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Modified Olfactory Training in Patients With Postinfectious Olfactory Loss

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Objectives/Hypothesis: Patients with olfactory dysfunction benefit from repeated exposure to odors, so-called olfactory training (OT). This does not mean occasional smelling but the structured sniffing of a defined set of odors, twice daily, for a period of 4 months or longer. In this prospective study, we investigated whether the effect of OT might increase through the use of more odors and extension of the training period.

Study Design and Methods: This study shows OT results when performed with four or 12 odors for 36 weeks in patients with postinfectious olfactory dysfunction. A total of 85 subjects participated (mean age 45.6 ± 10.5 years, range 24–68 years). Three groups were formed: 1) In the *modified olfactory training* (MOT) group, patients used three sets of four different odors sequentially. 2) Participants in the *classical odor training* (COT) group used four odors. 3) Participants in the control group did not perform OT. All groups were matched for age and sex distribution of participants.

Results: Both participants in the COT and MOT groups reached better scores than controls in terms of odor discrimination and odor identification. Continuing OT with four different odors after the 12th and 24th weeks produced better results in terms of odor discrimination and odor identification scores as compared to using the same four odors throughout the entire study.

Conclusion: This study confirmed the effectiveness of OT. Increasing the duration of OT and changing the odors enhances the success rate of this therapy.

Key Words: Olfaction, anosmia, smell, regeneration.

Level of Evidence: 2b.

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INTRODUCTION

Numerous studies show that olfactory dysfunction negatively affects the life of individuals; in addition, olfactory loss is found relatively frequently in the general population, with approximately 5% of the general population having anosmia and 15% having reduced olfactory function.[1–6] Upper respiratory-tract infections are among the most frequently seen causes of these olfactory dysfunctions.[7] Postinfectious olfactory dysfunction (PIOD) may recover spontaneously, but the success rate of spontaneous recovery after PIOD is still not entirely clear. Hummel et al.[8] reported a short-term recovery rate (which is not equal to complete restoration) of 6% to 8% within 4 months, whereas Reden et al.[9] reported a clinical improvement rate of 21% within about 7 months. A correlation between follow-up time and recovery rate after PIOD was emphasized.[10] Hendriks[11] reported a spontaneous recovery rate of 35% after a period of 12 months. In a different study, improvement was observed in 67% of participants with PIOD after a mean follow-up at 37 months.[10] However, the spontaneous recovery rate for PIOD was not satisfactory; and after spanning a 3-year follow-up period, limited improvement could be detected only in two-thirds of the patients.

To date, there is no validated pharmacotherapy for PIOD. However, repeated short-term exposure to odors (so-called olfactory training [OT]) seems to be effective. Hummel et al.[8] determined that OT over 12 weeks increased olfactory function in 28% of participants. In this study, four odors were used (eucalyptus, clove, lemon, and rose). In a recent randomized study, the application period of OT was extended from 12 weeks to 18 weeks, and the results were similar to the original study.[12]

In the current investigation, we were interested in the question of whether the use of more odors and an extension of the training period might increase the effectivity of OT. Thus, this study presents the results of OT,

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which was conducted by using 12 different odors for 36 weeks in patients with PIOD.

MATERIALS AND METHODS

Participants

All participants included in the study were either self-referrals or referred from another institution to the Department of Otorhinolaryngology of Istanbul Surgery Hospital, Istanbul, Turkey, over a period of 18 months. The study was approved by the Medical Ethics Committee of GATA Haydarpasa Training Hospital, Istanbul, Turkey (HNEAH-KAEK 71). All investigations were performed in accordance with the Declaration of Helsinki concerning biomedical studies involving human subjects, and written informed consent was obtained from all participants prior to the study.

Study Design

Study Protocol. Three age- and sex-matched groups were constituted from the PIOD patients who agree to volunteer for this study and met the study criteria. Patients were arbitrarily assigned to one of the three groups according to their order of inclusion in the study. Participants who performed the training using 12 different odors constituted the modified olfactory training (MOT) group; whereas participants who used the "classical" four-odor OT method, as explained by Hummel et al., for 36 weeks constituted the classical olfactory training (COT) group. Participants who were followed up without OT constituted the control group. Olfactory testing was performed at the beginning of the study and at weeks 12, 24, and 36.

