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Management of post-COVID olfactory disorder: is olfactory training effective on recovery of olfactory function?

COVID sonrası koku alma bozukluğunun yönetimi: Koku alma eğitimi koku alma fonksiyonunun iyileşmesi üzerinde etkili mi?

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Abstract

Background The number of patients presenting with sudden onset and persistant anosmia and other olfactory disorders, which is a finding related to coronavirus disease has increased considerably.

Objective In this study, we aimed to evaluate the efficacy of olfactory training in patients with persistent anosmia after Covid-19 infection.

Methods Forty-six patients who applied for a sudden loss of smell after Covid-19 infection and still had olfactory disorders were included in the study. Odor threshold and odor identification tests were performed on the patients before the treatment. As olfactory training, four scent bottles included the following groups: phenyl ethyl alcohol, eucalyptol group, citronellal group and eugenol group were given to patients, and they were instructed to sniff the odors twice a day, for five seconds each, when they woke up in the morning and before they went to sleep and make a daily check that they applied the treatment. Patients who continued the training for 12 weeks were re-evaluated with the odor threshold test and odor identification test.

Results The pre-training mean olfactory threshold score of the patients was 1.65±1.74, and the post-training mean olfactory threshold score was 3.89±2.73. It was observed that the olfactory threshold scores increased significantly after the olfactory training ($P<0.001$). The pre-training mean odor identification score of the patients before olfactory training was 4.09±3.53 and the post-training mean odor identification score was 8.24±4.53. It was observed that odor identification scores increased significantly after olfactory training ($P<0.001$).

Conclusion The results of this study show that olfactory training can be an effective treatment method for olfactory loss after Covid-19.

Key words: *anosmia, odor threshold, olfactory disorder, covid-19, olfactory training*

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Öz

Arka plan COVID-19 hastalığına bağlı ani başlangıçlı anosmi ve diğer koku alma bozuklukları ile başvuran hasta sayısı oldukça artmıştır.

Amaç Bu çalışmada Covid-19 enfeksiyonu sonrası inatçı anosmisi olan hastalarda koku alma eğitiminin etkinliğini değerlendirmeyi amaçladık.

Yöntem Çalışmaya COVID-19 enfeksiyonu sonrası ani koku kaybı şikayeti ile başvuran ve koku alma bozuklukları devam eden 46 hasta alındı. Tedavi öncesi hastalara koku eşiği ve koku tanımlama testleri yapıldı. Koku eğitimi olarak hastalara fenil etil alkol, okaliptol grubu, sitronelal grubu ve öjenol grubu olmak üzere 4 koku şişesi verilmiş ve hastalara sabah uyandıklarında kokuları günde iki kez 5'er saniye olmak üzere koklamaları söylenmiştir. Hastaların sabah ve yatmadan önce tedaviyi uyguladıkları günlük olarak kontrol edildi. Eğitime 12 hafta devam eden hastalar koku eşiği testi ve koku tanımlama testi ile yeniden değerlendirildi.

Bulgular Hastaların eğitim öncesi ortalama koku eşik puanı 1.65±1.74, eğitim sonrası ortalama koku eşiği puanı 3.89±2.73 idi. Olfaktör eşik puanlarının olfaktör eğitimden sonra anlamlı olarak arttığı görüldü (P<0,001). Olfaktör eğitim öncesi hastaların eğitim öncesi ortalama koku tanıma puanı 4.09±3.53, eğitim sonrası koku tanımlama puanı ortalama 8.24±4.53 idi. Koku eğitiminden sonra koku tanıma puanlarının anlamlı olarak arttığı gözlendi (P<0,001).

Sonuç Bu çalışmanın sonuçları, koklama eğitiminin Covid-19 sonrası koku kaybı için etkili bir tedavi yöntemi olabileceğini göstermektedir.

Anahtar kelimeler: *anosmi, koku eşiği, koku alma bozukluğu, covid-19, koku alma eğitimi*

Introduction

COVID-19 (coronavirus disease-19), reported for the first time in the Wuhan region of China at the end of 2019, led to the occurrence of pneumonia cases of unknown origin and was declared a pandemic by the World Health Organization in March 2020.[1]

The most common symptoms of the disease were malaise, fever and cough, among other common symptoms such as headache, muscle pain and shortness of breath. Symptoms of the upper respiratory system (runny nose, sore throat and nasal congestion, among others) and gastrointestinal system were less common.[2-4] In the later stages of the pandemic, sudden loss of smell and taste was observed in many patients.[5] Loss of smell was considered to be a symptom of Covid-19 that presents faster than fever, cough and shortness of breath.[6,7] With the disease becoming more common, many researchers thought that sudden loss of smell and taste was one of the important symptoms of Covid-19.[8]

