

The effect of olfactory training on the odor threshold in patients with traumatic anosmia

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ABSTRACT

Background: Olfactory training is a novel intervention that has been used to treat olfactory dysfunction. This study attempted to investigate the effect of olfactory training in patients with traumatic anosmia.

Methods: Patients with a clear history of anosmia after experiencing a head injury and whose phenyl ethyl alcohol (PEA) odor detection thresholds were -1 after steroid and zinc treatment were included. The patients were randomly divided into two groups, with patients in one group given a bottle of PEA and those in another group given a bottle of mineral oil for 3-month olfactory training. All the patients were followed up with a PEA threshold test and the traditional Chinese version of the University of Pennsylvania Smell Identification Test (UPSIT-TC). Magnetic resonance imaging was performed to measure the volume of the olfactory bulbs. Any patient whose PEA threshold result was below -1.01 or whose UPSIT-TC score increased four or more points was considered to have shown improvement in their olfactory function.

Results: Forty-two patients received PEA olfactory training, whereas 39 received olfactory training with mineral oil. The improvement of PEA thresholds function was observed in 10 patients within the PEA group and in 2 patients in the mineral oil group. The frequency of improvement of threshold within the PEA group was significantly higher than that of the mineral oil group. Neither olfactory bulb volume nor UPSIT-TC score was significantly different between the two groups.

Conclusion: Our results showed that olfactory training with PEA can improve PEA odor threshold levels in patients with traumatic anosmia.

(Am J Rhinol Allergy 31, 317–322, 2017; doi: 10.2500/ajra.2017.31.4466)

Head trauma is one of the most common causes of olfactory dysfunction.^{1,2} Although spontaneous recovery of olfactory function has been observed in approximately one-third of patients with posttraumatic olfactory dysfunction, the prognosis generally is poor.^{3,4} There is no standard treatment for patients with posttraumatic olfactory loss.⁵ In our previous study, a course of high-dose oral prednisolone (1 mg/kg) was administered to treat patients with traumatic anosmia and in whom a 16.4% improvement rate of odor threshold with the phenyl ethyl alcohol (PEA) threshold test was observed.⁶ In another study, a 28.2% improvement rate of odor threshold was observed 6 months after patients underwent a course of high-dose oral prednisolone, followed by taking zinc gluconate for a month.⁷ However, many of the patients did not show improvement.

Olfactory training is a novel intervention method used to improve olfactory function. Classic olfactory training involves sniffing, for 12 weeks, four odors that are representative of four odor categories.⁸ A systematic review and meta-analysis indicated that olfactory training may be an effective treatment for olfactory dysfunction due to multiple etiologies.⁹ However, it also was found that the olfactory training mainly improves the abilities to identify and differentiate odors when evaluated by the Sniffin' Sticks test.¹⁰⁻¹² Konstantinidis *et al.*¹⁰ used olfactory training with four odors, including PEA, over a period of 16 weeks in patients with postinfectious and posttraumatic olfactory loss. They found that the odor identification score in the Sniffin' Sticks test significantly increased after training for both disorders and that the odor discrimination score had a trend for a significant increase but their odor threshold score was not significantly different.¹⁰ However, in Sniffin' Sticks test, *n*-butanol instead of PEA was used to

measure the odor threshold.¹³ In this study, we tried to clarify the effect of olfactory training on the odor threshold in patients with traumatic anosmia for whom treatment of prednisolone and zinc failed by training with the same odor (PEA) as that used in the PEA odor detection threshold test.

METHODS

Subjects

The flow chart and the design of this study are shown in Fig. 1. Patients with a clear history of loss of smell after experiencing a head injury were selected for this study, which took place from June 2014 to February 2016. The history of head injury for each patient was recorded, including the time of injury, whether there was a loss of consciousness or intracranial hemorrhage after injury, and whether he or she were admitted to hospital or underwent a craniotomy. At the patient's first visit, birhinal odor thresholds were measured by using the PEA odor detection threshold test. The testing procedures were described in our previous article.¹⁴ If the birhinal threshold was -1 , then the patients were assumed to be anosmic. Any patient whose birhinal threshold was below -1 was excluded from the study. A nasal endoscopy was performed on all the patients. Any patient whose endoscopic examination showed mucopurulent discharge in his or her nasal cavities or edematous mucosa in the middle meati was also excluded from the study. This study was approved by the ethics committee of Taichung Veterans General Hospital, and written consent was obtained from each patient.

