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

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Background: **This study investigates the effect of olfactory training on odor identification in patients with traumatic anosmia.**

Methods: **Patients with a clear history of loss of smell after head injury, and whose phenyl ethyl alcohol (PEA) odor detection thresholds remained at –1 after steroid and zinc treatment, were included in this study between July 2016 and July 2018. They were randomly divided into 2 groups, with patients in the 4-odorant group given 4 bottles of PEA, lemon, eucalyptus, and clove oils and those in the PEA group given a bottle of PEA for 6-month olfactory training. After 3-month and 6-month training, the olfactory function was evaluated by both the 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 olfactory bulbs after training.**

Results: **There were 45 patients completing 4-odorant training and another 45 completing PEA training. The birhinal PEA threshold decreased significantly in both groups after 6-month training, but the decrease was not significantly different between the 2 groups. The UPSIT-TC score increased significantly in the PEA group but not in the 4-odorant group. The volume of olfactory bulbs was not significantly different between these 2 groups.**

Conclusion: **Our results show that olfactory training can slightly improve odor threshold levels in patients with traumatic anosmia, but did not improve the odor identification ability. Nevertheless, clinical improvement or benefit in quality of life from olfactory training needs further investigation.** © 2019 ARS-AAOA, LLC.

Key Words:
odor identification; olfactory training; phenyl ethyl alcohol threshold test; traumatic anosmia; University of Pennsylvania Smell Identification Test

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Head injury is one of the most common etiologies of olfactory loss.[1] The frequency of such olfactory loss has been reported to be between 4% and 7%.[2] Several pathophysiological mechanisms have been assumed to cause posttraumatic olfactory loss. These include shearing of olfactory fibers at the cribriform plate, mechanical nasal obstruction, and central brain trauma.[3] Although approximately one-third of patients with posttraumatic olfactory loss might have olfactory function recovered spontaneously, the prognosis is generally poor.[4,5]

There is no standard treatment for patients with posttraumatic olfactory loss.[2] A few drugs such as steroids, zinc, and minocycline have been used to treat posttraumatic olfactory dysfunction; however, the effectiveness of these regimens is inconclusive.[1,5,6] In our previous study, the phenyl ethyl alcohol (PEA) threshold improved in 16.4% of patients with posttraumatic olfactory loss after a course of high-dose oral prednisolone (1 mg/kg).[7] In the literature, zinc salts had been used to treat sensorineural olfactory loss, as it was expected that zinc would be helpful in the regeneration of olfactory receptor cells.[6] In our another study, a 28.2% improvement rate of PEA threshold was observed in patients with posttraumatic olfactory loss after a course of high-dose oral prednisolone followed by taking zinc gluconate