Bacterial and viral upper respiratory tract infections (URTI) are known to play a role in the etiology of sudden loss of smell. It is particularly more common after viral URTI, such as rhinovirus, parainfluenza, coronavirus, and Ebstein-Barr virus, among others.[9] The mechanism underlying the loss of smell after viral infections has not been fully elucidated and many theories have been proposed regarding the mechanism of loss of smell associated with Covid-19. Although some researchers suggest that the virus damages the olfactory epithelium in the nose, some researchers argue that the central pathways are affected and loss of smell is a neurological finding.[10,11]

Loss of smell is a condition that significantly affects a person's quality of life. It can affect the individual in many ways, from personal hygiene problems, loss of appetite and body weight, home security problems to loss of professional workforce and it can consequently lead to psychological problems. For this reason, the treatment of loss of smell can impact the social life of the individual as well as increase the quality of life. Many pharmacological or non-pharmacological treatment methods have been tried for loss of smell after post-URTI, idiopathic and sinonasal olfactory loss. Pharmacologically, agents such as systemic and nasal steroids, oral alpha lipoic acid, oral zinc, vitamin A, and gingko biloba are used.[12-14] Another treatment option is olfactory training. This method can be a preferred treatment method for those who experience loss of smell after Covid-19, owing to its

non-pharmacological and non-invasive nature, low cost, and ease of application.[15-17] The present study aimed to evaluate the efficacy of olfactory training in patients with persistent loss of smell after Covid-19.

Methods

We included 46 patients (25 women, 21 men) who applied to Mardin Public Hospital between April 2021 and June 2021 for sudden loss of smell after Covid-19 infection and still had olfactory disorders. This study was performed in line with the principles of the Declaration of Helsinki. Ethics committee approval for this prospective study was obtained from Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (No: 270/22-04-2021). The patients included in the study were those who stated that they had a normal sense of smell before Covid-19 infection, who developed sudden loss of smell in the last 1 year, and who were confirmed to have Covid-19 based on polymerase chain reaction (PCR) test performed during the development of loss of smell. Routine anamnesis was taken from the patients, and otolaryngological examination including nasal endoscopy was performed. Those who presented with sudden loss of smell and not confirmed to have had COVID-19 based on the PCR test during the time period loss of smell developed, those with loss of smell for more than 1 year, people with acute URTI, patients with a pathology creating a physiological barrier such as nasal polyposis, pregnant women, and patients aged<18 years were excluded from the study. All patients were informed about other currently recommended treatment options and olfactory training. Participants who selected olfactory training as a treatment option and did not receive any other pharmacological treatment were included in the study. The time between confirmation of Covid-19 by PCR and examination and initiation of treatment ranged from 1 to 6 months. Informed consent was obtained from the subjects who agreed to participate in the study.

Test Procedure

Odor threshold and odor identification tests were performed on the patients before starting the treatment. For the threshold test, 4% n-butanol diluted in geometric series was used. For this purpose, 4% n-butanol was placed in 16, 100 ml bottles with a length of 10 cm and a diameter of 3 cm. The first bottle contained the highest concentration and dilution was made with distilled water at a ratio of 1:2. Starting with the highest concentration, the subjects were asked whether they could smell anything in the bottles. The last threshold where the subjects were able to smell something in three consecutive bottles was noted. A 20-second break was provided between each bottle.

Aromatic oils taken from herbalists were used for the odor identification test (Karden, Karden Agricultural products, Ankara, Turkey). The scents consisted of 16 scents that were previously used as an identification test in our region. The scents were presented with dark colored bottles numbered 1-16 with a length of 5 cm and a diameter of 2 cm. The scents used were as follows: cinnamon, apple, rose, lemon, thyme, garlic, clove, cumin, coffee, black pepper, lavender, orange, banana, mint, fish, and menthol (table 1). The bottles were brought within 2 cm to the nose and the participants sniffed for 3 seconds and were then asked to define the scent from the four options presented (from a list containing three distracters and the correct scent). There was a 20-second break between the presentations, and a break was given when the patients were tired. The correct identification score (0-16) of the subject was recorded according to the result of the test. This two-stage test, in which odor threshold and identification are evaluated, is a modified test like the Sniffin's stick test, which has been used in our region before.[18,19]

