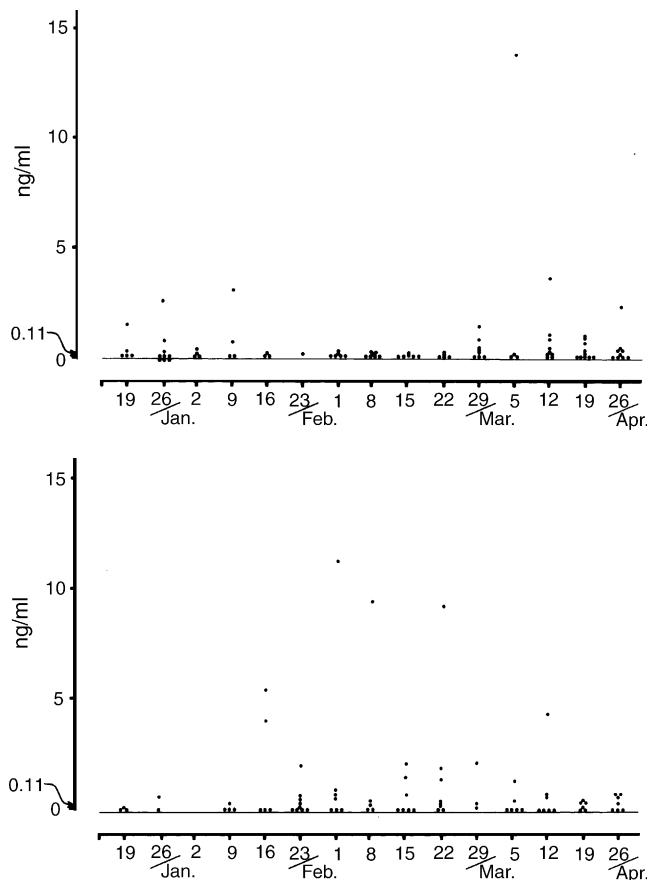


Fig. 2. Weekly variations in the levels of histamine in the nasal washings during the period from January 19 to April 26, 2000. Top: histamine levels in the TCA-group. Each dot represents the histamine level in each subject. The value stayed within the range of 0.11 to 4 ng/mL with only one exception. Bottom: histamine levels in the nonTCA-treated group.

showed a tendency toward suppression of type I allergic reactions in the TCA-treated group.

4. Discussion

In this study, all the cases were investigated by one clinical examiner during the Japanese cedar pollen dispersal season in the year 2000. The airborne pollen count for 2000 was high compared with the mean pollen count per year over the past 10 years, which is $4615.8/\text{cm}^2$ (minimum, $502/\text{cm}^2$ for 1994 and maximum, $15,387/\text{cm}^2$ for 1995). According to this, in the year 2000, Japanese cedar pollen scattering was relatively high, therefore the effects of TCA could be sufficiently observed. Nasal washings were collected from all of these cases, and the data from all the patients examined were used for the study to keep the study unprejudiced. Also, factors that might confound the results, such as treatment with anti-allergic medication, were removed. On the other hand, all the patients who desired to undergo chemosurgery with TCA were examined. However, it was difficult to apply

