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Evaluation of long-term results of olfactory training for persistent olfactory dysfunction after COVID-19 infection

COVID-19 enfeksiyonu sonrası kalıcı koku alma işlev bozukluğu için koku eğitiminin uzun dönem sonuçlarının değerlendirilmesi

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ABSTRACT

Objectives: The study aimed to evaluate the effect of long-term olfactory training (OT) in patients with persistent olfactory dysfunction (OD) following coronavirus disease 2019 (COVID-19) infection.

Patients and Methods: The study included patients who developed OD after COVID-19 infection between March 2021 and January 2022. Following the initial examination, olfactory Visual Analog Scale (VAS) scores were recorded before treatment and at 3, 6, and 12 months after treatment. Olfactory training was applied for a period of 12 months to all the patients diagnosed with persistent OD. The procedure was explained in a written document, and four intense smells (phenyl ethyl alcohol [rose], eucalyptol [eucalyptus], citronella [lemon], and eugenol [cloves]) in amber-colored jars were used. The OT scoring was interpreted as follows: 9-10 points, full recovery; 7-8 points, almost full recovery; 5-6 points, semi-recovery; 3-4 points, partial recovery; 1-2 points, no recovery. Kruskal-Wallis one-way analysis of variance was used to compare patients' VAS scores, with post hoc analysis with Bonferroni correction.

Results: Eighty-three patients (57 females, 26 males; mean age: 30.6±11.3 years; range, 17 to 62 years) were included in the analyses. The VAS score of all the patients was 0 before treatment. The mean VAS scores were 6.95±2.3 at three months, 7.59±2.13 at six months, and 7.96±1.97 at 12 months (p=0.0001). Full recovery of OD was obtained with OT in 41 (50%) patients, and one patient showed no recovery.

Conclusion: Long-term OT is an effective treatment for persistent OD that developed after COVID-19 infection.

Keywords: Anosmia, COVID-19, olfactory dysfunction, olfactory training, smell dysfunction.

ÖZ

Amaç: Bu çalışmada koronavirüs hastalığı 2019 (COVID-19) enfeksiyonunu takiben inatçı koku disfonksiyonu (KD) olan hastalarda uzun süreli koku eğitiminin (KE) etkisi değerlendirildi.

Hastalar ve Yöntemler: Çalışmaya Mart 2021 - Ocak 2022 tarihleri arasında COVID-19 enfeksiyonu sonrası KD gelişen hastalar dahil edildi. İlk muayenenin ardından tedavi öncesinde ve tedaviden 3, 6 ve 12 ay sonra koku Görsel Analog Ölçek (GAÖ) skorları kaydedildi. Persistan KD tanısı konulan hastaların tamamına 12 ay süre ile KE uygulandı. Prosedür yazılı bir belge ile anlatıldı ve KE sırasında amber renkli kavanozlarda dört yoğun koku (fenil etil alkol [gül], okaliptüs [okaliptüs], sitronella [limon] ve öjenol [karanfil]) kullanıldı. Koku eğitimi puanlaması şu şekilde yorumlandı: 9-10 puan, tam iyileşme; 7-8 puan, neredeyse tam iyileşme; 5-6 puan, yarı iyileşme; 3-4 puan, kısmi iyileşme; 1-2 puan, iyileşme yok. Hastaların GAÖ skorlarını karşılaştırmak için Kruskal-Wallis tek yönlü varyans analizi kullanıldı ve post hoc analizlerde Bonferroni düzeltmesi kullanıldı.

Bulgular: Analizlere 83 hasta (57 kadın, 26 erkek; ort. yaş: 30.6±11.3 yıl; dağılım, 17-62 yıl) dahil edildi. Tüm hastaların GAÖ skorları tedavi öncesi 0 idi. Ortalama GAÖ skorları üç ayda 6.95±2.3, altı ayda 7.59±2.13 ve 12 ayda 7.96±1.97 idi (p=0.0001). Kırk bir (%50) hastada KE ile KD'de tam iyileşme elde edildi, bir hastada ise iyileşme görülmedi.

Sonuç: Uzun süreli KE, COVID-19 enfeksiyonu sonrası gelişen inatçı KD için etkili bir tedavidir.

Anahtar sözcükler: Anosmi, COVID-19, koku alma bozukluğu, koku eğitimi, koku işlev bozukluğu.

