Intensive Olfactory Training in Post-COVID-19 Patients: A Multicenter Randomized Clinical Trial

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Abstract
Background: Olfactory dysfunction (OD)—including anosmia and hyposmia—is a common symptom of COVID-19. Previous studies have identified olfactory training (OT) as an important treatment for postinfectious OD; however, little is known about its benefits and optimizations after SARS-CoV-2 infection.

Objective: This study aimed to assess whether olfactory training performance can be optimized using more fragrances over a shorter period of time in patients with persistent OD after COVID-19. In addition, we determined the presence of other variables related to OD and treatment response in this population.

Methods: This multicenter randomized clinical trial recruited 80 patients with persistent OD and prior COVID-19 infection for less than 3 months. The patients were divided into 2 groups receiving either 4 or 8 essences over 4 weeks. Subjective assessments and the University of Pennsylvania Smell Identification Test (UPSIT) were performed before and after the treatment.

Results: Significant olfactory improvement was measured subjectively and using the UPSIT in both groups; however, no significant differences between the groups were observed. Additionally, the presence of olfactory fluctuations was associated with higher UPSIT scores.

Conclusion: These data suggest that training intensification by increasing the number of essences for 4 weeks does not show superiority over the classical method. Moreover, fluctuant olfaction seems to be related to a higher score on the UPSIT.

Keywords
olfactory training, olfactory dysfunction, olfactory improvement, olfactory fluctuations, anosmia, hyposmia, COVID-19, SARS-CoV-2, UPSIT, training intensification

Introduction
In December 2019, the transmission of the novel coronavirus (SARS-CoV-2), the causative agent of COVID-19, started in China.¹ The virus is transmitted mainly through respiratory droplets and physical contact. The most common symptoms are cough, fever, sore throat, shortness of breath, and sudden loss of smell or taste.¹

Olfactory dysfunction (OD) is recognized as one of the cardinal symptoms of COVID-19 having a high predictive value.² It is a common symptom of the disease; its magnitude

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appears to be even greater when assessed using psychophysical testing.\(^3\) The University of Pennsylvania Smell Identification Test (UPSIT®) is a psychophysical measurement tool used for identifying micro-encapsulated odors. It has been adapted and validated for use in different countries, including Brazil.\(^4\) Almost all patients with COVID-19 underwent UPSIT and were classified as either “anosmia” or “severe hyposmia.”\(^5\)

Previous studies have shown that olfactory training (OT) is one of the most important treatments for postinfectious OD.\(^6\) It consists of daily and repeated exposure to odors over a long period of time.\(^7\) Hummel et al\(^8\) initially described an OT method for improving general olfactory sensitivity, involving 4 essences (phenylethyl alcohol, eucalyptol, citronella, and eugenol) over a period of 12 weeks. Furthermore, Altundag et al\(^9\) observed that changing the odors every 12 weeks can increase its success rate in patients with postinfectious OD.

Therefore, this study aimed to compare post-OT olfactory responses using 4 and 8 essences over 4 weeks in patients with postinfectious OD. We prospectively investigated whether olfactory rehabilitation could be optimized with intensive OT by using more fragrances over a shorter period of time. In addition, we aimed to identify other variables related to the disorder or response to OT by prospectively evaluating patients with persistent postinfectious OD.

### Methods

This is a multicenter randomized clinical trial involving individuals with the following attributes: (1) aged between 18 and 60 years, (2) with previous COVID-19 infection for less than 3 months, (3) confirmed at that time by reverse transcriptase-polymerase chain reaction (RT-PCR) testing, and (4) complaints of olfactory alteration that persisted for at least 4 weeks after the onset of COVID-19 symptoms. Patients with the following attributes were excluded: (1) unable to provide valid written informed consent, (2) with a history of more than one SARS-CoV-2 infection, (3) exhibited sinusonal diseases such as chronic rhinosinusitis or nasal masses, (3) with a previous history of traumatic brain injury with olfactory sequelae, (4) experienced OD prior to SARS-CoV-2 infection, (5) with a neurologic disorder known to affect olfactory function, and (6) with other current or previous treatments for post-COVID-19 maintenance.

Patients were invited by information dissemination using the press and other social media networks; follow-up services were conducted in the otorhinolaryngology services of tertiary hospitals in Curitiba and Londrina, Brazil. If the patient agreed to participate in the study, an informed consent form was provided by one of the study physicians. The interval COVID-19 and the first appointment was between 1 and 3 months. All patients were re-evaluated after 1 month.