Treatment and Follow-up

Eligible patients were treated in the following manner. Initially, a 2-week course of high-dose prednisolone (1 mg/kg per day) with tapering was given. The patients then received another birhinal PEA threshold test 1 month after the beginning of treatment. Any patient whose birhinal threshold was below -1 was excluded from the study. During the second month, a course of zinc gluconate t.i.d. was administered for a month. After the zinc treatment, another PEA threshold test, which included bi- and unirhinal tests, and a birhinal test of the traditional Chinese version of the University of Pennsylvania Identification Test (UPSIT-TC) were given. Any patient whose bi- or unirhinal threshold was below -1 was excluded from the study.

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No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

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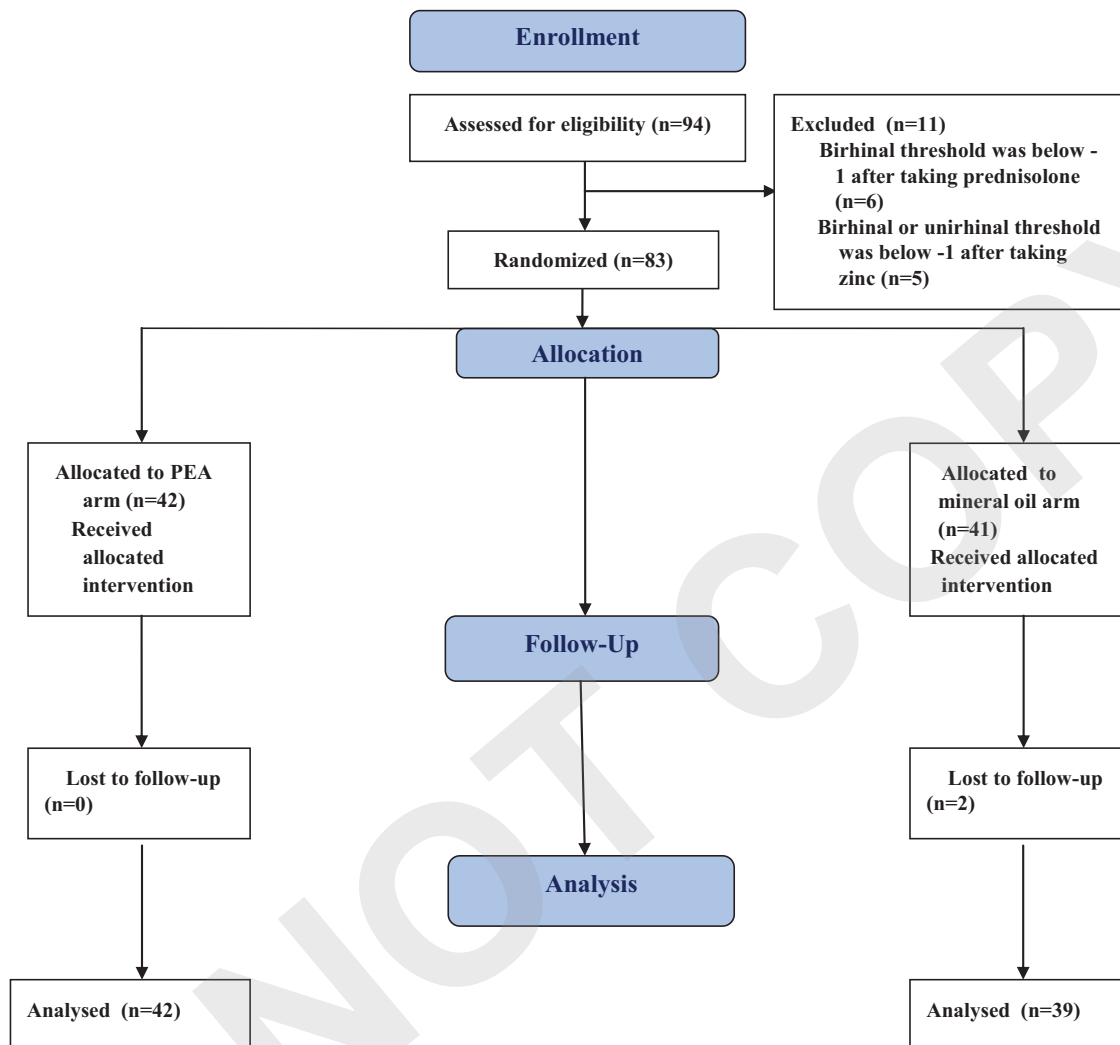