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The sense of smell is important for daily life. The ability to smell is not only linked to satisfaction experienced while eating but is also necessary to avoid dangerous situations such as fire, smoke, gas leaks, and boiled or burned food. Therefore, dysfunction in the sense of smell can diminish quality of life and cause life-threatening conditions.[1,2] Although previous studies have shown olfactory dysfunction (OD) in 5% of the general population,[3-6] recent studies have reported that more than 20% of the population suffer from OD.[7] Therefore, diagnosis and treatment are crucial for such a widespread issue.

Upper respiratory tract infections are among the most frequent causes of OD.[8] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was determined as the agent of the viral pandemic that started in China at the end of 2019 and then spread rapidly throughout the world. On April 23, 2020, the Centers for Disease Control and Prevention added the symptoms of newly formed loss of taste and smell to the key symptoms of cough, shortness of breath, fever, shivering, muscle pain, and sore throat for coronavirus disease 2019 (COVID-19).

Postinfectious OD (PIOD) can recover spontaneously, but in patients with PIOD, spontaneous recovery does not always equate to full recovery. In a study by Hummel et al.,[9] the rates of incomplete spontaneous recovery within four months were reported between 6 and 8%, and in another study, this rate was 21% within seven months.[10] The recovery of ≥4 points in smell tests was observed in 67% of persistent PIOD patients in a mean follow-up of 37±3.8 months.[11] This rate is not sufficient in terms of recovery, with limited recovery seen in two-thirds of patients despite a period of more than three years.

There is currently no drug treatment with proven validity for the treatment of PIOD. Drugs with many unproven effects, such as caroverine, alpha lipoic acid, vitamin A, vitamin D, zinc, and vitamin B12 are included for possible use in treatment.[12,13] However, as olfactory training (OT), which involves short-term exposure to smells, has been shown to have increased recovery rates, this is currently the most recommended modality in OD treatment. Hummel et al.[9] reported that OT applied for ≥12 weeks increased olfactory function by 28%. In another randomized study, the period of OT application was increased to 18 weeks, and similar results were reported.[14]

The aim of this study was to evaluate the 3-, 6-, and 12-month long-term results of OT treatment in patients with proven persistent PIOD following COVID-19 infection.

PATIENTS AND METHODS

This prospective, single-center study was conducted in the otorhinolaryngology clinic of the Ankara Dışkapı Training and Research Hospital. A written informed consent was obtained from each patient. The study protocol was approved by the Ankara Dışkapı Training and Research Hospital Ethics Committee (date: 22.03.2021, no: 107/27). The study was conducted in accordance with the principles of the Declaration of Helsinki. The study included patients who developed persistent PIOD following COVID-19 infection between March 2021 and January 2022. For all patients, the COVID-19 data from nasopharyngeal swabs tested for SARS-CoV-2 with reverse transcription-polymerase chain reaction were obtained from the Republic of Türkiye Ministry of Health hospital information management system.

The patients included were those who had a COVID-19 infection at least two months prior and developed persistent PIOD, confirmed with a nasopharyngeal test, which did not spontaneously recover. Patients were excluded from the study if they had any neurological or cognitive disorder, any systemic disease (e.g., diabetes mellitus, hypertension, and hypo- or hyperthyroidism), or any significant nasal obstruction (e.g., nasal polyps and severe nasal septum deviation). The initial detailed otorhinolaryngological examination was made by the single doctor for all the patients, and OT was explained to each patient. The patients were then examined again by the same doctor after 3, 6, and 12 months of treatment.

Olfactory Visual Analog Scale (VAS) scores were recorded before treatment and at 3-, 6-, and 12-months after treatment. To evaluate OD, any decrease in olfactory function or loss of function since the onset of COVID-19 and the changes experienced were scored from a total of 10 points by the patients. Before scoring, it was explained to the patients that 10 points represented full olfactory function and 0 represented complete absence of the sense of smell. The OT scoring was interpreted as follows: 9-10 points, full recovery; 7-8 points, almost full recovery; 5-6 points, semi-recovery; 3-4 points, partial recovery; 1-2 points, no recovery.