All participants underwent a medical examination by an otorhinolaryngologist, which included nasal endoscopy as well as the application of visual analog scales (VASs) for subjectively assessing nasal symptoms, olfaction, taste, and OD-associated effects.

In the VAS assessment, the patients were asked to give a score (0-10) for their olfactory and gustatory abilities in 3 periods of time: before COVID-19, during the acute phase of the infection, and at the time of appointment. Also, patients were asked to rate how much the OD annoyed them or caused a worsening of quality of life.

The functionality of the trigeminal nerve was evaluated through a specific questionnaire (“do you feel the heat of the pepper, the freshness of the mint and the gas in the soda?”). The somatosensory function of the nose was assessed using standardized questions during the initial presentation. The questionnaire was also used for the assessment of immunization against COVID-19 status, the presence of olfactory fluctuations, and previous nasal disturbances and treatments. The psychophysical assessment of smell was performed using the UPSIT® tool. It is a psychophysical and clinically validated standardized odor identification test using the “scrape and sniff” format; microencapsulated odorants are released from a strip upon physical stimulation, for example, scratching. With a total of 40 points, normosmia was defined as ≥ 34 points for men and ≥ 35 points for women; an increase of ≥ 4 points can be considered as a clinically significant improvement in symptoms.\(^9\) Both UPSIT and subjective assessments were repeated within 4 weeks after starting the proposed treatment.

Patients were randomly assigned to 2 OT groups in a 2:1 ratio. The first group received a classical olfactory training set (COT) with 4 essential oils: rose, eucalyptus, clove, and lemon. The second group received an advanced olfactory training set (AOT) with 8 essential oils: rose, eucalyptus, clove, lemon, citronella, mint, vanilla, and cedar wood.

The guidelines for performing OT were explained at the first appointment using simple and easy-to-understand language booklets. During training, the patients were exposed to each odor for 15-s twice daily, with a 30-s interval between odors. Patients also received video instructions a day after initiation and were contacted by telephone after 1 and 3 weeks to ensure adherence. In addition, a record diary was provided to the patients for tracking their progress. Those who had not taken the essences for at least 7 days were excluded from the study.

The study design was approved by the ethics committees of the institutions involved (CAAE: 46698721.5.0000.0096 and 47078821.5.0000.0020).

### Statistical Analysis

Quantitative variables were described as mean, standard deviation, median, minimum, maximum, and interquartile range. A binomial test was used to compare evaluations regarding the presence of OD. A comparison between the UPSIT® and VAS scores was made using the nonparametric Wilcoxon test; comparisons of more than 2 assessments were made using the Friedman’s nonparametric and Dunn’s
Results

Three hundred and forty patients were screened for eligibility; 80 were enrolled in the study. Only one patient required intensive care during his time of COVID-19 infection; others exhibited mild or moderate forms without requiring hospitalization. Characterization of all study participants revealed a mean age of 36.7 ± 10.3 years as well as a mean interval between the onset of COVID-19 symptoms and the start of OT treatment of 63.9 ± 24.2 days (Table 1). The mean time for OD onset after symptom onset was 4.6 ± 3.8 days. The other characteristics of the analyzed samples are shown in Table 2.

As seen in Table 3, anosmia was reported in 82.5% of patients during the COVID-19 period; conversely, it was present in only 13.8% of patients during their first appointment and was not reported after 4 weeks of OT. During the same period, the prevalence of self-reported hyposmia progressively increased. Similar results were observed for parosmia and phantosmia. Additionally, a history of ageusia was present in 63.8% of patients during the COVID-19 period; however, its prevalence rapidly decreased thereafter and was only 1.3% at the end of the study. Meanwhile, dysgeusia was reported by 23.8% of patients at the time of infection, 75% at the beginning of treatment, and 63.8% after 4 weeks. At the end of the study, only 3.8% of patients denied any chemosensory complaints.

There were no statistically significant differences between the treatment groups regarding sex, age, current or previous smoking, use of nasal corticosteroids, vaccination for COVID-19, the interval between the onset of COVID-19 infection and treatment, and the interval between the first and second visits (Tables 4 and 5).