Figure 1. Flow chart from enrollment to analysis.

The patients were then randomly divided into two groups. Patients in the PEA group were given a bottle of pure PEA, whereas those in the mineral oil group were given a bottle of odorless mineral oil. Both solutions were used in the PEA odor detection threshold test. One (PEA) was used as the odorant and the other (mineral oil) was used as the blank solution. All the patients were instructed to sniff the liquid in the bottles for 10 seconds, twice a day for 3 months. After this 3-month olfactory training, olfactory function was evaluated by the PEA threshold test, which included bi- and unirhinal tests as well as a birhinal test of UPSIT-TC. Magnetic resonance imaging (MRI) was then performed to measure the volume of the olfactory bulbs (OB) after olfactory training. Any patient whose bi- or unirhinal PEA threshold resulted in below -1.01 levels or whose UPSIT-TC score increased 4 or more points¹⁵ was considered to have shown improvement in his or her olfactory function. During patients' olfactory training period, any other medicine used for treating olfactory loss, including nasal steroids, antihistamines, and antibiotics, was prohibited.

PEA Test

The PEA test uses different concentration of a rose-like odor to evaluate the olfactory threshold. The PEA test is a two-alternative, forced-choice, single-staircase detection threshold procedure. Two glass sniff bottles that contained different concentrations of PEA

dissolved in mineral oil or mineral oil alone were presented to the subject. These two bottles were opened and positioned over the subject's nose in a random order. The subject indicated which bottle contained the stronger odor. If no difference was perceived, then a guess was required. The first pair of scents contained PEA odorant at 10^{-6} log vol/vol. Correct identification of the scent that contained the PEA odorant in five successive trials triggered a reversal of the staircase to the next lower concentration, whereas a single incorrect identification triggered the reversal of the staircase to the next higher concentration. In the following, correct identification of the scent that contained the PEA odorant in two successive trials triggered a reversal of the staircase to the next lower concentration. When a total of seven reversals were acquired, the test was completed. The geometric mean of the last four reversed points of the seven reversals was used as the PEA threshold estimate, and PEA concentrations ranged from 10^{-1} to 10^{-9} log vol/vol in half-log concentration steps.

UPSIT-TC Test

UPSIT-TC is an odor identification test translated from the North American version of the UPSIT. A few odorants and response alternatives were replaced to take into account cultural difference in the UPSIT-TC.¹⁶ Forty "scratch and sniff" odorants were embedded in 10- to 50- μ m microcapsules fixed in a propriety binder and positioned on brown strips located at the bottom of the pages of each test booklet.