The diagnosis of PIOD was made by an experienced otorhinolaryngologist following a detailed history plus nasal endoscopy.

Classical Olfactory Training. Olfactory training with four odors was applied, as described by Hummel et al.[8] Unlike this previous study, OT in the present study was performed over a period of 36 weeks. Patients exposed themselves twice daily to four odors: phenyl ethyl alcohol (PEA) (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves). These odorants had been chosen according to the "smell prism" by Henning[13]; this was supposed to define the six most significant odor qualities of the olfactory realm, based on which most other odors could be constructed. Olfactory training included exposure to odorants twice per day for 5 minutes. Every session included rotated exposure to each odorant for 10 seconds each, with time intervals of 10 seconds between odors. Patients were advised to sniff the odors in the morning before breakfast and in the evening before bedtime.

Modified Olfactory Training. To stimulate more and different olfactory receptors in the MOT group, we suggested periodically changing the training odors. According to this modification, participants exposed themselves twice daily to four odors, as described above for the COT group for 12 weeks. During the following 12 weeks, the odors of menthol, thyme, tangerine, and jasmine were used for the OT group. And during the last 12 weeks, the odors of green tea, bergamot, rosemary, and gardenia were used. Unlike the choice of odors for the COT group, here odors were selected based on availability; pleasantness; and, last but not least, prize. In addition, unlike for COT, these odors were not only based on single molecules but mixtures of odorants (e.g., tangerine). Accordingly, all odors used for the application of MOT were identical to the COT method in terms of the duration and application time of every session.

Psychophysical Testing of Olfactory Testing. The psychophysical testing of olfactory function was performed using the validated Sniffin' Sticks (Burghart, Wedel) test, for which odorants were presented in commercially available felt-tip pens.[14,15] First, the pen's cap was removed by the experimenter for approximately 3 seconds for odor presentation, and then the tip of the pen was placed about 1 cm to 2 cm in front of the nostrils. The test consisted of one threshold and two suprathreshold subtests, namely a test for thresholds of PEA, a test for odor discrimination (16 triplets with two different odors), and one for odor identification (16 common odors, presented in a four-alternative, forced-choice procedure). The maximum score of each subtest was 16, resulting in a maximum composite score of 48 (TDI [threshold, discrimination, and identification] score).[16] Normosmia is described for TDI composite scores of more than 30.3, with a cutoff between functional anosmia and hyposmia at 16.5.[17]

Visual Analog Scale. Participants rated their olfactory abilities on visual analog scales ranging from 1 to 10, with 10 indicating excellent olfactory function.

Statistical Analysis

Data analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL). Differences between the groups were evaluated using analysis of variance (ANOVA) or Chi-square, as appropriate. Post hoc Bonferroni tests were also performed to identify the differences among the groups. To explore olfactory function in relation to the continuous variables measured in this study, data were submitted to a multivariate ANOVA using the general linear model. Correlational analyses were calculated according to the Pearson's test, and the level of significance was set at 0.05.

RESULTS

This study was carried out in 85 subjects, with a mean age of 45.6 ± 10.5 years, ranging from 24 to 68 years. Participants in the MOT group performed the MOT using 12 different odors ($n = 37$; mean age 46 years; 20 females, 17 males; duration of disorder 7.5 months). Participants in the COT group used the four odor methods, as described above ($n = 33$; mean age 45 years; 17 females, 16 males; duration of disorder 6.9 months). Participants in the control group did not perform any training ($n = 15$; mean age 46 years; 8 females, 7 males; duration of disorder 7.1 months). There were no significant differences between groups in terms of age ($F[2,82] = 0.16$, $P = 0.85$), sex distribution ($Chi^2[2] = 0.05$, $P = 0.98$), or duration of disorder ($F[2,82] = 0.29$, $P = 0.75$). In addition, at baseline there was no significant difference between the study groups in terms of rated ($F[2,82] = 0.14$, $P = 0.87$) or measured olfactory function ($F[2,82] < 1.82$, $P > 0.16$). Descriptive statistics of the main results are shown in Table I.