Olfactory training was applied for a period of 12 months to all the patients diagnosed with PIOD. The procedure was explained in a written document and during OT. Four intense smells (phenyl ethyl alcohol [rose], eucalyptol, [eucalyptus], citronella [lemon], and eugenol [cloves]) in amber-colored jars were used. Twice a day, preferably once in the morning before breakfast and once in the evening

Table 1
Pre- and posttreatment VAS scores

	Mean±SD	95% CI		p
		Lower bound	Upper bound	
VAS at 3 months posttreatment	6.95±2.28	6.454	7.449	
VAS at 6 months posttreatment	7.59±2.13	7.125	8.055	0.0001
VAS at 12 months posttreatment	7.96±1.97	7.535	8.393	

VAS: Visual analog scale; SD: Standard deviation; CI: Confidence interval.

before going to bed, the patients smelled each of the four odors separately for at least 20 to 30 sec. The patients were instructed to breathe each odor in through the nose for 20 to 30 sec continuously. A break of 20 to 30 sec was given between each odor. To be able to understand whether or not the patients adhered to the training, they were requested to keep daily notes, which were questioned at each follow-up examination. Patients who did not perform the training regularly were excluded from the study.

Statistical analysis

Data analysis was performed using IBM SPSS version 20.0 software (IBM Corp., Armonk., NY, USA). The Kolmogorov-Smirnov test and P-P plots were used to verify the normality of the distribution of continuous variables. Continuous variables showing normal distribution were reported as mean ± standard deviation (SD), and nonnormally distributed variables were presented as median (min-max) values. Categorical variables were stated as frequency (n) and percentage (%). Nominal variables were assessed using the Pearson chi-square test or Fisher exact test. For parameters that did not show normal distribution, the nonparametric Kruskal-Wallis one-way analysis of variance was used in the comparisons, with post hoc analysis using Bonferroni correction. A p-value <0.05 was considered statistically significant.

RESULTS

The study initially assessed 120 patients. Of these, 37 were excluded; two due to a new diagnosis of systemic disease (hypertension) and 35 who could not comply with the OT treatment and did not attend follow-up appointments. Thus, analyses were conducted with 83 patients (57 females, 26 males; mean age: 30.6±11.3 years; range, 17 to 62 years). The initial complaint was cacosmia in 68.7% of the patients and anosmia in 31.3%. The VAS score at the first examination was 0 for all patients. The mean VAS score after starting treatment was 6.95±2.28 at three months, 7.59±2.13 at six months, and 7.96±1.97 at 12 months (p=0.0001; Table 1).

When male and female patients were evaluated separately, the mean VAS scores were determined to be 6.9±2.2 at three months, 7.6±2.1 at six months, and 7.9±1.9 at 12 months for the female patients, while they were 6.9±2.4 at three months, 7.5±2.1 at six months, and 7.9±1.9 at 12 months for the male patients (p=0.93, p=0.96, and p=0.99, respectively). At the end of the treatment, of all 83 patients, full recovery of OD was obtained with OT treatment in 41 (49.3%) patients, and one (1.2%) patient showed no recovery (Figure 1).

There was no allergic rhinitis or sinusitis present in 92.8% of the patients, and 85.5% of the patients were nonsmokers.

DISCUSSION

In this study of patients diagnosed with PIOD at least two months after a proven COVID-19 infection, the majority (68.7%) of patients presented with cacosmia, and the results demonstrated a decrease in the complaints with the application of OT treatment (mean VAS of 6.95 after three months of OT; p=0.0001).

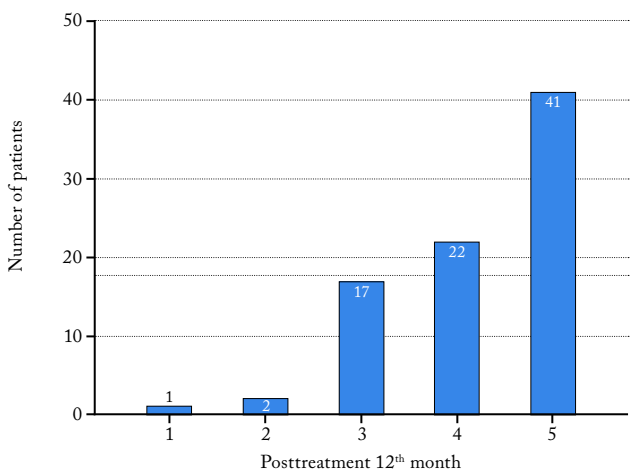

Figure 1. Twelve-month olfactory training treatment results.
1: VAS 1-2; 2: VAS 3-4; 3: VAS 5-6; 4: VAS 7-8; 5: VAS 9-10.
VAS: Visual Analog Scale.

It was also determined that with longer application of OT, the recovery rates increased (mean VAS scores of 6.95±2.28 at three months, 7.59±2.13 at six months, and 7.96±1.97 at 12 months; p=0.0001). As observed from these results, although there is no clear consensus on treatment, it is important to continue OT for longer than the recommended period for PIOD patients who adhere to the therapy.