The participants’ subjective sense of smell improved throughout the study and in between medical appointments, as measured by the olfaction VAS. As a result, the olfaction VAS showed a statistically significant difference in the comparison between all 4-time points for assessment (before COVID-19, during COVID-19 acute phase, first appointment, and follow-up) using general comparative (non-parametric Friedman test; \( P < .05 \)) and multivariate analyses (Dunn post-hoc test corrected by Bonferroni; \( P < .05 \)) (Table 6). Another subjective measurement (on a scale of 0 to 10) on the discomfort experienced due to olfactory deficits decreased between the first and the second appointment, with a mean score of 7.2 ± 2.7 and 6.2 ± 3 at the first and second appointments, respectively (\( P < .05 \)). In addition, there was a

### Table 2. Description of the Evaluated Participants and key Factors in the Characterization.

| Classification | n  | %  |
|----------------|----|----|
| Gender         |    |    |
| Female         | 52 | 65.0|
| Male           | 28 | 35.0|
| OT group       |    |    |
| AOT            | 26 | 32.5|
| COT            | 54 | 67.5|
| Smoking        |    |    |
| Current        | 8  | 10.0|
| Denied         | 66 | 82.5|
| Previous       | 6  | 7.5 |
| Hospitalization|    |    |
| No             | 76 | 97.4|
| Yes, ITU       | 1  | 1.3 |
| Mechanical ventilation during COVID-19 |    |    |
| No             | 77 | 98.7|
| Yes            | 1  | 1.3 |
| Partial improvement |    |    |
| No             | 10 | 12.8|
| Yes            | 68 | 87.2|
| Side effect with OT |    |    |
| No             | 62 | 77.5|
| Yes            | 18 | 22.5|
| Subjective improvement |    |    |
| No             | 15 | 18.8|
| Yes            | 65 | 81.3|
| Immunization against COVID-19 |    |    |
| No             | 10 | 12.5|
| Yes            | 70 | 87.5|
| Vaccine manufacturer |    |    |
| AstraZeneca    | 25 | 35.7|
| Pfizer         | 25 | 35.7|
| Coronavac      | 19 | 27.1|
| Janssen        | 1  | 1.4 |
| Vaccine before or after starting treatment |    |    |
| Before         | 48 | 68.6|
| After          | 22 | 31.4|
statistically significant improvement in the taste VAS scores between appointments (Table 7).

In the overall assessment of these participants, there was an improvement in the mean UPSIT score with a statistically significant difference when comparing the initial (25.2 ± 7.1) and final (26.7 ± 6.3) UPSIT scores, with a mean increase of 1.5 ± 3.9 in the final test score (Wilcoxon non-parametric test; \( P = .002 \)). When comparing the COT and AOT groups, UPSIT and olfaction VAS scores were examined; however, no significant differences were observed between the different treatment groups (Table 8). When comparing the outcome of the directly queried subjective improvement, where only “yes-or-no” responses were possible, 81.3% of the participants reported improvement; however, there was no statistically significant difference between the treatment groups.

In relation to other measured factors that could be related to the outcomes of olfaction, patients who reported fluctuations in their olfactory ability at the initial appointment

Table 3. Prevalence of Chemosensory Complaints in the Initial Appointment and in the Return After 1 Month.

| Classification | COVID-19 | Initial appointment | Follow-up |
|---------------|----------|---------------------|-----------|
|               | n | % | n | % | n | % |
| Anosmia       | No | 14 | 17.5 | 69 | 86.3 | 80 | 1000 |
|               | Yes | 66 | 82.5 | 11 | 13.8 | 0 | 0 |
| Hyposmia      | No | 68 | 85.0 | 15 | 18.8 | 5 | 6.3 |
|               | Yes | 12 | 15.0 | 65 | 81.3 | 75 | 93.8 |
| Parosmia      | No | 73 | 91.3 | 54 | 67.5 | 42 | 52.5 |
|               | Yes | 7 | 8.8 | 26 | 32.5 | 38 | 47.5 |
| Cacosmia      | No | 75 | 93.8 | 66 | 82.5 | 66 | 82.5 |
|               | Yes | 5 | 6.3 | 14 | 17.5 | 14 | 17.5 |
| Phantosmia    | No | 74 | 92.5 | 59 | 73.8 | 52 | 65.0 |
|               | Yes | 6 | 7.5 | 21 | 26.3 | 28 | 35.0 |
| Dysgeusia     | No | 61 | 76.3 | 20 | 25.0 | 29 | 36.3 |
|               | Yes | 19 | 23.8 | 60 | 75.0 | 51 | 63.8 |
| Ageusia       | No | 29 | 36.3 | 74 | 92.5 | 79 | 98.8 |
|               | Yes | 51 | 63.8 | 6 | 7.5 | 1 | 1.3 |

