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ORIGINAL ARTICLE

Therapeutic effects of olfactory training and systemic vitamin A in patients with COVID-19-related olfactory dysfunction: a double-blinded randomized controlled clinical trial

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HIGHLIGHTS

- Three-months olfactory training is effective to treat the COVID-19-related anosmia.
- Daily oral vitamin A did not lead to better results in improving anosmia.
- The intervention time was important in the final olfactory status of the patients.

KEYWORDS
COVID-19;
Anosmia;
Olfactory training;
Olfactory impairment;
Vitamin A

Abstract
Objectives: The new corona virus infection, has a wide range of clinical manifestations. Fever and cough are the most common symptoms. The olfactory function may be also affected with COVID-19. In this randomized clinical trial, we wanted to evaluate the therapeutic effect of olfactory training with and without oral vitamin A for COVID-19-related olfactory dysfunction.
Methods: Patients answered to the standard Persian version of anosmia reporting tool and performed the quick smell test before and after 12 weeks and at the end of the 12 months follow up. The patients were randomly allocated to three groups; Group A treatment with olfactory

Abbreviation: COVID-19, Coronavirus disease of 2019; SARS, Severe Acute Respiratory Syndrome; MERS, Middle East Respiratory Syndrome.

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training, Group B treatment with oral vitamin A and olfactory training, and Group C as control group which only underwent nasal irrigation twice a day. Patients were treated for 3 months and followed up for 12 months.
Results: Totally 90 patients were included in three groups. After interventions, 76.9% of patients in Group A, 86.7% of patients in Group B, and 26.7% of patients in Group C completely improved. The average intervention time was statistically significant in relationship with the final olfactory status of the patients in the 12 months follow-up. The olfactory training has significantly improved the smell alteration at the end of 3- and 12- months follow-up in A and B groups.
Conclusion: A three-months olfactory training is effective for improvement of COVID-19-related olfactory dysfunction. Adding daily oral vitamin A to olfactory training did not lead to better results in improving olfactory dysfunction.
Level of evidence: Step 2 (Level 2*): Randomized trial.

Introduction

Corona viruses, as members of Coronaviridae family, cause a wide range of diseases from common cold to more severe conditions such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Corona Virus Disease 2019 (COVID-19).[1] These viruses are more commonly prevalent among birds and mammalians. However, seven types of corona viruses have been so far discovered in humans, including new corona virus, which caused a pandemic starting from Wuhan, China since December 2019.[2]

The main symptoms of COVID-19 are fever, non-productive cough and shortness of breath followed by some alterations in sense of smell and taste.[3] Although, the new corona virus affects the respiratory system more commonly, other organs such as heart, kidneys and nervous system may be affected by the virus.[4] Some patients do not experience the main symptoms, such as fever, and may get recovered even without any symptoms.[5]

Earlier studies in South Korea, Italy, Iran and European countries mentioned the altered sense of smell (anosmia or hyposmia) and taste, as the most important complaint of the patients with COVID-19.[3,6] The main etiology of anosmia or hyposmia in COVID-19 patients is the damage to olfactory neurons and this makes the treatment more complicated in comparison with other etiologies such as polyps, rhinitis, sinusitis and surgical procedures.[7]

A variety of therapeutic strategies have been suggested for COVID-19-related anosmia. Vitamin A has been shown to repair the olfactory epithelium.[7,8] Also, olfactory training, a type of odor therapy and a method in which the patients are asked to smell various desired odors twice a day, has been reported to be effective for faster regain of sense of smell.[6] In addition, most of the patients will regain their sense of smell without any additional medical or non-medical actions.

In this randomized clinical trial, we investigated the therapeutic effect of olfactory training with and without oral vitamin A for COVID-19-related olfactory dysfunction.

Methods

This randomized clinical trial was conducted on patients with post COVID-19 anosmia, referred to two specialized hospital, Tehran, Iran from March 2020 to March 2021.

Inclusion criteria

We assessed all patients with a definite diagnosis of COVID-19 (positive PCR test) who had olfactory dysfunction within two weeks of the onset of the disease. We included 20- to 65-year-old patients.

Exclusion criteria

We excluded patients with mechanical nasal obstruction (polyps, mass, congestion, discharge and scar), chronic olfactory disorders, history of head trauma, sinonasal polyps, turbinectomy and radiotherapy, neurodegenerative diseases (Parkinson, Multiple Sclerosis and Alzheimer), psychiatric disorders, congenital olfactory alterations, and treatment with systemic corticosteroids, metronidazole, benzocaine, clofibrate, amphotericin B, ampicillin, allopurinol, captopril, baclofen, codeine, carbamazepine, and amphetamines. We also excluded patients who did not consent for participating in the study.