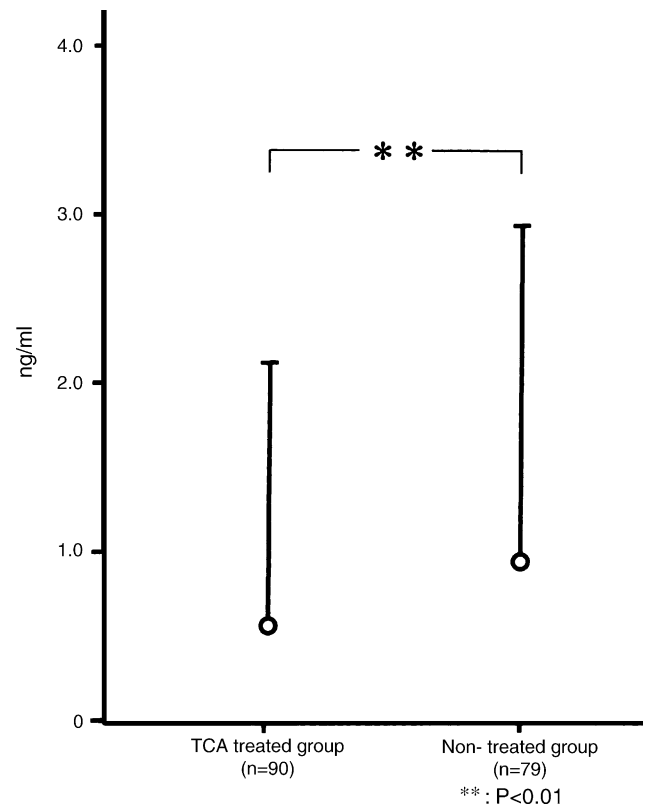


Fig. 3. Comparison of the average histamine levels between the two groups.

TCA during the pollen dispersal season in cases with mucosal reaction, nasal discharge or mucosal swelling. We also investigated those patients who had no choice but to be treated by oral medication during the pollen dispersal season, and treated these patients by chemosurgery with TCA after the pollen dispersal season ended and the nasal symptoms were relieved [6]. It was noteworthy that 90 TCA-treated patients did not need to be treated with oral medication. As compared with this, in the nonTCA-treated group, oral medication was used by the patients that might also have suppressed the allergic reaction. If the nonTCA-treated patients had not taken oral medication, the difference between the two groups might have been even more significant.

In our previous studies [7,8], we demonstrated that the number of activated eosinophils infiltrating the mucosa was significantly decreased in mucosal specimens obtained 164 ± 11 days after TCA treatment and also that infiltration of the mucosa by the two types of mast cells was significantly decreased in mucosal specimens obtained 88 ± 24 days after TCA treatment; we considered these as the reasons for the absence of any allergic symptoms over a 3-year follow-up period after TCA treatment [4,5]. Considering previously published reports showing that histamine is released from mast cells and ECP is released from activated eosinophils [17–20], the results of the present study, in which the levels of both histamine and ECP in the nasal washings were significantly lower in the TCA-treated

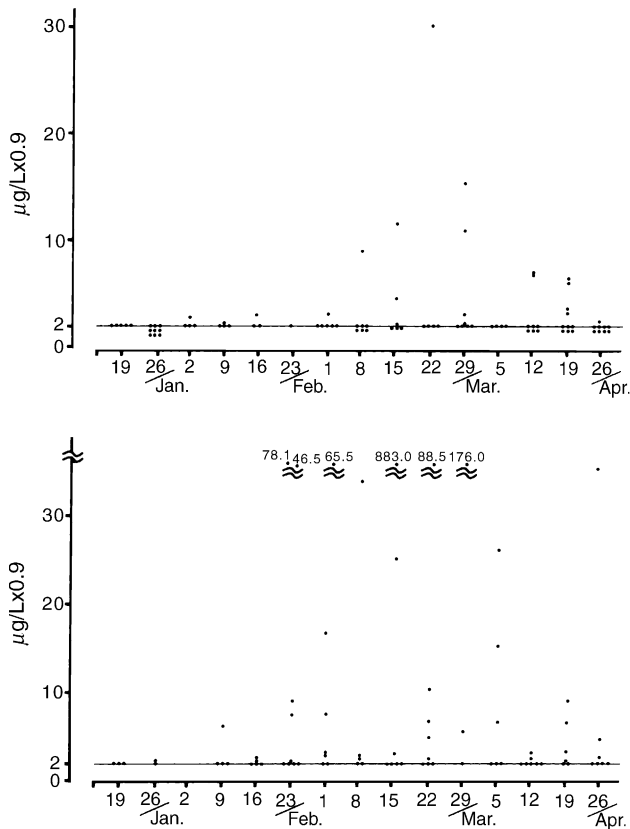


Fig. 4. Weekly variations in the levels of ECP in the nasal washings during the period from January 19 to April 26, 2000. Top: ECP levels in the TCA-treated group. In general, the values were low, except in four cases, in which the value exceeded the level of 10 ($\times 0.9$) $\mu\text{g/L}$. Bottom: ECP levels in the nonTCA-treated group.

group than in the nonTCA-treated group, appear to match and confirm the validity of our earlier histopathological findings.