Table 1 Comparison of profiles of head injury, olfactory function, and OB volume

	PEA Training (N = 42)	Mineral Oil Training (N = 39)	p Value
Head injury interval, mean (range), mo	6.3 (0.5–44)	7.0 (0.5–42)	0.981
Loss of consciousness, no. (%)	33 (78.6)	31 (79.5)	>0.99
Admission, no. (%)	39 (92.9)	29 (74.4)	0.05
Intracranial hemorrhage, no. (%)	32 (76.2)	26 (66.7)	0.482
Craniotomy, no. (%)	7 (16.7)	6 (15.4)	>0.99
UPSIT-TC score, mean (range)			
Before olfactory training	12.17 (5–22)	10.95 (4–20)	0.170
After olfactory training	12.21 (5–25)	11.49 (7–17)	0.924
OB volume, mean (range), mm ³			
Average	58.15 (0–148.54)	50.39 (0–107.01)	0.115
Right side	58.73 (5.26–148.54)	47.12 (0–106.57)	0.087
Left side	57.58 (0–115.65)	53.67 (0–107.01)	0.577

OB = Olfactory bulb; PEA = phenyl ethyl alcohol; UPSIT-TC = traditional Chinese version of the University of Pennsylvania Smell Identification Test.

The testing subjects released the odorants by scratching the strip with a pencil tip; then they identified the released odorant by choosing a name from a set of four odor descriptors. The test was scored as the number of odors correctly identified. A response was required for each test item even if no smell was perceived (*i.e.*, the test is forced choice), which allowed for the detection of malingering based on improbable responses.

MRI

The protocol for measuring the OB volume through the use of an MRI was explained in a previous article,¹⁷ and the testing procedures are briefly outlined below. MRI studies were performed by using a 1.5-Tesla Excite MRI system (GE Medical Systems, Milwaukee, WI) with a quadrature head coil. Routine imaging pulse sequences included axial T1-weighted images and Fluid attenuation inversion recovery images, along with axial and coronal T2-weighted fast spin-echo images. Contrast-enhanced T1-weighted images with axial and coronal sections were obtained. After a sagittal localizing scan, 2–2.5-mm-thick T2-weighted coronal and sagittal (Repetition time, 5000 ms; time to echo, 106 ms; Number of excitations, 2; matrix, 256 × 256) images without an interslice gap were acquired with a 12-cm field of view as per the standardized protocol for OB analysis. OB volumes were measured by using MATLAB 7.0 (Mathworks, Inc., Natick, MA). The OB volume was measured side by side in each subject. The OB volume was considered to be zero if it could not be measured on MRI due to severe head injury.

Sample Size and Statistical Analysis

Sample size was calculated with the study design of the Mann-Whitney *U* test by use of the power analysis program G* Power 3.¹⁸ The clinically significant differences were estimated according to a previous study.¹⁹ The alpha value was set at 0.05, and the power value was set at 0.8. This calculation enabled us to have ~39 study patients in each study group. The Pearson χ^2 test was used to compare sex, incidences of loss of consciousness, intracranial hemorrhage after head injury, admission, craniotomy, and frequency of improvement of olfactory function between the two groups. The age of the patients, the interval period between the head injury and the patient's first visit, and the OB volumes were compared between the two groups through the use of the Mann-Whitney *U* test. The PEA threshold and the UPSIT-TC score were compared before and after olfactory training by using the Wilcoxon signed rank test. All analyses were performed by using SPSS version 12.0 (SPSS Inc., Chicago, IL). Two-tailed *p* values <0.05 were considered statistically significant.

RESULTS

Patients

There were 94 patients enrolled in the study. Among them, six were excluded because their birhinal threshold was below –1 after taking prednisolone, and an additional five were excluded because their bi- or unirhinal threshold was below –1 after taking zinc. Therefore, 83 patients were eligible to receive olfactory training with PEA or mineral oil. Two patients did not come back for follow-up, so 42 patients in the PEA group and 39 in the mineral oil group finished the study. There were 27 men and 15 women in the PEA group, whose ages ranged from 18 to 69 years, with a mean of 37.7 years. There were 20 men and 19 women in the mineral oil group, whose ages ranged from 18 to 84 years, with a mean of 40.7 years. There were no significant differences in sex (*p* = 0.337) and age (*p* = 0.733) between the two groups.