At first, patients were asked to fill the standard Persian version of anosmia reporting tool, developed by American Academy of Otolaryngology-Head and Neck Surgery.[6,9]

The smell test was performed using the ''quick smell test'' kit (Sabamed Medical Engineering Company) (University of Pennsylvania Smell Identification Test –UPSIT) before and after 12-weeks and at the end of the 12-months follow up. The UPSIT is designed and standardized based on the culture and lifestyle of the Iranian people.[10] According to the brochure, the person first shaves the relevant strip and immediately smells it. The patient marks the detected odor. Based on the number of correct answers, the person's olfactory function is estimated. The categories of answers

according to the kit guide are as follows: 1) The number of correct answers between 5 and 6 items, normal smell (normosmia); 1–4 items, olfactory disorder (1 and 2 severe hyposemia, 3 and 4 mild hyposemia), and without the correct answer, the person has a lack of smell (anosmia).

Then, patients were randomly allocated to three groups using simple randomization method (random number table).

Group A treated with olfactory training and placebo pill for three months. Group B treated with oral vitamin A (10,000 units daily) and olfactory training for three months. Group C was control group which only received placebo pills. Since neither the participants, nor the researchers who gave the medicine to the patients, nor the statistical evaluators knew the type of intervention of each group, this study is a double-blinded randomized controlled clinical trial.

All patients took nasal irrigation with normal saline (10cc in each nostril) twice a day.

For olfactory training, patients were exposed to four odors with standard concentration twice a day for 10 s: phenyl-ethyl alcohol (Rose flower), eucalyptol (eucalyptus), citronellal (lemon) and eugenol (clove). All bottles were labeled with the name of the odor. These four odors were selected as representatives of four categories of odors, claimed by Henning.[11]

It should be noted that this method does not harm the patient's health. The patients were followed up during 12 weeks (3 months) and 12 months, and if the anosmia and hyposmia improved, the time of this event was recorded. To ensure that the test is done by the patients in their home, the telephone monitoring was performed during the follow up.

Before participating in the study, the researcher held a briefing session for the project participants and explained the objectives of the study to them. Then the informed written consent was obtained from all patients, and they were assured that all information would remain confidential. Patients were able to withdraw from the study at any time. For illiterate people, all items of the consent form were read by one of the patient's colleagues or companions. The ethical principles and the Declaration of Helsinki were followed. The control group followed up like the two intervention groups.

Statistical analysis

The sample number was calculated using the Cochrane formula ($n = Z^2pq/d^2$, $Z = 1.96$, $p = q = 0.5$, $d = 0.0106$). The total study population was estimated to be 90 people, each group had 30 people.

We used a simple random method for sampling.

After intervention, data were analyzed using IBM SPSS Statistics for Windows, Version 20.0. Descriptive analysis was performed using mean, standard deviation, percentages, and frequencies. The independent variable (intervention groups) is categorical and the outcome (the results of UPSIT score is ordinal) is ordinal. Since the number of participants in the groups was the same, we used the non-parametric Friedman test to compare the results of intervention. We also used Mann–Whitney *U* test to compare the two groups.

We used tests one way ANOVA and Pearson Chi-Square tests, respectively, to compare the results according to quantitative and qualitative contextual groupings. The *p*-value less than 0.001 was considered statistically significant.

Results

Table 1 summarizes the demographic and baseline characteristics of the patients. We included 113 patients in the study. Two people died and 9 people did not continue the 3-month follow-up and 12 people did not continue the 12 month follow-up and were excluded from the study. Finally, we reached the desired number of 90 people (30 people in each group). In each group, the most number (16 patients, 53.3%) were women. The average of ages was 42.26 ± 10.98 years in Group A, 37.06 ± 12.09 years in Group B and 40.40 ± 11.84 years in Group C. Five number (50%) of patients in Group A, 14(46.7%) patients in Group B, and 6 (20%) patients in Group C were healthcare providers. Indoor exposure to COVID-19 patient was seen in 2 (6.7%) of patients in Group A and 3 (10%) patients in Group B. Only one (3.3%) homeless patient was in Group C. Traveling to cities with high prevalence of COVID-19 was reported in 1 (3.3%) patient in Group A and 1 (3.3%) in Group C. Only 2 (6.7%) patients in Group C were living in overcrowded places. In the first intervention group of patients in 93.3% of the cases and in the second and third groups in 90% of the cases, there was a rapid and sudden decrease in the sense of smell.

