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Impact of olfactory training on enhancing olfaction sense among patients with COVID-19 related olfactory dysfunction: A randomized controlled trial

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Abstract

Background: Olfactory dysfunction, a prominent complication of COVID-19, significantly impacts patients' quality of life, persisting for months after infection. Exploring diverse methodologies to address this issue necessitates scholarly investigation. Therefore, our primary objective was to assess the impact of olfactory training on enhancing olfaction sense among COVID-19 patients.

Methods: This randomized controlled trial employed a pretest-posttest design to assess COVID-19 patients experiencing olfactory dysfunction at the Babol Health Center in northern Iran. Patients were allocated to either the control or intervention group using closed envelopes. Both groups, consisting of 50 patients each, completed the Olfactory Disorders - Negative Statements (QOD-NS) questionnaire before the intervention. Over a six-week period, participants in the intervention group were exposed to Phenylethyl alcohol, Eucalyptus, Citronol, and Eugenol twice daily, rotating each scent for 20 seconds with ten-second breaks in between, while the control group received no intervention. Independent and paired t-tests were utilized to analyze the relationship between the groups before and after the intervention, with analysis conducted using SPSS 16. The significance level was set at less than 0.05.

Results: The mean score of olfactory disorder among patients before the intervention in both the intervention and control groups was 24.32 ± 6.60 and 22.85 ± 8.04, respectively, showing no significant difference (P = 0.33). However, following the intervention, the scores decreased to 19.60 ± 5.74 and 22.52 ± 7.39 in the intervention and control groups, respectively, with a statistically significant difference observed (P = 0.034).

Conclusion: Olfactory training demonstrated effectiveness in enhancing olfaction sense among patients with COVID-19 experiencing olfactory disorders. Consequently, it is recommended that nurses be trained to administer this program to COVID-19 patients with olfactory disorders upon discharge, facilitating their recovery process.

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Highlights

What is current knowledge?

COVID-19 treatment demonstrates inefficacy in addressing olfactory disorders in approximately one-third of patients.
The olfactory exercise represents a novel approach to enhancing olfactory function through repetitive sniffing or exposure to potent aromas.

What is new here?

A six-week olfactory training regimen incorporating scents of lemon, rose, clove, and eucalyptus leaves yielded a significant improvement in the sense of smell among patients.

Introduction

COVID-19, an emerging outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was initially detected in Wuhan, China, in late 2019 (1). The global dissemination of COVID-19 has posed a significant public health challenge worldwide. From March 11, 2020, until August 28, 2023, the number of confirmed COVID-19 cases worldwide has surpassed 686 million, with a death toll exceeding 6,860,000 (2). Extensive research has been conducted on the symptomatology, pathophysiology, high-risk populations, treatments, complications, and associated interventions related to the disease's global spread (3).

Despite the predominantly asymptomatic nature of Coronavirus Disease 2019 (COVID-19) for a majority of affected individuals, common symptoms such as shortness of breath, cough, fever, and fatigue have been widely reported (4). Importantly, the SARS-CoV-2 infection extends beyond the respiratory system, affecting various organs and systems within the body. By utilizing olfactory and hematogenous routes, the virus infiltrates the central nervous system (CNS), leading to a spectrum of neurological symptoms, including seizures, headaches, myalgia, and nausea, which are not exclusive to the disease (5).

Olfactory and gustatory disruptions are recognized as early manifestations of this illness (6). The olfactory sense is mediated by specialized sensory cells in vertebrates. Human olfaction sense occurs when aromatic molecules bind to specific sites on olfactory receptors (7). According to Karimi Galougahi et al. (2022), 54.85% of 1531 COVID-19 patients exhibited hypoxemia (reduced sense of smell), while 45.15% experienced anosmia (complete loss of smell) (8).

Olfactory dysfunction emerges as the most prevalent type of olfactory impairment following the COVID-19 infection. Given the involvement of the coronavirus as a pathogenic agent, it is reasonable to categorize and assess olfactory disorders in COVID-19 as "Pulmonary Veno-Occlusive Disease" (9). On the other hand, olfactory disturbances profoundly affect individuals' quality of life and are linked to an elevated mortality risk (10). A comprehensive review indicates that approximately one-third of patients continue to experience olfactory dysfunction six months post-COVID-19 infection, even following COVID-19 treatment (11).

The prevalence and significant impact of this disorder necessitate an urgent quest for effective treatments. Olfactory training, involving repeated sniffing or exposure to potent odors, has emerged as a novel intervention showing promise in enhancing olfactory function, as evidenced by clinical studies (12, 13). In this context, aromatherapy, a recognized branch of medical science, is noted for its capacity to promote recovery, induce relaxation, and augment overall energy levels in individuals (14).