Profiles of Head Injuries

The comparison of the interval periods between head injury and the first hospital visit, the incidences of loss of consciousness and intracranial hemorrhage after the head injury, and the ratios of admission and craniotomy between the PEA and mineral oil groups are summarized in Table 1. More patients in the PEA group had been admitted to the hospital after their head injuries. There were no significant differences in the interval period between the head injury and the patient's first visit, incidences of loss of consciousness and intracranial hemorrhage after the head injury, or the ratios of craniotomy between the two groups.

Improvement of Odor Threshold and Factors that Predicted Olfactory Improvement

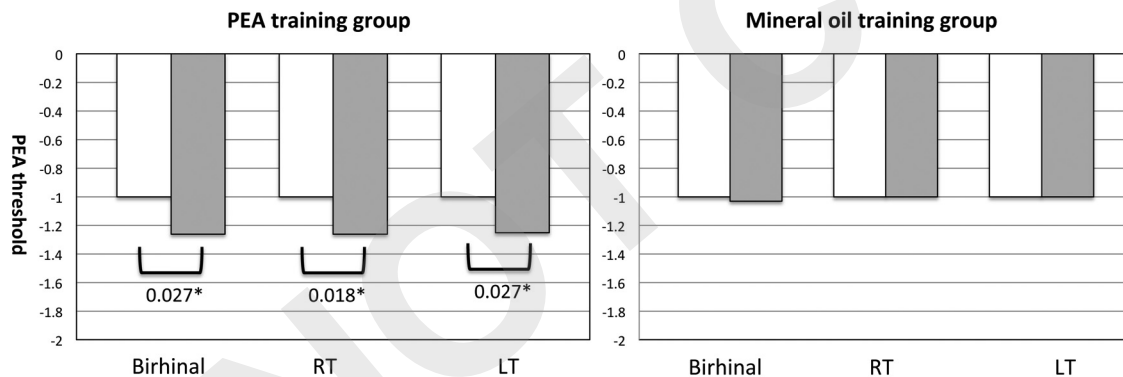
The improvement of olfactory function with a bi- or unirhinal PEA threshold below –1.0 after olfactory training was observed in 10 patients (23.8%) who received olfactory training with PEA and in two patients (5.1%) who received olfactory training with mineral oil (Table 2). The frequency of improvement of olfactory function in the PEA group was significantly higher than that of the mineral oil group (*p* = 0.04). However, the UPSIT-TC score increased four or more points after olfactory training in six patients (14.3%) who had received olfactory training with PEA and in six (15.4%) who had received olfactory training with mineral oil. The frequency of an increase in UPSIT-TC scores of four or more points in the PEA group was not significantly different from that of the mineral oil group (*p* > 0.99). The UPSIT-TC scores were not significantly higher after olfactory training in either the PEA group (*p* = 0.839)

Table 2 Patients with bi- or unirhinal PEA threshold below -1.0 after OT

Patient No.	Group	Age, y	Interval, mo	PEA Threshold			UPSIT-TC Score	
				Birhinal	Right	Left	Before OT	After OT
1	PEA	69	6	-1	-1	-1.75	14	22
2	PEA	28	3	-2.5	-2.25	-1	10	13
3	PEA	31	1	-2.25	-1.75	-6.25	9	17
4	PEA	44	2	-1	-1.5	-1	19	22
5	PEA	49	3	-1	-1	-1.625	13	11
6	PEA	18	6	-2.625	-3.75	-3.125	16	15
7	PEA	22	0.5	-3.875	-4.875	-2	22	21
8	PEA	23	10	-3.25	-1	-1.625	13	11
9	PEA	31	9	-1	-1.25	-1	12	17
10	PEA	36	1	-2.25	-2.75	-1	11	13
11	MO	24	1	-2	-1	-1	14	11
12	MO	41	24	-1.25	-1	-1	17	10

PEA = Phenyl ethyl alcohol; OT = olfactory training; UPSIT-TC = traditional Chinese version of the University of Pennsylvania Smell Identification Test; MO = mineral oil.