In the first group, 90% of the patients in the second group, 96.7% and in the control group, 46.7% were in the corona recovery phase. The prevalence of taste reduction in the first group was 90%, in the second group was 80%, and in the control, group was 96.7%. The prevalence of other concurrent symptoms, alteration in sense of smell in family members, past history of other treatments, alteration in sense of smell, smoking, Hookah smoking, and prevalence of taste and smell alteration before COVID-19 diagnosis in each group is listed in the Table 1.

Table 2 summarizes the frequency of each smell alteration in study individuals, after 3- and 12-months follow-ups. Prior to intervention, 9 (30%) patients in Group A, 15 (50%) patients in Group B, and 21 (70%) patients in Group C were suffering from Anosmia. Mild hyposmia was found in 9 (30%) patients in Group A, 2 (6.7%) patients in Group B, and 4 (13.3%) patients in Group C. Severe hyposmia was seen in 12 (40%) patients in Group A, 13 (43.3%) patients in Group B, and 5 (16.7%) patients in Group C.

The results of olfactory training and systemic Vitamin A application in patients with COVID-19-related olfactory dysfunction

Finally, 76.9% of patients in Group A, 86.7% of patients in Group B, and 26.7% of patients in Group C experienced the complete improvement. As shown in the Table 2, olfactory training has significantly improved the smell alteration at the end of 3 and 12- months follow up (Friedman – test $p < 0.001$) in A and B groups. But in the control group, there was no significant change in the number of normosmia patients compared to their previous situation in baseline (Friedman – test $p = 0.007$). Also, the comparison between groups A and B

Table 1 Basic characteristics of patients participating in the study.

Variables: *n* (%)	Group A (*n* = 30)	Group B (*n* = 30)	Group C (*n* = 30)
Male gender	14 (46.7%)	14 (46.7%)	14 (46.7%)
Fast and rapid loss in sense of smell	28 (93.3%)	27 (90%)	27 (90%)
Taste alteration	27 (90%)	24 (80%)	29 (96.7%)
Phase of COVID-19 with alteration in smell:			
Active phase	3 (10%)	1 (3.3%)	16 (53.3%)
Recovery phase	27 (90%)	29 (96.7%)	14(46.7%)
Fever, cough or sore throat before alteration in sense of smell	23 (76.7%)	27 (90%)	22 (73.3%)
Concurrent severe headache	24 (80%)	23 (76.7%)	24 (80%)
Alteration in sense of smell in family members:			
No one	14 (46.7%)	23 (76.7%)	23 (76.7%)
One person	9 (30%)	6 (20%)	7 (23.3%)
More than one person	7 (23.3%)	1 (3.3%)	0 (0%)
Concurrent fever and chills	20 (66.7%)	26 (86.7%)	17(56.7%)
Concurrent severe cough	16 (53.3%)	18 (60%)	16 (53.3%)
Concurrent dyspnea	14 (46.7%)	16 (53.3%)	14 (46.7%)
Parosmia	3 (10%)	4 (13.3%)	1 (3.3%)
No treatment and no improvement	30 (100%)	28 (93.3%)	30 (100%)
Alteration in sense of smell:			
Steady and stable	30 (100%)	26 (86.7%)	24 (80%)
Fluctuant	0 (0%)	4 (13.3%)	6 (20%)
History of nose or sinus surgery	2(6.7%)	3 (10%)	4 (13.3%)
Asthma/Rhinosinusitis without polyposis	0 (0%)	3 (10%)	2 (6.7%)
Smoking:			
Never smoker	27 (90%)	30 (100%)	28 (93.3%)
Quitter	1 (3.3%)	0 (0%)	0 (0%)
Less than 10 cigarettes per day	1 (3.3%)	0 (0%)	0 (0%)
More than 10 cigarettes per day	1 (3.3%)	0 (0%)	2 (6.7%)
Hookah smoking:	1 (3.3%)	0 (0%)	0 (0%)
Never smoker	30 (100%)	29 (96.7%)	30 (100%)
1 to 3 times per week	0 (0%)	1 (3.3%)	0 (0%)
Hypothyroidism	0 (0%)	0 (0%)	1 (3.3%)
Diabetes	3 (10%)	4 (13.3%)	2 (6.7%)
Hypertension or cardiovascular diseases	1 (3.3%)	1 (3.3%)	1 (3.3%)
Nasal drop using before smell alteration	0 (0%)	2 (6.7%)	0 (0%)
History of hospitalization by COVID-19	10 (33.3%)	6 (20%)	20 (66.7%)
Prevalence of taste and smell alteration before COVID-19 diagnosis	29 (96.7%)	27 (90%)	23 (76.7%)

after 3- and 12-months did not show a significant difference in the development of normosmia following the intervention (Mann-Whitney *U* test $p > 0.001$).