Aromatic essential oils exert influence over physical, mental, and emotional states, entering the body through various pathways, such as the sense of smell, touch, and taste, thereby eliciting changes in the nervous system (15). Encouraging results have been observed with olfactory exercises in Pulmonary Veno-Occlusive Disease (PVOD) (16). In this regard, Le Bon et al. (2021) demonstrated the safety and potential effect of a brief regimen of oral corticosteroids combined with olfactory training in patients with persistent anosmia following coronavirus infection (17). Furthermore, reports suggest that olfactory training may alleviate symptoms of depression in individuals with olfactory impairments (18). Borsetto and Hopkins also reported a notable improvement in olfactory dysfunction among approximately 90% of participants following olfactory training initiated 4 to 6 weeks post-COVID-19 onset (19).

Given the profound impact of olfactory disorders on the quality of life of individuals with COVID-19 and the dearth of similar studies in Iran, this study sought to investigate the impact of olfactory training on enhancing olfaction sense in patients with COVID-19-related olfactory impairments.

Methods

Study design and settings

The present study was conducted as a randomized controlled trial registered under the code IRCT20220803055612N1, employing a pre-test-post-test design. The study population comprised individuals referred to the Babol health center

in Northern Iran, who tested positive for COVID-19 via polymerase chain reaction (PCR) and experienced olfactory disorders.

Inclusion criteria encompassed both male and female participants aged over 18 years, with no pre-existing history of olfactory disorders before contracting COVID-19, absence of nasal polyps or history of nasal surgery, no reliance on long-term corticosteroid therapy for conditions such as asthma or chronic obstructive pulmonary disease, absence of allergy to budesonide or other topical steroids, positive laboratory confirmation of COVID-19 infection, subjective complaint of post-infection anosmia, and proficiency in reading and writing. The selected participants were randomly assigned to either the control or intervention group using closed envelopes in a simple random manner (Figure 1).

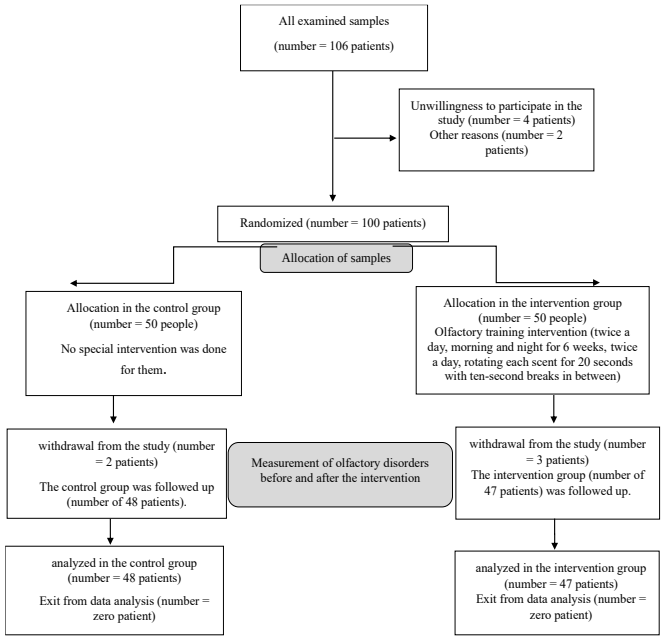

Figure 1. CONSORT diagram.

Sampling

The sample size was determined using the methodology outlined by Chen et al. (1), with a type 1 error rate of 0.05 and a test power of 80%, accounting for a 20% attrition probability in each group. A total of 50 participants were selected for each group using the convenient sampling method. The sample size calculation followed the formula:

$$n \geq 2\frac{\left(z_{\alpha/2}+z_{\beta}\right)^2\sigma^2}{\left(\mu_1-\mu_2\right)^2}$$

Study instruments

The data collection instrument comprised a questionnaire encompassing demographic characteristics such as age, gender, education level, medical history, history of smoking or drug addiction, and allergy history. Additionally, a concise version of the QOD-NS olfactory disorders negative statements questionnaire was included.

QOD-NS olfactory disorders negative statements questionnaire – brief version

The 17-item Questionnaire of Olfactory Disorders - Negative Statements (QOD-NS) constitutes a vital tool for assessing olfactory-specific quality of life (QOL) (21). The olfactory disorder score, derived from the negative statements' questionnaire, reflects the extent of olfactory dysfunction experienced by individuals. The questionnaire comprises seventeen questions employing a 4-point scale (ranging from 0 to 3), where higher scores denoted improved subjective olfactory performance (8). Previous studies have confirmed the validity of the abridged version of the questionnaire, yielding a coefficient of 0.92 (21). The reliability of this instrument was further evaluated through Cronbach's alpha coefficient, yielding a value of 0.89 for the entire questionnaire, based on a pilot test sample of 20 individuals. In the study by Yang et al., test-retest reliabilities were reported at 0.802 (P<0.001), while Cronbach's alpha coefficients for internal consistency were calculated at 0.882 (20).