A. PEA threshold level



B. UPSIT score

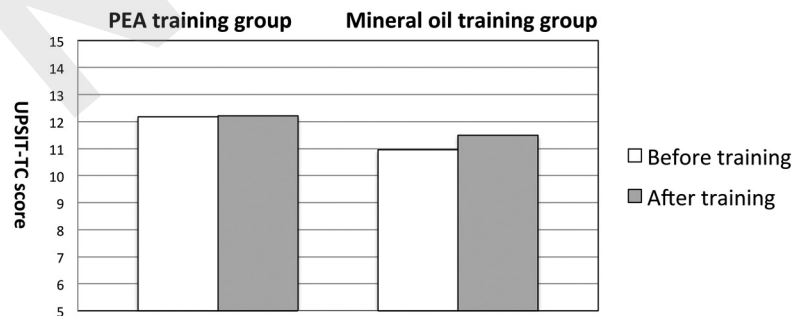


Figure 2. Changes of olfactory function of study subjects after olfactory training. * $P < 0.05$.

or the mineral oil group ($p = 0.181$) (Table 1). The changes of olfactory function of study subjects before and after olfactory training are demonstrated in Fig. 2.

The sex, age, interval period between the head injury and the first hospital visit, incidences of loss of consciousness and intracranial hemorrhage after head injury, and ratios of admission and craniotomy, along with UPSIT-TC scores before and after olfactory training were compared between 12 patients with their bi- or unirhinal PEA threshold below -1.0 after olfactory training, and 69 patients with their bi- or unirhinal PEA threshold that remained at -1.0 after olfactory training (Table 3). The UPSIT-TC scores after olfactory training in 12 patients with a bi- or unirhinal PEA threshold below -1.0 after olfactory training were significantly higher than those in the 69

patients with bi- or unirhinal PEA threshold that remained at -1.0 after olfactory training.

OB Volumes

An MRI was performed on all 81 patients to measure their OB volumes (Table 1). There were no significant differences in OB volumes between the PEA and the mineral oil groups. Among them, the unirhinal PEA threshold result was below -1.0 after olfactory training in 13 sides in which the OB volumes ranged from 0 mm^3 to 78.74 mm^3 , with a mean of 47 mm^3 , but remained at -1 in the remaining 149 sides, in which the OB volumes ranged from 0 mm^3 to 148.54 mm^3 , with a mean of 55.06 mm^3 . The difference in OB volume

Table 3 Factors that predicted olfactory improvement with bi- or unirhinal PEA threshold below -1.0 after olfactory training

	Patients with Improvement (N = 12)	Patients without Improvement (N = 69)	p Value
Men, no. (%)	6 (50)	41 (59.4)	0.769
Age, mean (range), y	34.7 (18–69)	39.9 (18–84)	0.258
Head injury interval, mean (range), mo	5.5 (0.5–24)	6.8 (0.5–44)	0.491
Loss of consciousness, no. (%)	8 (66.7)	56 (81.2)	0.451
Admission, no. (%)	11 (91.7)	57 (82.6)	0.717
Intracranial hemorrhage, no. (%)	6 (50)	52 (75.4)	0.147
Craniotomy, no. (%)	3 (25)	10 (14.5)	0.625
UPSIT-TC score, mean (range)			
Before olfactory training	13.8 (9–22)	11.2 (4–20)	0.053
After olfactory training	15.3 (10–22)	11.3 (5–25)	0.003*

PEA = Phenyl ethyl alcohol; OT = olfactory training; UPSIT-TC = traditional Chinese version of the University of Pennsylvania Smell Identification Test. * $p < 0.05$.

between the patients with or without threshold improvement was not significant ($p = 0.333$).