In a study by Lechien et al.,[15] the application of OT for 18 months with treatment compliance in patients with PIOD that developed after a COVID-19 infection was determined to increase the chance of success. In an intensified OT study by Pires et al.,[16] eight different odors were used rather than four, and patients were followed up for four weeks. The efficacy of OT treatment was found to be high despite the short follow-up period.

In postviral OD, the treatment to obtain normal and correct perception of odors is a difficult process, particularly in cases that experienced COVID-19 infection. Olfactory training was first defined by Hummel et al.,[9] and the beneficial effects of the treatment and various modifications were reported in several meta-analyses.[17-19] In a meta-analysis including 16 studies, Kattar et al.[19] evaluated the response of PIOD patients to OT treatment, and the efficacy of OT treatment was determined to increase in direct proportion to a mean treatment period of 5.5±2.2 months. Similarly in the current study, it was observed that the recovery rates of the patients increased as the period of OT application increased, and this increase was statistically significant (p=0.0001).

The male-to-female ratio in PIOD after COVID-19 shows variability in the literature. In a multicenter European study by Lechien et al.[20] on 417 post-COVID-19 PIOD patients, the mean age was 36.9±11.4 years, 63.1% of the patients were female, and 86.6% were nonsmokers. In another study of 100 hospitalized patients, it was determined that 42% of the patients had complaints of PIOD, and the mean age of these patients was higher (mean age: 65±15 years). Although olfactory dysfunction affects females more frequently, this study revealed a male predominance due to the male predisposition to and higher incidence of hospitalization related to COVID-19.[21] However, in the current study, the mean age was 30.6±11.3 years, and 68.7% of the patients were female.

In the high patient volume (n=417) multicenter study by Lechien et al.,[20] the early and late (<15 days and >15 days, respectively) spontaneous recovery rates were evaluated in post-COVID-19 PIOD patients. The early recovery rate of OD was determined to be 44% (within 1 to 4 days), and spontaneous recovery within eight days was determined in 72.6% of the patients. The current study results showed extremely high spontaneous recovery rates within the first few months. By including only patients with persistent OD at least two months after a COVID-19 infection, an attempt was made to reduce potential bias by minimizing the number of patients likely to recover spontaneously.

Although PIOD was more prevalent in male patients in the study by Meini et al.,[21] they also recovered more quickly. Furthermore, they determined that OD was less prevalent in female patients and lasted longer despite OT treatment (26 *vs.* 14 days, p=0.009). In the current study, the mean VAS scores were determined to be 6.9±2.2 at three months, 7.6±2.1 at six months, and 7.9±1.9 at 12 months for female patients, whereas mean VAS scores were 6.9±2.4 at three months, 7.5±2.1 at six months, and 7.9±1.9 at 12 months for male patients (p=0.93, p=0.96, and p=0.99, respectively). The male and female recovery rates were similar. The differences in sex and recovery time may be attributed to the change in the inflammation reaction process, which can affect this function in the olfactory bulb, olfactory nerve, and olfactory centers in the brain. Evidence of this could be provided in further more comprehensive and detailed studies.

The study had some limitations. Patient evaluations were made with a subjective questionnaire rather than objective and specific smell tests. The main reason for this was that smell tests are not routinely used in the hospital where the study was conducted or in Türkiye in general. The lack of a control group can be considered another limitation. However, by including patients with persistent OD for two months, the probability of spontaneous recovery was reduced. Strong aspects of the study included its prospective and monocentric design, the homogeneity of the patient group with respect to the etiological agent, and the presentation of long-term results of OT.