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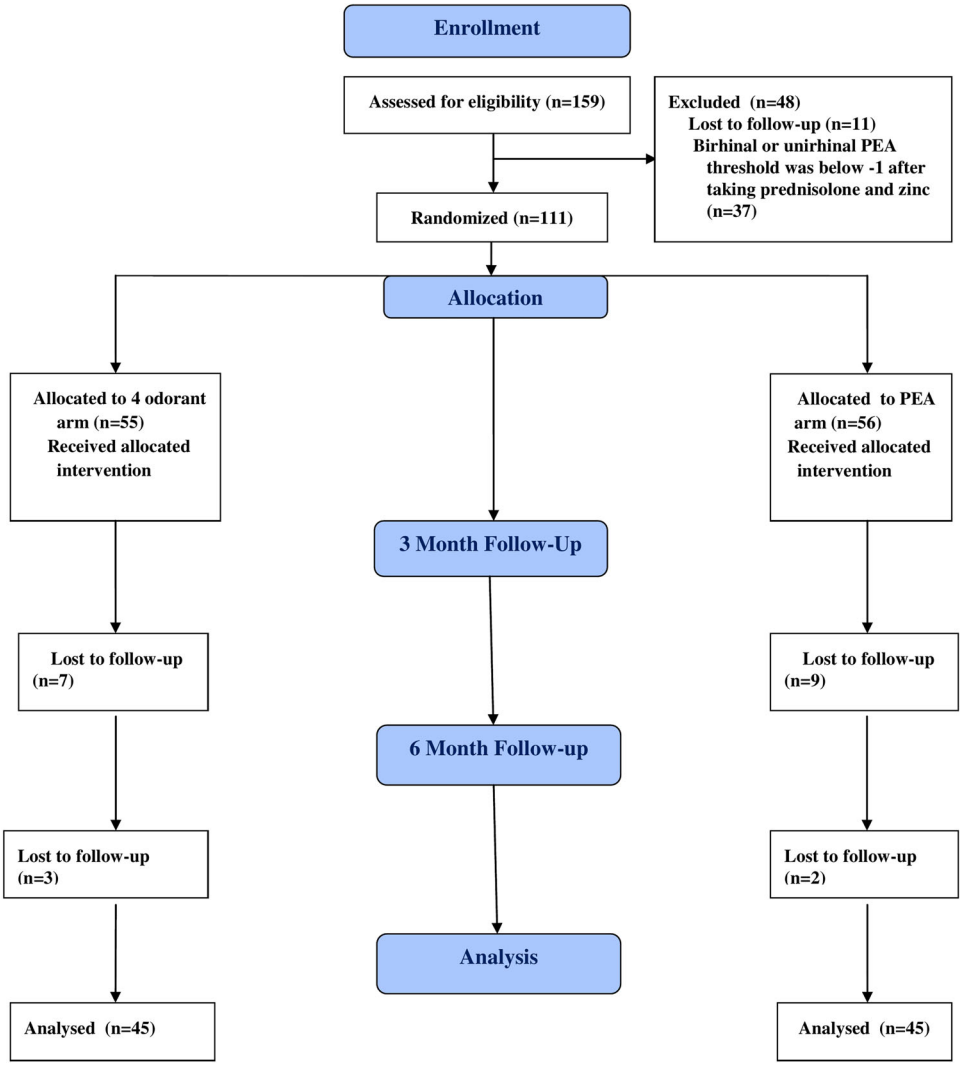

FIGURE 1. Flowchart from enrollment to analysis.

for a month.[8] The improvement from aforementioned medication is not as good as expectation. Patients usually seek for alternative treatment to avoid long-term drug intake.

Recently, olfactory training has been used to treat olfactory loss. A systematic review and meta-analysis indicated that it might be an effective treatment for olfactory dysfunction due to multiple etiologies.[9] However, the role of olfactory training on olfactory function is still controversial. Konstantinidis et al.[10] applied olfactory training with traditional 4 odorants to treat patients with postinfectious and posttraumatic olfactory loss. They found the odor identification score significantly increased after training, but the odor threshold score was not significantly increased. Al Aïn et al.[11] also noticed that olfactory training improved general olfactory function, especially odor identification. On the other hand, our previous study showed that olfactory training only with PEA decreased the PEA odor threshold in patients with traumatic anosmia.[12] Pellegrino et al.[13] also reported that olfactory training significantly increased odor threshold ability for patients with traumatic anosmia. In this study, we tried to clarify the effect of olfactory training on odor identification in patients with traumatic anosmia who had failed prednisolone and zinc treatment.

Patients and methods

Patients

The flowchart and design of this study are shown in Figure 1. Patients with a clear history of loss of smell after an episode of head trauma were collected for this study between July of 2016 and July of 2018. At their first visit, the history of head trauma was recorded, including the time of head trauma, whether they suffered from loss of consciousness or intracranial hemorrhage after trauma, and whether they were admitted to hospital or underwent a craniotomy. Then, birhinal odor thresholds were measured using the PEA odor detection threshold test. If the PEA threshold was –1, patients were assumed to be anosmic. Any patient whose birhinal threshold was below –1 was 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.

Medical treatment before olfactory training

Patients whose birhinal odor thresholds were –1 were treated with a 2-week course of prednisolone (1 mg/kg per day, maximal dose 60 mg/day, tapering 10 mg every 3 days) and a month course of zinc gluconate (10 mg 3 times a day). Following treatment, they received birhinal and unirhinal PEA threshold tests. Any patient whose birhinal or unirhinal threshold was below –1 was excluded from the study.