DISCUSSION

Recently, a systematic review and meta-analysis indicated that olfactory training may be beneficial to patients with olfactory dysfunction due to multiple etiologies.⁹ Most studies included patients with postinfectious olfactory loss. It was found that the olfactory training improved the abilities to identify and differentiate odors in these patients with postinfectious olfactory loss when evaluated by the Sniffin' Sticks test.^{10–12} Konstantinidis *et al.*¹⁰ reported a 33.2% improvement rate in olfactory function in patients with posttraumatic olfactory dysfunction. In the study by Konstantinidis *et al.*,¹⁰ the investigators used PEA for olfactory training but evaluated the odor threshold with n-butanol. They reported that olfactory training mainly improved the abilities of odor identification and discrimination rather than n-butanol odor threshold. In our study, we found that PEA olfactory training could improve PEA odor threshold in patients with posttraumatic anosmia.

The mechanism of olfactory training used to improve olfactory function remains unclear.⁸ It was assumed that repeated exposure to an odorant might modulate the regeneration of the olfactory mucosa in patients with postinfectious olfactory dysfunction.^{11,20} It seems, however, that a lack of improvement in odor threshold implies that olfactory training may change a patient's OB neurogenesis.^{8,21} Moreover, it was also questioned whether sniffing alone, without exposure to odors, could offer the same results.¹⁹ Wysocki *et al.*²² conducted a olfactory training for subjects who did not have infectious or traumatic olfactory loss but who did not perceive an odor of androstenone. They found that androstenone perception could be induced by repeated stimulation of androstenone in some subjects.²² Their hypothesis for the inducible perception of an odor might result from both peripheral neuron proliferation and OB stimulation.

In our previous study, an improvement in the PEA odor threshold was observed in 28% of patients with traumatic anosmia 6 months after undergoing a course of high-dose oral prednisolone followed by 1 month of zinc gluconate.⁹ In this study, we attempted to clarify the effect of olfactory training on the odor threshold in patients with traumatic anosmia for whom treatment with steroids and zinc failed when using the PEA odor detection threshold test. After olfactory training, only with PEA for 12 weeks, the PEA threshold improved in 10 of 42 patients (23.8%). However, when the patients only sniffed (mineral oil group), the PEA threshold improved in 2 of the 39 patients (5.1%). A significant increase frequency of improvement was observed in the patients who received olfactory training with PEA as opposed to those who only sniffed. These results indicated that the

odor thresholds could be improved through the use of olfactory training in patients with traumatic anosmia.

When odor identification function was evaluated by UPSIT-TC, it was not contradictory that these scores did not increase in the PEA and mineral oil groups, and was not significantly different between the two groups after olfactory training, because only one odor (PEA) was used during olfactory training. Analysis of our results showed that the OB volume after olfactory training was not significantly different between the PEA and mineral oil groups; however, although it seemed that odor exposure did not change the OB volume, it must be emphasized that we used only one odor during the 12-week olfactory training. If the standard method of olfactory training with four odors had been used for a longer period, we may have had a different result. Furthermore, the patients did not perform MRI pre- and postolfactory training for comparison in this study.

In addition to olfactory training, several other factors were analyzed to predict the recovery of olfactory function. In the patients in the study by Fujii *et al.*,⁵ the earlier the treatment began, the higher the recovery rate of olfactory function became. However, the interval period between the head injury and the time that treatment began seemed not to be a factor when predicting the recovery of olfactory function in our patients. The patient's age was also reported to be a significant factor in predicting the recovery of olfactory function^{6,7} because younger patients had a better ability to recover their olfactory function. This finding was not seen in our study either. Therefore, it was suggested that olfactory training was the most important factor toward the improvement of olfactory function.

CONCLUSION

Analysis of our results indicated that olfactory training with PEA could improve PEA odor threshold levels in patients with traumatic anosmia and that this effect seemed to not come from only sniffing. However, further investigation is required to study what effects the standard method of olfactory training by using four odors for a longer period of time can have in patients with traumatic anosmia.

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Erratum

In the Editorial by Alexander G. Chiu, *Am J Rhinol Allergy* 31:209–210; doi: 10.2500/ajra.2017.31.4460, in the reference section the Journal titles and volume numbers are incorrect. The reference list has been corrected online.

The printer regrets the error.

doi: 10.2500/ajra.2017.31.4468