Table 4. Comparison Between Age and Intervals Between Treatment Groups.

| Variables | Group | Mean ± standard deviation | Median (min-max; IQR) | P* |
|-----------|-------|---------------------------|-----------------------|----|
| Age (years) | AOT | 38.0 ± 9.9 | 39.7 (20.8-54.7; IQR = 14.9) | .45 |
|           | COT | 36.1 ± 10.6 | 36.6 (18.7-57.7; IQR = 16.8) |    |
| Interval COVID-19-OT (days) | AOT | 61.7 ± 22.8 | 64 (24-101; IQR = 36) | .71 |
|           | COT | 64.9 ± 25.0 | 62 (30-126; IQR = 37) |    |
| Appointment interval (days) | AOT | 37.5 ± 8.8 | 35 (25-60; IQR = 9) | .13 |
|           | COT | 35.4 ± 10.6 | 32 (21-78; IQR = 13) |    |

Table 5. Comparison of Homogeneity of Groups Regarding Selected key Factors.

| Variables | Group | AOT | COT |
|-----------|-------|-----|-----|
| Gender    | Female | 19 | 33 | 61.1 |
|           | Male | 7 | 26 | 13.0 |
| Smoker    | Current | 1 | 3 | 22.2 |
|           | Denied | 22 | 44 | 81.5 |
| Previous  | Yes | 3 | 8 | 16.7 |
| Immunization against COVID-19 | No | 25 | 45 | 83.3 |
| Vaccine  | Pfizer | 14 | 56 | 24.4 |
| manufacturer | AstraZeneca | 6 | 24 | 42.2 |
|           | Coronavac | 4 | 16 | 33.3 |
|           | Janssen | 1 | 4 | 0.0 |

Abbreviations: IQR, interquartile range (quartile 3 – quartile 1); OT, olfactory training; AOT, advanced olfactory training; COT, classical olfactory training.

*aStudent’s t-test for independent samples or non-parametric Mann-Whitney U-test, \( P < .05 \).

*bFisher’s exact test or chi-squared test, \( P < .05 \).
Table 6. Global Comparison Between VAS Scores at Separate Times.

| Olfaction VAS | Mean ± Std. deviation | Median (min-max) | IQR | P* |
|---------------|-----------------------|------------------|-----|-----|
| Before COVID-19 | 80 9.7 ± 0.7 | 10 (7-10) IQR = 0 | < .001 |
| COVID-19 First appointment | 80 0.9 ± 1.7 | 0 (0-7) IQR = 1.5 | |
| Return | 80 5.8 ± 2.1 | 6 (0-10) IQR = 3 | |

Abbreviations: VAS, visual analog scale; IQR, interquartile range (quartile 1 – quartile 3); AOT, advanced olfactory training; COT, classical olfactory training.
*Friedman’s non-parametric test, P < .05.
*At this evaluation, the analysis was for OAT and COT combined.

Table 7. Improved Taste on the Visual Analog Scale.

| Gustation VAS | Mean ± Std. deviation | Median (min-max) | IQR | P* |
|---------------|-----------------------|------------------|-----|-----|
| First appointment | 80 6.1 ± 2.7 | 6 (0-10) IQR = 4 | .009 |
| Second visit | 80 6.9 ± 2.5 | 7 (1-10) IQR = 4 | |
| Taste improvement | 80 0.8 ± 2.9 | 1 (-8-8) IQR = 3.5 | |

Abbreviations: VAS, visual analog scale; IQR, interquartile range (quartile 3 – quartile 1); AOT, advanced olfactory training; COT, classical olfactory training.
*Wilcoxon’s non-parametric test, P < .05.
*At this evaluation, the analysis was for OAT and COT combined.

(Mann-Whitney non-parametric test) had higher UPSIT scores at baseline (26.8 ± 6.1 vs 22.3 ± 7.9; P = .011) and at final presentation (28.1 ± 4.8 vs 24.0 ± 7.6; P = .029), as compared with participants who did not report this symptom. In addition, these patients had more nasal symptoms at the first visit (5.2 ± 3.4 vs 2.9 ± 3.0) than those without (P = .003). Nevertheless, subjective improvement, as measured by olfaction VAS, was statistically lower in these patients (1.8 ± 2.5 vs 2.9 ± 1; P = .03). The smell fluctuation differed between the first and return visits (binominal test; P = .02). At the first assessment, 62.8% of the patients reported this symptom; at the return, only 78.8% reported its occurrence.