As olfactory training, four scent bottles (scents placed in 5 ml black glass bottles) prepared as standard by the researcher were given to the patients. These scents included the following groups: phenyl ethyl alcohol

Table 1. Comparison of olfactory threshold scores and identification scores of patients before and after olfactory training

Groups	n	Median	Mean±SD	Z	*P*
1. Pre-TOTS	46	1.00	1.65±1.74		
2. Post-TOTS	46	3.00	3.89±2.73	5.483	<0.001
1. Pre-TIS	46	4.50	4.09±3.53	5.589	<0.001
2. Post-TIS	46	9.00	8.24±4.53		

Pre-TOTS, pre-training olfactory threshold score; Post-TOTS, post-training olfactory threshold score; Pre-TIS, pre-training identification score; Post-TIS, post-training identification score; n, number; SD, standard deviation; Z, Wilcoxon Test test value; *P*, statistics significance value

(rose), eucalyptol group (eucalyptus), citronellal group (lemon), and eugenol group (clove). These scents were not randomly selected but represented the main odor groups defined by Henning in the odor prism.[20] The patients were instructed to sniff the bottles given for therapy twice a day, for fiveseconds each, when they woke up in the morning and before they went to sleep and make a daily check that they applied the treatment and evaluate their sniffing status between a range of 1 to 10. The patients were interviewed by the researcher every four weeks, their questions about the treatment were answered, and the olfactory training bottles were renewed. Patients who continued the training for 12 weeks were re-evaluated at the end of the 12th week with the odor threshold test and odor identification test. Participants whose findings were evaluated at the end of the study were those who continued the 12-week training and stated that they applied the procedure regularly.

Statistical Analysis

IBM SPSS 21.0 for windows statistical software package was used for the statistical analysis of the research data. Quantitative variables were presented as mean±standard deviation (SD), and categorical variables were presented as number and percentage (%). The data was checked for conformity to normal distribution. Wilcoxon Test was used to compare pre- and post-therapy data for non-normally distributed variables. Independent t-test was used to compare two independent groups with normal distribution. All hypotheses were two tailed, and $P \leq 0.05$ indicated statistical significance.

Results

Of the 46 patients included in the study, 25 (54.3%) were women, 21 (45.7%) were men. The mean age was 29.80±10.18 years in women and 28.29±8.56 years in men. There was no significant difference between the patients in terms of age and gender (P=0.592).

The pre-training mean olfactory threshold score (pre-TOTS) of the patients was 1.65±1.74, and the post-training mean olfactory threshold score (post-TOTS) was 3.89±2.73. It was observed that the olfactory threshold scores increased significantly after the olfactory training (P<0.001) (Table 1).

The pre-training mean odor identification score (pre-TIS) of the patients before scent therapy was 4.09±3.53 and post-training mean odor identification score (post-TIS) after scent therapy was 8.24±4.53. It was observed that odor identification scores increased significantly after olfactory training (P<0.001) (Table 1).

The patients were divided into three groups in terms of age. Patients aged <20, 20-30, and >30 years were categorized into the 1st, 2nd, and 3rd groups, respectively. Intra- and intergroup evaluations revealed that the difference in the pre-training and post-training evaluation scores was statistically significant in terms of both the olfactory threshold and the odor identification score (Table 2, 3).

Patients were divided into three groups in terms of the duration of olfactory loss. Patients with loss of smell for <2, 2-4, and >4 months were classified into the 1st, 2nd, and 3rd groups, respectively. In terms of duration of loss of smell, the difference between pre- and post-training scores was statistically significant for all three groups (Table 4).

In the evaluation made in terms of sex, the increase in odor scores after olfactory training was statistically significant for both sexes (Table 5).

Table 2. Comparison of olfactory thresholds of patients before and after training with respect to age groups

Groups	n	Pre-TOTS Median	Pre-TOTS Mean±SD	Post-TOTS Median	Post-TOTS Mean±SD	Z	*P*
Group 1: <20 years	13	1.00	1.46±1.33	4.00	4.08±2.56	3.089	0.002
Group 2: 21-30 years	16	1.00	1.63±1.78	3.00	3.56±2.56	3.219	0.001
Group 3: >30 years	17	1.00	1.82±2.04	3.00	4.06±3.13	3.324	0.001

Pre-TOTS, pre-training olfactory threshold score; Post-TOTS, post-training olfactory threshold score; n, number; SD, standard deviation; Z, Wilcoxon Test test value; *P*, statistical significance value

Table 3. Comparison of odor identification scores of patients before and after training with respect to age groups