Olfactory training

Eligible patients were randomly divided into 2 groups. Patients in the 4-odorant group were given 4 traditional odorant bottles of PEA, lemon, eucalyptus, and clove oils, whereas those in the PEA group were given a bottle of PEA. Patients in the 4-odorant group were instructed to sniff the liquid in each bottle for 10 seconds, twice a day for 6 months. In contrast, those in the PEA group were instructed to sniff the liquid in the PEA bottle for 40 seconds, twice a day for 6 months. During the olfactory training period, any medicine used to treat olfactory dysfunction, including nasal steroids, antihistamines, and antibiotics, was prohibited.

Evaluation of olfactory function

Before olfactory training, all patients received birhinal and unirhinal PEA threshold tests and birhinal and unirhinal tests of the traditional Chinese version of the University of Pennsylvania Identification Test (UPSIT-TC) to evaluate their olfactory function. After 3-month olfactory training, the olfactory function was followed up by birhinal and unirhinal PEA threshold and UPSIT-TC tests. At the end of 6-month olfactory training, the olfactory function was evaluated by birhinal and unirhinal PEA threshold and UPSIT-TC tests again, and magnetic resonance imaging (MRI) was performed to measure the volume of olfactory bulbs (OBs). Any patient whose birhinal or unirhinal PEA threshold decreased below –1.0, or whose birhinal or unirhinal UPSIT-TC score increased 4 or more points,[14] was considered to have improvement in his or her olfactory function.

PEA odor detection threshold test

The PEA threshold test uses different concentrations of a rose-like odorant to measure the odor threshold. The PEA test employs a 2-alternative forced-choice single-staircase procedure. Two sniff bottles that contain PEA dissolved in mineral oil or mineral oil alone are opened and positioned under the subject's nose in a random order. The subject indicates in which bottle the odor is stronger. If a difference cannot be made, a guess is required. The test begins with a bottle containing PEA odorant at 10^{-6} log vol/vol. At the beginning of the test, correct identification of PEA bottles in 5 successive trials is needed to trigger a reversal of the staircase to the next lower concentration, whereas a single incorrect identification triggers the reversal of the staircase to the next higher concentration. In the following, correct identification of PEA bottles in 2 successive trials is enough to trigger a reversal of the staircase to the next lower concentration. A total of 7 reversals are acquired to finish the test, and the geometric mean of the last 4 reversed concentrations is used as the PEA threshold estimate. In this study, PEA concentrations ranged from 10^{-1} to 10^{-9} log vol/vol in half-log concentration steps.

UPSIT-TC

UPSIT-TC is an odor identification test modified from the North American version of University of Pennsylvania Smell Identification Test. Eight odorants have been replaced to take into account the cultural difference in the UPSIT-TC.[15] The UPSIT-TC consists of 40 tests. In each test, an odorant is embedded in 10-μm to 50-μm microcapsules fixed in a propriety binder and positioned on the brown bottom strips of the test page. The subject releases each odorant by scratching the strip with a pencil tip. Then the subject sniffs the released odorant and identifies the odorant by choosing a name from a set of 4 odor descriptors. The test is scored as the number of odors identified correctly. A guess is required for each test even if no odor is perceived.

MRI

The protocol for measuring the OB volume using MRI was described in our previous work.[16] The examination procedures are outlined below. MRI studies were performed through the use of a 1.5-T Exite MRI system (GEMS, Milwaukee, WI, USA) with a quadrature head coil. Routine imaging pulse sequences included axial T1-weighted images, fluid attenuation inversion recovery (FLAIR) images, along with axial and coronal T2-weighted fast spin-echo images. Contrast-enhanced T1-weighted images with axial and coronal sections were taken. After a sagittal localizing scan, 2-mm-thick to 2.5-mm-thick T2-weighted coronal and sagittal (both time to repetition [TR] = 5000 ms, echo time [TE] = 106 ms, number of excitations [NEX] = 2, matrix size = 256 × 256) images without an interslice gap were obtained with a 12-cm field of view, as per the standardized protocol for OB analysis. OB volumes were measured using Mimics Medical 21.0 (Materialise, Leuven, Belgium).