There was no association between the reported changes in the nasal function of the trigeminal nerve and the presence of any chemosensory disorders at any evaluated time points (Fisher’s exact test, P < .05). We also found no association between these complaints and the mean UPSIT or applied VAS scores (non-parametric Mann-Whitney test, P < .05).

Discussion

To date, there have been few randomized clinical trials involving OT in patients with OD associated with COVID-19; no study has compared variants of this therapy in this subset of patients. This was the first study to evaluate an alternative method for OT in patients with OD, in which 8 concurrent essential oils were utilized for evaluation. Another highlight of our study was the complete evaluation of patients by an otolaryngologist, including nasal endoscopy and the use of a validated psychophysical test. Several associated factors that might be related to olfactory complaints or response to therapy were also controlled, including age, smoking history, duration of the olfactory dysfunction, qualification of the disorder, smell fluctuations, report of impaired trigeminal function, OT adherence, sinonasal symptoms, and use of topical corticosteroids. Patients also received explanatory OT videos on their smartphones and were contacted via telephone to ensure adherence.

The selection of AOT essential oils was made by a fragrance expert in our research group, which was based on olfactory training methods used for training the recognition and memorization of odors, such as the Carles method.6 We sought to discover different families of odors to improve training by enhancing receptor activation during therapy. In addition to lemon, rose, eucalyptus, and clove, representatives of the citrus, floral, aromatic, spice, minty, sweet, and woody odors were added to the essential oils of citronella, mint, vanilla, and cedar wood. We hoped that adding more scents to OT could optimize olfactory recovery in patients with postinfectious OD. However, no statistical difference was found in the UPSIT score progression between the AOT (1.0 ± 4.2) and COT groups (1.7 ± 3.8) (P = .281). Similarly, no differences were found in the VAS scores between the groups. These data suggested that OT intensification is not superior to classical training during the 4-week period proposed in this study.

In a study conducted by Altundag et al.7, a modified form of OT, in which patients separated into 2 groups were trained in 4 different essences every 12 weeks over a 36-week period, was assessed; the group that performed such alternations scored better on the Snif Sticks test than that which performed the classical 4 essence OT. It was also found that the shorter the duration of anosmia, the better the response to OT. This correlation was also observed in other studies.11–13 In our study, we sought to include only patients with recent OD to maximize the potential benefit of training and to improve the analysis of differences between groups. However, a major difference between our study and that by Altundag et al concerns the period of OT use, which was significantly shorter in our study and probably related to the lack of benefit in the AOT group.

In a clinical study comparing periodic alternation of odors with classical training in patients with posttraumatic OD, no significant difference was found between the training modalities.14 Furthermore, olfactory rehabilitation by OT showed different results depending on the etiology of the dysfunction. For example, patients with posttraumatic etiology responded worse than those with postinfectious OD.11 To date, no study has examined the efficacy of modified OT in patients with COVID-19.
OT adherence is another challenge in the analysis and applicability of OD treatments. As described by Fornazieri et al., adherence to treatment progressively decreases over time. Therefore, the possibility of intensifying OT by increasing the number of scents for shorter treatment durations has been suggested. As a result, only 3.75% of the patients discontinued treatment at the end of the study: one in the AOT group and 2 in the TOC group. Regarding daily adherence, none of the patients failed to use the OT for 7 days; therefore, there was no exclusion based on this criterion. The occurrence of side effects was limited to mild symptoms, without the need for treatment interruption. The most commonly reported complaints were headache, nausea, and worsening of nasal symptoms.

Another important analysis concerned self-assessment and performance on psychophysical tests. In our study, 81.3% of participants reported that their sense of smell improved: 84.6% in the AOT group and 79.6% in the COT group (P = .763). In all groups, the increase in the mean UPSIT score was 1.5 ± 3.9 points (P = .002). Changes in the UPSIT of ≥ 4 points can be considered as a clinically relevant improvement; however, this difference was observed in only a few patients in the study.

The weak association between these tests and the subjective assessment has been described in previous papers, which underlined the importance of assessing patients with olfactory complaints using standardized tests in addition to self-assessment.