Groups	n	Pre-TIS Median	Pre-TIS Mean±SD	Post-TIS Median	Post-TIS Mean±SD	Z	*P*
Group 1: <20 years	13	3.00	3.85±3.24	9.00	8.38±4.21	3.190	0.001
Group 2: 21-30 years	16	4.00	4.00±3.74	8.50	7.50±4.55	3.192	0.001
Group 3: >30 years	17	5.00	4.35±3.74	9.00	8.82±4.91	3.419	0.001

Pre-TIS, pre-training identification score; Post-TIS, post-training identification score; n, number; SD, standard deviation; Z, Wilcoxon Test test value; *P*, statistical significance value

Table 4. Comparison of olfactory thresholds and odor identification scores of patients before and after training in terms of duration of olfactory loss

Groups	n	Pre-TOTS Median	Pre-TOTS Mean±SD	Post-TOTS Median	Post-TOTS Mean±SD	Z	*P*
Group 1: <2 months	14	1.00	1.79±1.72	3.50	4.07±2.30	3.208	0.001
Group 2: 2-4 months	16	1.00	1.19±1.52	2.00	3.13±2.63	3.201	0.001
Group 3: >4 months	16	1.50	2.00±1.97	4.50	4.5±3.14	3.203	0.001
	n	**Pre-TIS Median**	**Pre-TIS Mean±SD**	**Post-TIS Median**	**Post-TIS Mean±SD**	**Z**	***P***
Group 1: <2 months	14	5.00	4.93±3.54	9.50	9.00±4.04	3.187	0.001
Group 2: 2-4 months	16	2.00	3.15±3.54	7.00	6.81±4.32	3.302	0.002
Group 3: >4 months	16	4.50	4.31±3.52	10.5	9.00±5.05	3.306	0.001

Pre-TOTS, pre-training olfactory threshold score; Post-TOTS, post-training olfactory threshold score; Pre-TIS, pre-training identification score; Post-TIS, post-training identification score; n, number; SD, standard deviation; Z, Wilcoxon Test test value; *P*, statistical significance value

Table 5. Comparison of olfactory thresholds and odor identification scores of patients before and after training in terms of gender

Groups	n	Pre-TOTS Median	Pre-TOTS Mean±SD	Post-TOTS Median	Post-TOTS Mean±SD	Z	*P*
Group 1: women	25	1.00	1.56±1.87	3.00	3.68±2.88	3.955	0.001
Group 2: men	21	1.00	1.76±1.61	4.00	4.14±2.59	3.850	0.001
	n	**Pre-TIS Median**	**Pre-TIS Mean±SD**	**Post-TIS Median**	**Post-TIS Mean±SD**	**Z**	***P***
Group 1: women	25	4.00	3.68±3.4	8.00	7.88±4.60	4.122	0.001
Group 2: men	21	5.00	4.57±3.71	10.0	8.67±4.52	3.832	0.001

Pre-TOTS, pre-training olfactory threshold score; Post-TOTS, post-training olfactory threshold score; Pre-TIS, pre-training identification score; Post-TIS, post-training identification score; n, number; SD, standard deviation; Z, Wilcoxon Test test value; *P*, statistical significance value

Discussion

Based on the results of this study, it was our understanding that olfactory training can be effective in treating loss of smell due to Covid-19. In the present study, significant increases were observed in both olfactory thresholds and odor identification scores of patients who regularly applied olfactory training. In addition to the olfactory evaluation, most of the patients stated that there was a significant improvement in their quality of life related to olfactory disorder after the therapy.

Although the prevalence of post-infectious loss of smell due to Covid 19 is 85% in the mild form of the disease, it is less common in the more severe forms of the disease (4.5%).[21] Spontaneous remission is observed in 85%-90% of the patients within an average of 3-4 weeks, whereas some patients develop persistent loss of smell and do not show spontaneous remission. Severe, resistant loss of smell due to Covid 19 is seen in 5% of the patients and it is more common in certain risk groups.[22]

Persistent olfactory dysfunction seems likely after the Covid-19 pandemic. As a result, the number of applications to otolaryngologists will increase. Evidence of treatment options for recovery will be crucial when guiding our patients in this regard.

Olfactory training is non-invasive and non-pharmacological, easy to apply and low cost, and it can be applied after the loss of smell due to any etiology; this is the reason why it has recently been frequently recommended as a treatment option after olfactory loss. Hummel et al. administered olfactory training consisting of four scents for 12 weeks to 56 subjects with post-infectious, posttraumatic and idiopathic loss of smell and found a significant improvement in the training group to the control group.[23] Konstantinidis et al. applied classical olfactory training for 16 weeks to 119 subjects with post-infectious and posttraumatic loss of smell and found a significant improvement in both groups compared to the control group (with a higher difference in the post-infectious group).[24] In the present study, we applied classical scent therapy with four scents for 12 weeks and observed a significant improvement in all scores after training.