Statistical analysis

The sex and age of patients were compared between the 4-odorant and PEA groups using the Pearson chi-square test and Mann-Whitney *U* test, respectively. The incidence of loss of consciousness and intracranial hemorrhage after head injury, the ratios of admission and craniotomy, and frequency of improvement of olfactory function were compared between the 2 groups by the Pearson chi-square test. The interval periods between head injury and the patient's first visit were compared between the 2 groups through the use of the Mann-Whitney *U* test. The improvement rates of olfactory function were compared between the

TABLE 1. Comparison of profiles of head injury and olfactory bulb volumes

Characteristic	4-Odorant group(n = 45)	PEA group(n = 45)	*p*
Age (years), mean ± SD (range)	43.07 ± 14.38 (22–79)	39.71 ± 14.41 (20–72)	0.237
Sex, male/female, n	20/25	18/27	0.831
Head injury interval (months), mean ± SD (range)	16.27 ± 38.41 (1–250)	9.64 ± 15.07 (1–85)	0.151
Loss of consciousness, n (%)	35 (77.8)	36 (80.0)	1
Admission, n (%)	43 (95.6)	42 (93.3)	1
Intracranial hemorrhage, n (%)	37 (82.2)	36 (80.0)	1
Craniotomy, n (%)	8 (17.8)	6 (13.3)	0.771
Right OB volume (mm^3), mean ± SD	26.32 ± 22.05	31.15 ± 21.13	0.138
Left OB volume (mm^3), mean ± SD	27.16 ± 21.03	33.41 ± 24.97	0.264

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

2 groups using the Pearson chi-square test. The PEA threshold and UPSIT-TC score were compared before and after olfactory training by the Friedman and Wilcoxon signed rank test. The decrease in the PEA threshold and OB volumes were compared between the 2 groups using the Mann-Whitney *U* test. All analyses were performed using IBM SPSS for window, version 22.0 (IBM Corp., Armonk, NY). Two-tailed p values <0.05 were considered statistically significant.

Results

Patients

There were 159 patients enrolled in the study (Fig. 1). Among them, 37 were excluded because their birhinal or unirhinal PEA thresholds improved after taking prednisolone and zinc, and another 11 were lost follow-up. Therefore, 111 were randomly selected to receive olfactory training with traditional 4 odorants or PEA. Twenty-one patients did not complete the 6-month olfactory training, so there remained 45 patients in the 4-odorant group and 45 in the PEA group to finish the study.

There were 20 males and 25 females in the 4-odorant group, whose ages ranged from 22 to 79 years (mean, 43.07 years). There were 18 males and 27 females in the PEA group, whose ages ranged from 20 to 72 years (mean, 39.71 years). There were no significant differences in gender ($p = 0.831$) and age ($p = 0.237$) between the 2 groups.

Profiles of head trauma

The comparison of the interval periods between head trauma and first hospital visit, the incidences of loss of consciousness, intracranial hemorrhage after head trauma, and the ratios of admission and craniotomy between the 4-odorant and PEA groups are shown in Table 1. There were no significant differences between the 2 groups.

Olfactory function after 3-month and 6-month olfactory training

The comparisons of the olfactory function before and after olfactory training are shown in Table 2. In addition, the changes in repeated olfactory tests are shown in Figure 2. The birhinal and right unirhinal PEA thresholds decreased significantly after 3-month training in the PEA group, but the thresholds did not decrease significantly in the 4-odorant group. The right unirhinal UPSIT-TC score increased significantly in the PEA group after the 3-month training, but the UPSIT-TC score did not increase significantly in the 4-odorant group. After 6 months of training, the birhinal and unirhinal PEA thresholds decreased significantly in the PEA group, and the birhinal PEA threshold also decreased significantly in the 4-odorant group, but the decrease in the birhinal PEA threshold was not significantly different between the 2 groups ($p = 0.637$). The birhinal UPSIT-TC score increased significantly in the PEA group, but birhinal and unirhinal UPSIT-TC score did not increase significantly in the 4-odorant group. There were no significant differences between birhinal olfactory threshold and UPSIT-TC scores between the 3-month and 6-month evaluation visits ($p = 0.314$ and $= 0.646$, respectively, for the 4-odorant group; $p = 0.346$ and $= 0.088$, respectively, for the PEA group).