Table 8. Comparison of Objective and Subjective Variables That Assess Olfactory Function Between Treatment Groups.

| Group | n | Mean ± Std. deviation | Median (min-max) IQR | P* |
|-------|---|-----------------------|----------------------|----|
| Initial UPSIT | | | | |
| AOT 26 | 26.2 ± 6.1 | 27.5 (15-34) IQR = 11 | |
| COT 54 | 24.7 ± 7.5 | 25.5 (5-36) IQR = 9 | .481 |
| Final UPSIT | | | | |
| AOT 26 | 27.2 ± 4.8 | 27 (15-35) IQR = 6 | |
| COT 54 | 26.4 ± 6.9 | 28.5 (10-38) IQR = 9 | .992 |
| UPSIT score improvement | | | | |
| AOT 26 | 1.0 ± 4.2 | 1 (−7-10) IQR = 4 | |
| COT 54 | 1.7 ± 3.8 | 2 (−7-12) IQR = 5 | .281 |
| Olfaction VAS before COVID-19 | | | | |
| AOT 26 | 9.6 ± 0.7 | 10 (8-10) IQR = 1 | |
| COT 54 | 9.7 ± 0.7 | 10 (7-10) IQR = 0 | .508 |
| Olfaction VAS in COVID-19 | | | | |
| AOT 26 | 1.0 ± 1.9 | 0 (0-7) IQR = 1 | |
| COT 54 | 0.9 ± 1.5 | 0 (0-5) IQR = 2 | .761 |
| Olfaction VAS at the initial appointment | | | | |
| AOT 26 | 3.8 ± 1.5 | 4 (1-8) IQR = 1 | |
| COT 54 | 3.5 ± 2.5 | 3 (0-7) IQR = 5 | .471 |
| Gustation VAS at the initial appointment | | | | |
| AOT 26 | 6.0 ± 2.4 | 6 (2-10) IQR = 4 | |
| COT 54 | 6.2 ± 2.8 | 6 (0-10) IQR = 3 | .608 |
| Annoyance with the OD at the initial appointment based on the VAS | | | | |
| AOT 26 | 7.9 ± 2.4 | 9 (0-10) IQR = 4 | |
| COT 54 | 6.8 ± 2.8 | 7 (1-10) IQR = 5 | .122 |
| Nasal symptoms at the initial appointment based on the VAS | | | | |
| AOT 26 | 4.7 ± 3.4 | 6 (0-10) IQR = 7 | |
| COT 54 | 4.1 ± 3.4 | 3 (0-10) IQR = 6 | .548 |
| Olfaction VAS at 1-month follow-up | | | | |
| AOT 26 | 5.6 ± 2.2 | 6 (0-10) IQR = 3 | |
| COT 54 | 5.8 ± 2.1 | 6 (0-9) IQR = 3 | .499 |
| Gustation VAS at 1-month follow-up | | | | |
| AOT 26 | 7.2 ± 2.2 | 7.5 (2-10) IQR = 3 | |
| COT 54 | 6.8 ± 2.7 | 7 (1-10) IQR = 4 | .655 |
| Annoyance with the OD at 1-month follow-up | | | | |
| AOT 26 | 6.5 ± 2.8 | 6.5 (0-10) IQR = 4 | |
| COT 54 | 6.0 ± 3.1 | 7 (0-10) IQR = 6 | .609 |
| Nasal symptoms at 1-month follow-up | | | | |
| AOT 26 | 4.3 ± 3.2 | 5 (0-10) IQR = 7 | |
| COT 54 | 4.4 ± 3.4 | 5 (0-10) IQR = 6 | .872 |
| Gustation improvement (VAS) | | | | |
| AOT 26 | 1.2 ± 2.9 | 1 (−6-6) IQR = 4 | |
| COT 54 | 0.6 ± 2.9 | 1 (−8-8) IQR = 3 | .491 |
| Improved sense of smell (VAS) | | | | |
| AOT 26 | 1.8 ± 2.3 | 2 (−4-7) IQR = 3 | |
| COT 54 | 2.4 ± 2.3 | 2 (−5-7) IQR = 3 | .254 |
| Annoyance improvement (VAS) | | | | |
| AOT 26 | −1.3 ± 2.9 | −1 (−8-6) IQR = 3 | |
| COT 54 | −0.8 ± 3.4 | −1 (−10-7) IQR = 3 | .384 |
| Nasal symptoms improvement (VAS) | | | | |
| AOT 26 | −0.3 ± 3.2 | 0 (−6-7) IQR = 4 | |
| COT 54 | 0.3 ± 4.7 | 0 (−10-8) IQR = 5 | .244 |

Abbreviations: UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale; COT, classical olfactory training; AOT, advanced olfactory training; OD, olfactory dysfunction.