Geissler et al. and Damm et al. applied olfactory training on 39 subjects for 32 weeks and on 144 subjects for 16 weeks, respectively, and observed significant improvement in the training groups compared with the control group.[25,26] Pekala et al. in their meta-analysis of

10 studies including 639 patients, thought that olfactory training could be an effective treatment for olfactory dysfunction due to various etiologies.[27] Altundag et al. divided 85 subjects with post-infectious loss of smell into 3 groups. They applied classical olfactory training for 36 weeks to one group and modified scent therapy with three changing sets of 12 odors to one group and observed significant improvement in both groups compared with the control group.[28] Although there are many researchers recommending long-term olfactory training (between 12 and 36 weeks), researchers who think that olfactory improvement after training may be temporary (the duration of well-being is around 6 months) especially recommend keeping the therapy period long.[28] Kattar et al. in their meta-analysis which was focused on the efficacy of olfactory training due to post viral olfactory disorders, stated that this treatment provided clinically significant improvement although there is not a standard olfactory training protocol.[29] Our recommendation is to apply olfactory training for a longer period. However, owing to the ongoing struggles with the Covid-19 pandemic, olfactory training in the present study was planned as 12 weeks in order to provide quicker literature support for the treatment options for loss of smell after Covid-19. Altundag et al. stated that changing the scents used in training at periodic intervals prevents patients from getting bored with the training. The study lasted 36 weeks. Since the present study lasted for 12 weeks, there was no treatment non-compliance.

In the present study, the etiology of the patients who experienced loss of smell was post-infectious olfactory loss after Covid-19. Although the mechanism underlying the development of post-infectious olfactory loss after Covid-19 remains unclear, the theory of neuroepithelial injury through the olfactory cleft, and viral damage after infiltration of the olfactory bulb and central nervous system as a result of viral spread through this route is gaining traction.[30,31] However, there is no definitive data explaining the olfactory dysfunction caused by the virus yet.

In their study, Altundag et al. did not see any improvements in odor thresholds in the patient group that received olfactory training but observed an improvement in odor identification scores.[28] Researchers explained this situation by the fact that the odor threshold is more related to the peripheral olfactory system while odor identification is more related to the upper cognitive pathways. They argued that repetitive olfactory training causes cognitive changes that increase odor perception. Gudziol et al. in their study mentioned that the patient's subjective opinion of an increase in odor perception affected the continuation of the treatment more than the improvement of applied odor tests.[32]

As olfactory training, patients were given four scents, i.e., clove, rose, eucalyptus, and lemon. In the test battery where the odor identification assessment of the subjects was performed, three of these scents were included as descriptive odors. Since the eucalyptus scent is not well known in our region both verbally and as a scent, it was not included in the test battery, but was used in olfactory training. When we look at the odor identification rates before and after the training, the identification rates of the scents used in the the training after the treatment were considerably higher than the others. Therefore, as previously suggested by Altundağ et al., it was thought that extended olfactory training procedures with a larger number of scents can be more beneficial in the treatment of post-infectious loss of smell after Covid-19.[28]

In a latest study, Altundag et al. investigated effect of olfactory training in Covid-19 related parosmia patients, using their modified olfactory training method. They founded both olfactory training and spontan recovery groups were better after a time period, but they also say that olfactory training group had a better improvement than the other group.[33] Post-Covid long-term anosmi-parosmia (over 1 year) can be seen as a long-term effect of Covid.[34] For the proper management of this condition, the literature needs

more participatory studies in which extended scent therapy protocols are applied.

Conclusions

In conclusion, although do not include a control group, results of this study show that olfactory training could be an effective treatment method for olfactory loss after Covid-19. The limitation of these study is the absence of a control group. It is our understanding that this treatment can be further improved with olfactory training including a larger number of scents. Multicenter, double blinded studies with larger samples will provide more precise data to elucidate this issue.

Ethics committee approval: This study was performed in line with the principles of the Declaration of Helsinki. Ethics committee approval for this prospective study was obtained from Non-Interventional Clinical Research Ethics Committee (No: 270/ 22-04-2021).

Conflict of Interest: The Authors declare that they have no conflict of interests.

Consent for Participation: Informed consent was obtained from patients who volunteered to participate in the study.

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