According to a recent study, allergic rhinitis is an immune disease caused by a predominance of the Th2 cell cytokines [21,22]. The results of intensive studies of this condition indicate that the expression of the thymus and activation-regulated chemokine (TARC), which plays an important role in the regional recruitment of Th2 cells [22,23], was significantly suppressed in the inferior turbinate mucosa after TCA treatment [9]. It was also found that TARC expression was positive in the covering epithelial cells and in the nasal glandular epithelium only up to a depth of 120 μm from the epithelial surface in the nonTCA-treated mucosa [9]. As already reported, precise application of TCA with cotton applicators to the inferior turbinates caused degeneration of the nasal mucosa from the epithelial layer up to a depth of approximately 120 μm [4,5]. It was thus considered that regenerated epithelium was probably produced from the remaining TARC-negative glandular epithelium after TCA treatment. When a TARC-negative condition is established, Th2 cell infiltration of the mucosa could be suppressed, resulting in the suppression of the local allergic reaction.

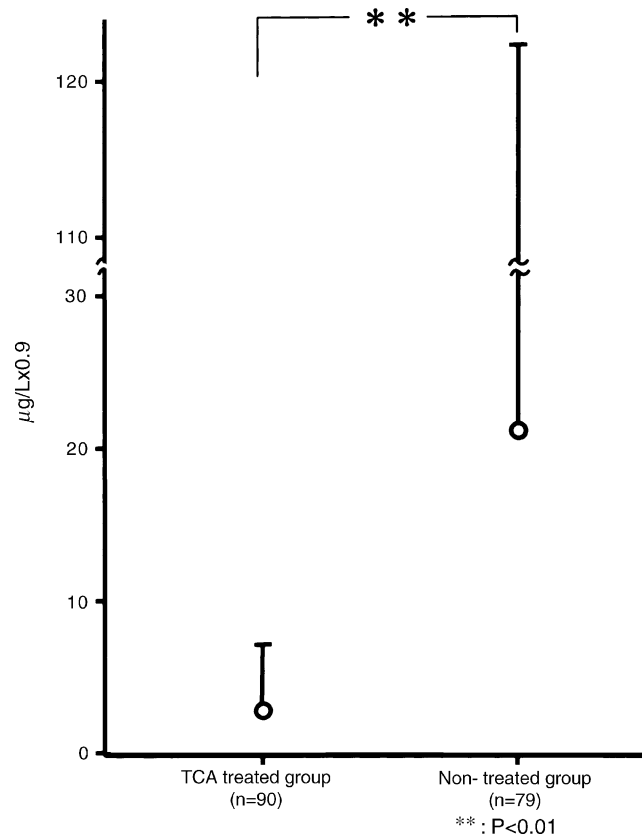


Fig. 5. Comparison of the average ECP level between the two groups.

Table 1

The result of the provocation test for the protein Cry j I in the *Cryptomeria japonica* pollen with reference to the standard valuation (SV) [11,12]

Group \ SV	-	1+	2+	3+	Total
TCA-treated group	26	11	4	1	42
Non-treated group	1	5	22	5	33
Total	27	16	26	6	75

The categorization of the SV was as follows: (-) no reaction; (1+) sneezing and watery discharge, but no nasal obstruction; (2+) sneezing (<10 times), watery discharge and nasal obstruction; (3+) sneezing (≥ 10 times), watery discharge and nasal obstruction.

The above findings of TARC expression in relation to the effectiveness of TCA treatment show that differences in the degree of Th2 cell-infiltration of the mucosa in the TCA-treated and nonTCA-treated group needs to be investigated further. However, the negative reactivity in the provocation test observed predominantly in the TCA-treated group in the present study indicates that type I allergic reaction might be regionally suppressed as a result of TCA treatment in patients with Japanese cedar pollenosis.

5. Conclusion

The histamine and ECP levels in the nasal washings were significantly lower in the group of patients who underwent one-day chemosurgery with TCA (TCA-treated group) than in the group of patients who did not undergo this treatment (nonTCA-treated group). The frequency of positive reactivity in the Japanese cedar pollen provocation test was also significantly lower in the TCA-treated group than in the nonTCA-treated group. It is therefore concluded that TCA treatment, performed as a day surgery, suppressed regional type I allergic reactions in the nasal mucosa in patients of Japanese cedar pollenosis.

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