*Mann-Whitney non-parametric test, P < .05.

**Improved sense of smell,” “Annoyance improvement,” or “gustation improvement” are related to the comparison between VAS in the initial appointment and the 1-month follow-up.
The average time reported for the onset of OD after the onset of COVID-19 was 4.6 ± 3.8 days, which was consistent with what has been reported in the literature.22,23

Several studies have shown that COVID-19-related OD has a short recovery period in most patients, occurring 1 to 2 weeks after the onset of the disease.22,24,25 In a study by Vaira et al.,24 a higher risk of long-lasting olfactory disturbance was observed in patients whose symptoms persisted for 20 days after the onset of OD. In our study, all patients were selected after at least 4 weeks of olfactory complaints to reduce the number of patients who showed spontaneous recovery, regardless of therapy.

In the present study, sudden anosmia was observed in the acute stage of COVID-19, leading to a progressive recovery that was accompanied by the appearance of other qualitative olfactory disorders.26 Although parosmia seemed to be indicative of their recovery,27 no relationship was observed between its presence and patient outcome by UPSIT or olfaction VAS.

In the global analysis of patients by gustation VAS, mean values of 6.1 ± 2.7 and 6.9 ± 2.5 were obtained at the first and second appointments, respectively; this corresponded to an improvement of 0.8 ± 2.9 (P = .009). However, the data showed no statistical difference between the OT groups, neither in the means of the first appointment (P = .608) nor in the return (P = .491).

During both assessments, the patients were asked about their perceptions of olfactory fluctuations. At baseline, these complaints occurred in 62.8% of patients; conversely, in 78.8% of patients who experienced similar symptoms at the end of the study, a marked prevalence than that reported by Jerome et al was observed.28 As expected, patients with fluctuations in olfaction also had higher VAS scores for nasal symptoms (P = .003). Thus, fluctuations in olfaction were commonly associated with nasal conditions, such as allergic diseases.29 Furthermore, these were less pronounced in patients with postinfectious OD.30

The presence of this symptom at the first appointment was associated with better scores at both the first (P = .011) and second (P = .029) appointments. These results suggested that fluctuations were related to the regeneration of the neuro-epithelium.

Interestingly, olfactory fluctuations were related to worse smell evolution, as measured by the VAS (P = .029). Considering that self-assessment of this sense seemed to reflect changes in nasal patency and olfactory function,21 this would explain why fluctuations in our study were more pronounced in patients with more severe nasal symptoms, who therefore reported worse VAS scores.

The trigeminal nerve has an important influence on olfactory perception; it is associated with the sensation of freshness in minty odors and the tickling sensation of carbonated beverages.31 The relationship between trigeminal function impairment and reported chemosensory disturbances at 3 time points was assessed as follows: (1) the acute period of SARS-CoV-2 infection, (2) first appointment, and (3) 1-month follow-up. None of the reported disturbances was found to be related to trigeminal function, thus suggesting a pathophysiology likely distinct from that of olfaction.

The main limitation of the present study was the short duration of its proposed treatment. The aim of this study was to evaluate an alternative to TOC originally described by Hummel et al.,8 which was performed intensively and included twice as many scents with fewer weeks of stimulation. Most studies conducted on this topic have maintained OT for a longer period, which limited our analysis of the potential benefits of AOT. Another possible limitation was the method of the psychophysical test, as the UPSIT limited the assessment to odor identification only and did not consider the discrimination or olfactory threshold abilities present in other tests. However, a study conducted by Doty et al.32 suggested that different psychophysical tests measured the common source of variation; thus, olfactory impairment and improvement can be effectively assessed using only the identification of odors.

Conclusion

Prospective evaluation using subjective scales and psychophysical tests in patients with persistent OD post-COVID-19 showed an improvement in smell capacity upon undergoing a 4-week OT. However, the data suggested that training intensification by increasing the number of essences did not show superiority over the 4-week classical method. Additionally, the data indicated that patients with fluctuating olfactory abilities had better psychophysical assessment scores. Therefore, future studies with an extended treatment period are needed to better analyze the potential benefits of AOT.

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