In conclusion, OT treatment in patients with persistent PIOD that developed after COVID-19 infection increases olfactory sensitivity. The 12-week period recommended in traditional OT treatment is a useful and practical regimen that can be applied with high participation of the patient. Prolonging the application period of OT is an important treatment modality that can be currently applied in persistent PIOD patients by supervising and supporting patient participation.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Miwa T, Furukawa M, Tsukatani T, Costanzo RM, DiNardo LJ, Reiter ER. Impact of olfactory impairment on quality of life and disability. Arch Otolaryngol Head Neck Surg 2001;127:497-503. doi: 10.1001/archotol.127.5.497.
2. Santos DV, Reiter ER, DiNardo LJ, Costanzo RM. Hazardous events associated with impaired olfactory function. Arch Otolaryngol Head Neck Surg 2004;130:317-9. doi: 10.1001/archotol.130.3.317.
3. Wysocki CJ, Gilbert AN. National geographic smell survey. Effects of age are heterogenous. Ann N Y Acad Sci 1989;561:12-28. doi: 10.1111/j.1749-6632.1989.tb20966.x.
4. Hoffman HJ, Ishii EK, MacTurk RH. Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the 1994 disability supplement to the National Health Interview Survey (NHIS). Ann N Y Acad Sci 1998;855:716-22. doi: 10.1111/j.1749-6632.1998.tb10650.x.
5. Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. JAMA 2002;288:2307-12. doi: 10.1001/jama.288.18.2307.
6. Schubert CR, Cruickshanks KJ, Fischer ME, Huang GH, Klein BE, Klein R, et al. Olfactory impairment in an adult population: The Beaver Dam Offspring Study. Chem Senses 2012;37:325-34. doi: 10.1093/chemse/bjr102.
7. Rawal S, Hoffman HJ, Bainbridge KE, Huedo-Medina TB, Duffy VB. Prevalence and risk factors of self-reported smell and taste alterations: Results from the 2011-2012 US National Health and Nutrition Examination Survey (NHANES). Chem Senses 2016;41:69-76. doi: 10.1093/chemse/bjv057.
8. Seiden AM. Postviral olfactory loss. Otolaryngol Clin North Am 2004;37:1159-66. doi: 10.1016/j.otc.2004.06.007.
9. Hummel T, Rissom K, Reden J, Hähner A, Weidenbecher M, Hüttenbrink KB. Effects of olfactory training in patients with olfactory loss. Laryngoscope 2009;119:496-9. doi: 10.1002/lary.20101.
10. Reden J, Herting B, Lill K, Kern R, Hummel T. Treatment of postinfectious olfactory disorders with minocycline: A double-blind, placebo-controlled study. Laryngoscope 2011;121:679-82. doi: 10.1002/lary.21401.
11. Duncan HJ, Seiden AM. Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection. Arch Otolaryngol Head Neck Surg 1995;121:1183-7. doi: 10.1001/archotol.1995.01890100087015.
12. Harless L, Liang J. Pharmacologic treatment for postviral olfactory dysfunction: A systematic review. Int Forum Allergy Rhinol 2016;6:760-7. doi: 10.1002/alr.21727.
13. Hummel T, Whitcroft KL, Rueter G, Haehner A. Intranasal vitamin A is beneficial in post-infectious olfactory loss. Eur Arch Otorhinolaryngol 2017;274:2819-25. doi: 10.1007/s00405-017-4576-x.
14. Damm M, Pikart LK, Reimann H, Burkert S, Göktas Ö, Haxel B, et al. Olfactory training is helpful in postinfectious olfactory loss: A randomized, controlled, multicenter study. Laryngoscope 2014;124:826-31. doi: 10.1002/lary.24340.
15. Lechien JR, Vaira LA, Saussez S. Effectiveness of olfactory training in COVID-19 patients with olfactory dysfunction: A prospective study. Eur Arch Otorhinolaryngol 2023;280:1255-63. doi: 10.1007/s00405-022-07665-4.
16. Pires ÍAT, Steffens ST, Mocelin AG, Shibukawa DE, Leahy L, Saito FL, et al. Intensive olfactory training in post-COVID-19 patients: A multicenter randomized clinical trial. Am J Rhinol Allergy 2022;36:780-7. doi: 10.1177/19458924221113124.
17. Pekala K, Chandra RK, Turner JH. Efficacy of olfactory training in patients with olfactory loss: A systematic review and meta-analysis. Int Forum Allergy Rhinol 2016;6:299-307. doi: 10.1002/alr.21669.
18. Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: A meta-analysis. Rhinology 2017;55:17-26. doi: 10.4193/Rhino16.195.
19. Kattar N, Do TM, Unis GD, Migneron MR, Thomas AJ, McCoul ED. Olfactory training for postviral olfactory dysfunction: Systematic review and meta-analysis. Otolaryngol Head Neck Surg 2021;164:244-54. doi: 10.1177/0194599820943550.
20. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicenter European study. Eur Arch Otorhinolaryngol 2020;277:2251-61. doi: 10.1007/s00405-020-05965-1.
21. Meini S, Suardi LR, Busoni M, Roberts AT, Fortini A. Olfactory and gustatory dysfunctions in 100 patients hospitalized for COVID-19: Sex differences and recovery time in real-life. Eur Arch Otorhinolaryngol 2020;277:3519-3523. doi: 10.1007/s00405-020-06102-8.