The birhinal or unirhinal PEA threshold after 6-month olfactory training decreased in 10 patients (22.2%) of the 4-odorant group, and in 12 patients (26.7%) of the PEA group. The frequency of improvement of PEA threshold function was not significantly different between the 2 groups ($p = 0.807$). The birhinal or unirhinal UPSIT-TC score increased 4 or more points in 18 patients (40%) of the 4-odorant group, and in 21 (46.7%) of the PEA group. The frequency of increase in UPSIT-TC scores for 4 or more points was not significantly different between the 2 groups ($p = 0.671$).

TABLE 2. Olfactory function after 3-month and 6-month olfactory training

Variable	3-month olfactory training			6-month olfactory training		
	4-Odorant group	PEA group	Between-group *p* value	4-Odorant group	PEA group	Between-group *p* value
PEA threshold						
Birhinal threshold						
Before training	–1	–1	1.0	–1	–1	1.0
After training, mean ± SD	−1.16 ± 0.55	−1.46 ± 0.98	0.079	−1.34 ± 0.97	−1.34 ± 0.96	0.637
Before vs after *p* value	0.066	0.005*		0.018*	0.008*	
Right unirhinal threshold						
Before training	–1	–1	1.0	–1	1	1.0
After training, mean ± SD	−1.21 ± 0.71	−1.36 ± 0.96	0.349	−1.15 ± 0.86	−1.24 ± 0.79	0.437
Before vs after *p* value	0.068	0.018*		0.109	0.043*	
Left unirhinal threshold						
Before training	−1	−1	1.0	1	1	1.0
After training, mean ± SD	−1.12 ± 0.48	−1.17 ± 0.82	0.439	−1.08 ± 0.34	−1.61 ± 1.36	0.010*
Before vs after *p* value	0.068	0.18		0.109	0.002*	
UPSIT-TC score						
Birhinal score						
Before training, mean ± SD	10.78 ± 4.48	10.71 ± 3.02	0.475	10.78 ± 4.48	10.71 ± 3.02	0.475
After training, mean ± SD	10.96 ± 3.10	11.33 ± 2.59	0.839	11.20 ± 3.29	12.27 ± 2.96	0.263
Before vs after *p* value	0.577	0.377		0.42	0.017*	
Right unirhinal score						
Before training, mean ± SD	10.64 ± 3.95	11.20 ± 2.97	0.442	10.64 ± 3.95	11.2 ± 2.97	0.442
After training, mean ± SD	9.89 ± 2.56	12.13 ± 2.74	<0.001*	10.76 ± 2.96	11.47 ± 2.67	0.335
Before vs after *p* value	0.372	0.029*		0.452	0.72	
Left unirhinal score						
Before training, mean ± SD	11.44 ± 3.79	11.82 ± 2.26	0.236	11.44 ± 3.79	11.82 ± 2.26	0.236
After training, mean ± SD	10.82 ± 2.91	12.00 ± 2.82	0.126	11.40 ± 3.19	11.58 ± 3.12	0.922
Before vs after *p* value	0.429	0.77		0.994	0.727	

*$p < 0.05$.
PEA = phenyl ethyl alcohol; SD = standard deviation; UPSIT-TC = traditional Chinese version of the University of Pennsylvania Smell Identification Test.

OB volumes

An MRI scan was performed on all 90 patients to measure their OB volumes after the 6-month olfactory training (Table 1). There were no significant differences in OB volumes between the 4-odorant and PEA groups.

Discussion

Olfactory training has been considered to be effective for patients with olfactory loss, but the optimal training duration or number of used odorants or beneficial patient population is still undecided.[17] It has been reported that olfactory training improves the abilities to identify and differentiate odors in patients with postinfectious olfactory loss.[10,18,19] In Konstantinidis et al.'s study,[10] they also found that olfactory training mainly improved odor identification rather than threshold in patients with posttraumatic olfactory loss. In contrast, our previous study found that PEA olfactory training could improve PEA odor threshold in patients with traumatic anosmia.[12] Pellegrino et al.[13] also reported that olfactory training significantly increased odor threshold ability for patients with traumatic anosmia.