When comparing the effects of treatment between the three groups using ANOVAs for repeated measures, the within-subject factor time point was significant for both measured and rated olfactory function ($F[3,246] > 11.9$, $P < 0.001$), indicating that overall olfactory function improved from baseline to the end of the observation period (Fig. 1). In addition, with the exception of only the odor thresholds, results were significantly different for the three groups investigated ($F[2,82] > 12.0$, $P < 0.001$). As indicated by the significant interaction between the factors *group* and *time point*

TABLE I.
Descriptive Statistics of Measured and Rated Olfactory Function Separately for the Three Study Groups at Beginning of Study and at Weeks 12, 24, and 36.

		MOT n = 37		COT n = 33		Control Group n = 15	
		Mean	SEM	Mean	SEM	Mean	SEM
Odor	baseline	2.4	0.1	2.5	0.1	2.5	0.2
Threshold	week 12	2.7	0.1	2.6	0.1	2.5	0.2
(in dilution steps)	week 24	2.8	0.1	2.7	0.1	2.6	0.2
	week 36	2.8	0.1	2.7	0.1	2.6	0.2
Odor	baseline	7.7	0.1	7.5	0.1	7.4	0.2
Discrimination	week 12	9.7	0.2	9.2	0.2	7.7	0.2
(correct identified)	week 24	11.1	0.4	9.8	0.4	7.8	0.2
	week 36	10.9	0.3	10.1	0.3	8.1	0.3
Odor	baseline	8.0	0.1	8.2	0.1	8.1	0.2
Identification	week 12	10.7	0.3	10.6	0.3	8.2	0.2
(correct identified)	week 24	12.5	0.3	11.4	0.3	8.5	0.2
	week 36	12.6	0.3	11.5	0.3	8.9	0.2
TDI score	baseline	18.1	0.3	18.2	0.3	18.0	0.6
	week 12	23.2	0.5	22.4	0.5	18.4	0.5
	week 24	26.4	0.7	23.8	0.6	18.8	0.5
	week 36	26.3	0.7	24.3	0.6	19.7	0.6
Rated	baseline	2.5	0.2	2.6	0.2	2.6	0.4
Olfactory	week 12	4.6	0.2	4.1	0.2	2.7	0.3
Function	week 24	5.5	0.3	5.1	0.3	2.7	0.4
(units)	week 36	5.6	0.3	5.2	0.3	2.8	0.4

COT = classical olfactory training; MOT = modified olfactory training; SEM = standard error of the mean; TDI = threshold-discrimination-identification.

(again with the exception of odor thresholds), improvement was most pronounced for the MOT group compared to the COT group ($F[6,246] > 8.3$, $P < 0.001$). Little change during the observation period was found within the control group. These results were confirmed by post hoc tests, with scores for the MOT and COT groups being higher as compared to the control group ($P \leq 0.05$), again with the exception of odor thresholds. When directly comparing the MOT and COT groups for week 36, participants in the MOT group scored higher for odor identification ($t_{68} = 2.34$, $P = 0.022$) and for the overall TDI score ($t_{68} = 2.16$, $P = 0.034$).

Moreover, the change in measured olfactory function was evaluated according to its clinical significance. Because the improvement of olfactory function was considered a change in the TDI score of ≥ 6, the results were classified according to this criterion for each group (Table II).[18,19] As shown in the table, in the MOT group and COT group, the number of participants that showed an increase in measured olfactory function after week 24 and after week 36 did not change.

Across all participants, there also was a significant correlation between duration of the olfactory loss and the change in TDI score after 36 weeks ($r_{85} = -0.62$, $P < 0.001$), with more improvement the shorter the duration of olfactory loss.

DISCUSSION

According to several publications in the current literature,[8,12,19,20] OT can be accepted as a treatment modality for PIOD. Olfactory training may generate a stimulus that triggers regeneration of olfactory receptor neurons. However, to date no consensus has been reached on a standardized OT protocol, particularly for the implementation period. There also is not enough data in the current literature about the use of odors other than rose, eucalyptus, lemon, and cloves, which were previously proposed for OT.