First, participants were sampled using Convenience Sampling, and subsequently, they were allocated into two groups, namely control and intervention, utilizing the sealed envelope method. Written Informed consent was obtained from all participants, and the right to choose whether to participate or not was thoroughly explained at each stage of the study. Before the intervention, both groups underwent assessment for olfactory-related quality of life using the summary version of the Questionnaire of Olfactory Disorders Negative Statements (QOD-NS) after sample selection and random allocation to the intervention and control groups.

The control group received only standard treatment and routine care. The olfactory training intervention group was exposed to four main scent categories: phenylethyl alcohol (rose scent from rose geranium), eucalyptus (eucalyptus scent), citronol (lemon scent), and eugenol (clove scent), twice daily, in the morning and evening, over a six-week period, rotating each scent for 20 seconds with a ten-second break between each scent. Throughout the olfactory training, patients were continuously monitored via virtual platforms.

Data analysis

A descriptive and analytical analysis of the data was conducted using the Statistical Package for the Social Sciences (SPSS Version 16 from IBM). Descriptive statistics, including mean and standard deviation, were utilized to summarize quantitative data, while frequency and percentages were employed for qualitative data. Additionally, the Chi-square test was applied to assess the relationship between qualitative variables and intervention groups, with the Fisher test being utilized when necessary. Independent t-tests and Mann-Whitney tests were performed to evaluate the association between quantitative variables and intervention groups, taking into consideration the normality of the data. Furthermore, independent and paired t-tests were employed to examine the relationship between the two groups before and after the intervention. All statistical tests were conducted at a significance level of 0.05.

Results

In this study, a total of 100 patients participated, with three withdrawing from the intervention group and two from the control group for unspecified reasons, leaving the remaining patients to complete the study. Age was compared using the Mann-Whitney test, and the P-value was 0.768. Gender, education level, smoking history, and drug use history were compared using Fisher's exact test. Patients in the intervention group exhibited a slightly lower mean age (38.0 ± 12.45 years) compared to those in the control group (39.10 ± 13.76 years), although this difference was not statistically significant (P=0.768). Additionally, a chi-square test was employed to compare the history of drug use and exposure to chemicals between the groups, revealing no statistically significant difference (P>0.05) (refer to Table 1).

Table 1. Participants' demographic characteristics at baseline (N=100).

Variable	Group	Intervention group	Control group	P-value
		N (%)	N (%)	
Gender *	Male	26 (55.3)	29 (60.4)	0.680
	Female	21 (44.7)	19 (39.6)	
Education*	High school	2 (4.3)	3 (6.3)	0.919
	diploma	4 (8.5)	4 (8.3)	
	Associate degree	4 (8.5)	6 (12.5)	
	Bachelor of Science	24 (51.1)	25 (52.1)	
	Masters	13 (27.7)	10 (20.8)	
Smoking history*	No	28 (59.6)	32 (66.7)	0.884
	Yes – mild	9 (19.1)	7 (14.6)	
	Yes – moderate	7 (14.9)	7 (14.6)	
	Yes - extreme	3 (6.4)	2 (4.2)	
History of drug use**	No	46 (97.9)	48 (100.0)	0.495
	Yes	1 (2.1)	0 (0)	
History of medicine use*	No	36 (76.6)	40 (83.3)	0.452
	Yes	11 (23.4)	8 (16.7)	
History of exposure to chemicals **	No	38 (80.9)	40 (83.3)	0.794
	Yes	9 (19.1)	8 (16.7)	

* Fisher's exact test
** Chi-square test

The mean and standard deviation of olfactory disorder scores among patients before the intervention were 24.32 ± 6.60 in the intervention group and 22.85 ± 8.04 in the control group, with no significant difference observed according to the independent t-test (p=0.335). Following the intervention, the mean and standard deviation of olfactory disorder scores for patients in the intervention group (19.60 ± 5.74) and control group (22.52 ± 7.39) showed a significant difference based on the independent t-test (p=0.034) (refer to Table 2).

Table 2. Between-group and within-group comparison of the participants' olfactory disorders mean scores before and after the intervention.

Time of Olfactory disorder	Before intervention		After the intervention		Result	
	Mean	SD	Mean	SD	P-value	Statistics
Intervention	24.32	6.60	19.60	5.74	**P<0.001	**-9.563**
Control	22.85	8.04	22.52	7.39	0.191**	**-1.326**
P-value	0.335*		0.034*		-	
Statistics	0.970		0.1512*			

* Independent t-test results (between-group comparison)
** paired t-test results (within-group comparison)

Discussion

This study aimed to assess the impact of olfactory training on enhancing olfaction sense in patients with COVID-19 experiencing olfactory disorders. Initially, no significant difference was observed between the groups regarding patients' olfactory disorder scores. However, a significant difference emerged following the intervention, with a significant reduction in olfactory disorders observed within the intervention group.