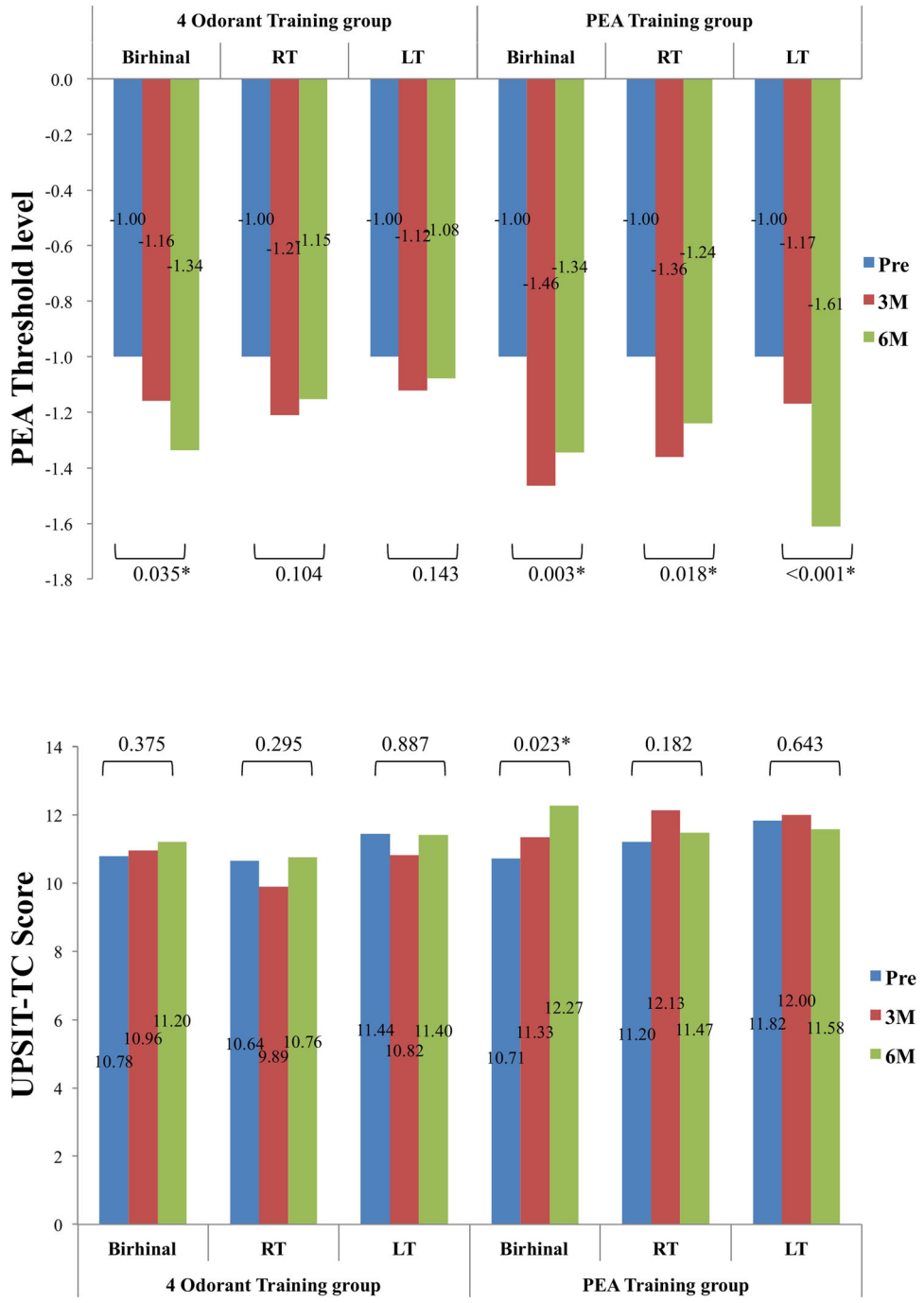

FIGURE 2. Olfactory threshold and UPSIT-TC scores after 3-month and 6-month training (data analyzed with Friedman test). UPSIT-TC = traditional Chinese version of University of Pennsylvania Smell Identification Test.