At the end of the 3 months follow-up, 6 (20%) patients in Group A, 1 (3.3%) patient in Group B, and 10 (33.3%) patients in Group C had parosmia. While phantosmia was seen in 2 (6.7%) patients in each Group A and C. Also, after 12 months follow up, 4 (13.3%) patients in Group A, 1 (3.3%) patient in Group B and 6 (20%) patients in Group C had parosmia. None of the patients had phantosmia at the end of the 12 months follow up.

There was no statistically significant relation between the final outcome and mean age (one way ANOVA test, $p = 0.672$), gender (Pearson Chi-Square test, $p = 0.122$), cigarette smoking (Pearson Chi-Square test, $p = 0.261$), Hookah smoking (Pearson Chi-Square test, $p = 0.881$), and underlying disorders (Pearson Chi-Square test, $p = 0.902$).

Mean time from diagnosis to smell rehabilitation was 5.36 ± 2.12 weeks in Group A and 6.2 ± 2.15 weeks in Group B. The average intervention time was statistically insignificant in relationship with the final olfactory status of the patients in the 3 months follow-up (one way ANOVA test, $p = 0.003$) and was significant after 12 months follow-up (one way ANOVA test, $p = 0.001$).

Discussion

Summary of evidence

In the present study, we found that olfactory training significantly improves the smell function in patients with post COVID-19 olfactory dysfunction. We also evaluated the combined effect of olfactory training and daily oral vitamin A on olfactory dysfunction. Although this intervention improved

Table 2 Frequency of alteration in smell and normosmia comparing at baseline and after 3- and 12-months follow up.

Time of evaluation	Groups	Anosmia	Mild Hyposmia	Sever Hyposmia	Normosmia	Death	p-value[a] (normosmia comparing with the baseline dysfunctions)
Baseline	A	9 (30%)	9 (30%)	12 (40%)	0 (0%)	–	–
	B	15 (50%)	2 (6.7%)	13 (43.3%)	0 (0%)	–	–
	C	21 (70%)	4 (13.3%)	5 (16.7%)	0 (0%)	–	–
After 3-month follow-up	A	3 (10%)	4 (13.3%)	1 (3.3%)	22 (73.3%)	0 (0%)	<0.001
	B	0 (0%)	5 (16.7%)	0 (0%)	25 (83.3%)	0 (0%)	<0.001
	C	7 (23.3%)	2 (6.7%)	15 (50%)	5 (16.7%)	1 (3.3%)	0.007
After 12-month follow-up	A	1 (3.3%)	3 (10%)	3 (10%)	23 (76.7%)	0 (0%)	<0.001
	B	0 (0%)	4 (13.3%)	0 (0%)	26 (86.7%)	0 (0%)	<0.001
	C	1 (3.3%)	10 (33.3%)	11 (36.7%)	7 (23.3%)	1 (3.3%)	0.007

Group A, Treated with olfactory training and placebo pill; Group B, Treated with oral vitamin A (10000 units daily) and olfactory training; Group C: Control group.
[a] Friedman test.

the olfactory dysfunction, this improvement was not significantly different from the smell rehabilitation alone.

As shown in our study, olfactory dysfunction may be accompanied by other symptoms such as fever, headache, sore throat, cough and dyspnea. Recent data have shown that, more exposure to odors does not necessarily result in higher olfactory function and other factors such as smoking, history of olfactory disorder, using nasal drops, underlying disorders and sinonasal surgeries may have determining roles in the final outcome. We evaluated all these factors in the present study which had the prevalence of lower than 30%. In the present study, we also assessed the effect of time and found significant relation between the intervention initiation time and the smelling condition of patients, at the end of the 12 months follow up.

Comparing with previously published articles

Viral infection with new corona virus, has a wide range of clinical manifestations which are categorized in two respiratory and non-respiratory symptoms. They can attack the Central Nervous System (CNS) and neurotropism is one of the common specificities of human coronaviruses.[12,13] Losing sense of smell or taste, encephalopathy, multiple sclerosis, neuropathic pains, meningitis, Guillain-Barre syndrome and stroke are the CNS complications of COVID-19 infection.[13,14] As the epidemic of COVID-19 was developing, the number of patients with olfactory dysfunction was increasing in various provinces of Iran.[6]

Olfactory dysfunction may be reversible or not and may take a couple of months to be resolved completely. Our results are in agreement with previous studies in the belief that sense of smell should be changeable and improvable.[15] These findings show that intermittent and short-time exposure to odors may trigger growth of olfactory neurons and more exposure results in more expression of olfactory receptors. So, the increase in olfactory sensitivity occurs not only in the olfactory epithelium, but also in the level of olfactory bulb and central processing of olfaction.[16] In some studies, olfactory dysfunction has been reported as the only symptom of disease.[17]

In a similar randomized clinical trial by Choi et al., 104 Korean patients with olfactory dysfunctions following COVID-19 infection evaluated. They used smell rehabilitation and followed up the patients for 12 weeks. Choi et al. reported a remarkable improvement in threshold and odor identification. However, no significant changes were seen in odor discrimination.[18] These findings are in line with the findings of our study.