The current investigation produced three major findings: 1) Both participants in the COT group and MOT group reached better scores than controls in terms of the D and I subtasks. 2) Continuing the OT with four different odors after the 12th and 24th weeks produced better results in terms of D and I scores compared to the use of the same four odors throughout the entire study. 3) Although there were significant differences between the MOT group and COT group in terms of D and I subtasks at the end of the 24th and 36th weeks, we did not find clinically significant changes at the TDI scores of the participants between the 24th and 36th weeks of the study both for MOT and COT groups.

Interestingly, in the present study we did not see a significant improvement of odor thresholds in relation to treatment, whereas scores in suprathreshold tasks improved significantly. Assuming that changes in odor thresholds relate more to peripheral changes in the olfactory system, whereas changes in odor discrimination and identification relate more to higher cognitive tasks,[21,22] the current data seem to indicate that OT produced cognitive changes leading to an improved perception of odors. However, previous work on OT indicated

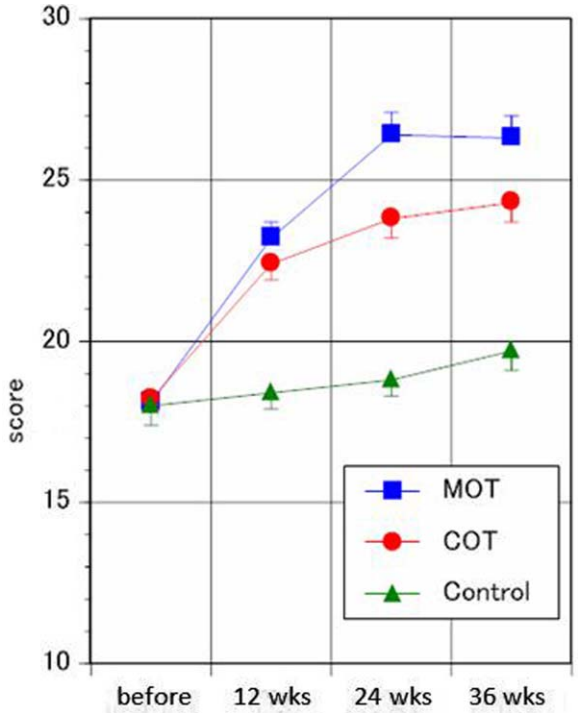

Fig. 1. Means and standard errors of means of changes of threshold-discrimination-identification score over time (beginning of the study and at weeks 12, 24, and 36) separately for the three groups. Note that the y-axis starts at 10. Control group = no training; COT = classical olfactory training; MOT = modified olfactory training. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

that gain in odor thresholds is also involved in the improvement seen after OT.[23] Currently, the exact effects of OT are a matter of speculation. It might be that OT improves odor thresholds, and by implication, the architecture of the peripheral olfactory system,[24] or/and that OT changes the processing of olfactory information (e.g. 25). More research is needed to clarify this issue.

Another issue is the question of whether the OT-induced improvement produces lasting results or is only temporal in nature. Current unpublished data (oral communication by I. Konstantinidis, November 2014) seem to indicate that the improvement lasts for at least 6 months, probably longer.

According to the present results, we suggest that OT is a good alternative treatment method for patients with PIOD. Changing the "training odors" periodically may improve the success of the therapy. Also, in order to obtain satisfactory results from olfactory training, this therapy may be continued at least 24 weeks. Moreover, based on our personal experience, changing the odors periodically increases compliance of the patients with the therapy.

TABLE II.
Number of Participants With Clinically Significant Improvement of Olfactory Function in Relation to Baseline.*

	12th Week	24th Week	36th Week
MOT (n = 37)	N = 12 (32%)	N = 21 (56%)	N = 21 (56%)
COT (n = 33)	N = 7 (21%)	N = 15 (46%)	N = 15 (46%)
Control group (n = 15)	–	–	–

*Difference in TDI score of 6 and more points.
COT = classical olfactory training; MOT = modified olfactory training.

CONCLUSION

This study demonstrated the effectiveness of OT in patients with postinfectious olfactory disease. In addition, changing the types of odors periodically during OT can enhance the likelihood of success of this form of therapy. More studies are needed to confirm these encouraging results.

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