In our previous study, we evaluated the effect of olfactory training in patients with traumatic anosmia who failed treatment with steroids and zinc.[12] After olfactory training with PEA for 12 weeks, the PEA threshold improved in 10 of 42 (23.8%) patients in the PEA group. In contrast, when patients only sniffed mineral oil, the PEA threshold improved in 2 of 39 (5.1%) patients in the mineral oil group. The results found that the odor thresholds could be improved by olfactory training in patients with traumatic anosmia. When odor identification function was evaluated by birhinal UPSIT-TC, the score did not increase in both the PEA and mineral oil groups. In this study, we extended the training period to 6 months. Nevertheless, improvement mostly occurred within 3 months. There were no significant differences between birhinal olfactory threshold and UPSIT-TC scores between 3-month and 6-month evaluation visits. Fleiner et al.[20] analyzed the effect of an 8-month period of olfactory training in patients with

olfactory dysfunction. The authors found that the olfactory function did not further increase between 4 and 8 months of training. In contrast, Konstantinidis et al.[19] compared 2 groups of patient with postinfectious olfactory loss having olfactory training for 15 and 56 weeks. They reported that the long-term group seemed to have better results than the short-term group. The recommended period for olfactory training might be different depending upon the etiology of the olfactory dysfunction.

In this study, we attempted to clarify the effect of olfactory training on the odor identification in patients with traumatic anosmia who failed treatment with steroids and zinc through the use of traditional 4-odorant olfactory training for 6 months. After 3 months of training, the PEA threshold decreased in the PEA group as in our previous study, but the effect on the PEA threshold was not significant in the 4-odorant group. In the PEA group, we asked patients to sniff the PEA odorant for 40 seconds twice a day, whereas in the 4-odorant group we asked patents to sniff 4 odorants each for 10 seconds, twice a day. The birhinal UPSIT-TC score did not significantly increase in both groups after 3 months of training. After 6 months of olfactory training, the birhinal PEA threshold decreased significantly in both groups, but the decrease in the PEA threshold was not significantly different between the 2 groups. The UPSIT-TC score increased significantly in the PEA group, but did not increase significantly in the 4-odorant group. In brief, the olfactory threshold improved after 6 months of olfactory training but olfactory identification only improved in the PEA groups. In addition, there were no significant differences between the 2 training methods.

As mentioned in the first paragraph of this section, in Konstantinidis et al.'s study,[10] they reported that olfactory training improved the abilities of odor identification in patients with posttraumatic olfactory loss, but they did not specify whether the olfactory function of their patients was anosmic or hyposmic. In a recent report, Pellegrino et al.[13] classified their patients with posttraumatic olfactory loss into anosmic or hyposmic. They found that after at least 24 weeks of olfactory training with the traditional 4 odorants, the odor threshold improved significantly in anosmic patients, but the odor identification ability did not. In contrast, a trend toward improvement in odor identification ability was present in hyposmic patients. Our results seem to be compatible with Pellegrino et al.'s.[13]

Although previous studies and ours suggested that olfactory training improves the olfactory threshold or identification, the results might not refer to a significant clinical improvement. Konstantinidis et al.[10] compared the subjective self-rating olfactory function after 16 weeks of olfactory training for postinfectious and posttraumatic olfactory loss patients. They found the self-rating olfactory function improved after the 16-week olfactory training. Nevertheless, a recent randomized controlled study reported that 12-week olfactory training mildly improved the olfactory threshold in posttraumatic smell-impaired subjects, whereas the self-rating and smell identification did not improve.[21]

The OB volume after the 6-month olfactory training was not significantly different between the 4-odorant and PEA groups in this study, and this finding is similar to Pellegrino et al.'s[13] results. They suggested that olfactory training might give a top-down effect through brain plasticity and increased attention in patients with olfactory loss.

There are some limitations to this study: First, premorbid olfactory loss could not be identified before enrollment. Second, there were no normosmic traumatic subjects for control. Third, olfactory testing and training methods varied in different institutes, making our results difficult to compare with others. In addition, our study did not assess self-rating olfactory function or quality of life of study subjects. Further investigation is necessary to build a uniform training process, and assess the functional improvement and quality of life of patients after olfactory training.

Conclusion

Our results show that olfactory training can improve odor threshold levels in patients with traumatic anosmia, but did not improve the odor identification ability. Further investigation should be required to study which patient population and which aspect of the olfactory function the olfactory training can help.

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