Reden et al., evaluated the effect of 3 months oral vitamin A on olfactory dysfunction following viral infections and found no significant difference between the intervention and placebo group.[19] Hummel et al. in a retrospective cohort study, found a significantly higher improvement in olfactory dysfunction by prescribing daily intra-nasal vitamin A and smell rehabilitation in comparison with smell rehabilitation alone.[20] This controversy may be attributable to the difference in study design as the retrospective design may cause a systematic error regarding data collection and topical vitamin A may be more effective than systemic consumption.

Initiation time and type of olfactory dysfunctions is different among COVID-19 patients. The olfactory dysfunctions may present as primary symptoms or be at later course of the disease.[21] It occurs suddenly or gradually. Our results showed that about 90% of patients were suddenly affected by olfactory dysfunction and this alteration had a stable and steady trend.

As the sense of smell has important effects on taste processing, so losing sense of smell may affect the taste diagnosing (dysgeusia or ageusia). Also, dysgeusia may be resulted from the damage to taste buds, mucosal inflammation or involvement of the central taste pathway.[22,23] In the present study, we found a remarkable proportion of dysgeusia in all three groups ($\geq$80%).

Phantosmia or smell hallucination, has been categorized as a qualitative disorder in olfactory function and has not been sufficiently addresses during the COVID-19 pandemic. The prevalence of Phantosmia has been reported up to 25% in patients with olfactory dysfunction and it is more

prevalent in elderly people.[24] Phantosmia in COVID-19 was first reported by Akif İşlek in patients with no anosmia or hyposmia.[25] We found some cases of phantosmia in the 3 months follow up which were resolved at the end of the 12 months follow up.

In the two previous coronavirus epidemics (SARS and MERS), corticosteroids were commonly used.[26,27] However, WHO prohibited corticosteroids for treatment of COVID-19 patients in the initial period of pandemic.[28] After a notable number of controversies, a systematic review in 2021 showed that some corticosteroids such as methylprednisolone and dexamethasone, have remarkable effectiveness for COVID-19 patients, especially those who had underwent mechanical ventilation.[29] On the other hand, in Cumings' textbook it has suggested that systemic corticosteroids should prescribe only in chronic rhinosinusitis-related olfactory dysfunctions.[30] Thus, we didn't use corticosteroids in the present study; while, beneficial effects of corticosteroids on COVID-19- related smell and taste disorders have been proven.[31]

Strengths and limitations

The present study has some limitations. Despite proper randomization, there was a significant difference between the three groups in terms of the severity of the disease. This may be due to the nature of COVID-19 and its individualized range of effect. Also, it would have been better to evaluate the intra-nasal vitamin A application method. Further randomized clinical trials with a larger sample size are recommended to evaluate the therapeutic effects of smell rehabilitation and other non-medical treatments, such as acupuncture, in management of COVID-19 related olfactory dysfunction.

Conclusions

Losing sense of smell in a majority of patients with COVID-19 infection, has revealed the need for evidence-based medicine in treatment of patients. In conclusion, we found that olfactory training is significantly effective for improvement of olfactory dysfunction in COVID-19 patients. Although adding daily oral vitamin A to olfactory training resulted in higher rates of improvement, this was not significantly different with olfactory training alone.

Authors' contributions

Dr. A. T is the main manager. He had the main rule in the of conceptualization and investigation in the research. Dr. M. N had the main role in data curation and writing the original draft of the manuscript. Dr. M. S helped in formal analysis. Dr. N. J. J and Dr. H. E. K were the project consultants and helped in methodology and data curation. Dr. R. A helped in validation, reviewing, and editing the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Declarations

Consent for publication: Not applicable.

Availability of data and material: All data generated during the meta-analysis are included in the manuscript.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Code availability: Not applicable.

Ethics approval and consent to participate: The protocol has been registered with ethics committee of Baqiyatallah University of Medical Sciences (ref. nº IR.BMSU.REC.1399.066) and Iranian Registry of Clinical Trials (ref. nº IRCT20210205050247N1).

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