According to Yaylacı et al. (2023), patients experiencing persistent olfactory disorders following COVID-19 infection may derive benefit from a twelve-week regimen of classical olfactory training (22). Denis et al. (2021) demonstrated that a dedicated web-based program, combined with olfactory training and visual stimulation, significantly enhanced olfactory function. Similarly, olfactory and visual stimulation training, administered through a web-based platform, proved effective for patients with persistent olfactory impairment after SARS-CoV-2 infection. Although the intervention in our study was similar, the absence of web-based components distinguishes it. The researcher attributes the success of the intervention primarily to olfactory training (23).

Le Bon et al. (2021) also demonstrated the efficacy of a short course of oral corticosteroids combined with olfactory training for recovering from coronavirus-induced olfactory loss (17). Notably, our study differs from theirs in the simultaneous application of two distinct interventions. In this regard, Whitcroft and Hummel identified olfactory training as a beneficial approach among other methods and interventions for mitigating olfactory dysfunction in patients with COVID-19. Olfactory training entails repeated inhalation of a combination of scents, typically lemon, rose, clove, and eucalyptus, for at least 20 seconds, at least twice daily, over a period of three months or longer, if feasible (24).

Meanwhile, Huang et al. (2021) observed that the intervention might effectively alleviate olfactory disorders following trauma; however, they suggested the necessity for further studies with control groups to substantiate these findings (25). on the other hand, Kattar et al. (2021) conducted a meta-analysis on the effects of olfactory training on olfactory disorders induced by viral diseases. Their findings indicated that exposure to diverse odors could be beneficial and efficacious in restoring the sense of olfaction (26).

Sorokowska et al. (2017) conducted a similar study, reporting in their meta-analysis that olfactory training had a positive impact on identifying, detecting, and distinguishing thresholds of odors across various olfactory abilities. They noted that the effectiveness of such training varied based on the participants' origin of olfactory disorder and the duration of olfactory training. The researchers suggested that olfactory training should be incorporated or considered as an alternative to existing olfactory treatment modalities (27). Notably, the methodology and study subjects differed significantly between the present study and others such as those by Huang et al. (2021), Kattar et al. (2021), and Sorokowska et al. (2017). Additionally, Qiao et al. (2019) demonstrated a significant reduction in olfactory disorders and the restoration of the sense of smell through the use of the Sniffin Sticks Test (18). Damm et al. (2013) conducted a study in Germany demonstrating that olfactory exercises effectively restore the sense of smell following an infectious disease (28). Similarly, Konstandinidis et al. (2013) stated that olfactory exercises are effective in improving the sense of smell in individuals with olfactory disorders resulting from trauma and infection (29).

In contrast to the present study, Bérubé et al. (2023) in Canada found no significant difference in the olfactory disorder scores of COVID-19 patients following intervention using the UPSIT tool (30). The researcher suggested several reasons for these disparate results, including variations in the research environment, the choice of instrument for measuring olfactory dysfunction, the utilization of a placebo for the control group, and even differences in the mental conditions of the patients. In the present study, the control group received routine care without olfactory training, while in Bérubé et al. (2023), similar glass vials containing only odorless substances were used (30). Given the psychological aspects associated with olfactory disorders, it is possible that these factors contributed to the lack of change in results compared to the intervention group.

One limitation of the research pertains to the potential impact of patients' lethargy and fatigue on their responses. Additionally, reliance on self-reporting for questionnaire completion and the implementation of the intervention by the patients themselves could also be considered as limitations.

Conclusion

Based on the findings, the utilization of olfactory training for a duration of six weeks has demonstrated efficacy in enhancing the sense of smell among COVID-19 patients experiencing olfactory disorders, employing scents such as lemon, rose, clove, and eucalyptus. Consequently, this therapeutic regimen, coupled with nursing intervention, holds promise in ameliorating olfactory impairments in individuals afflicted with COVID-19, thereby introducing a practical, accessible, and straightforward intervention method. However, it is important to acknowledge potential limitations, such as the reliance on self-reported questionnaire responses and the necessity for patients to self-administer the intervention.

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Ethical statement

The ethical code assigned to this research project is IR.SBMU.PHARMACY.REC.1401.059, and it is duly registered in the Iranian Registry of Clinical Trials with the code IRCT20220803055612N1.

Conflicts of interest

The authors declared no conflict of interest.

Author contributions

Mohammad Hossein Akbarpour: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing, Data collection
Mitra Zandi: Writing - Original Draft, Writing - Review & Editing, Methodology, Conceptualization, Supervision
Ladan Sedighi: Conceptualization, Writing - Original Draft, Writing - Review & Editing
Mojtaba Ghanbari Ghalesar: Writing - Original Draft, Writing - Review & Editing

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