Olfactory training for the treatment of COVID-19 related smell loss: a randomised double-blind controlled trial

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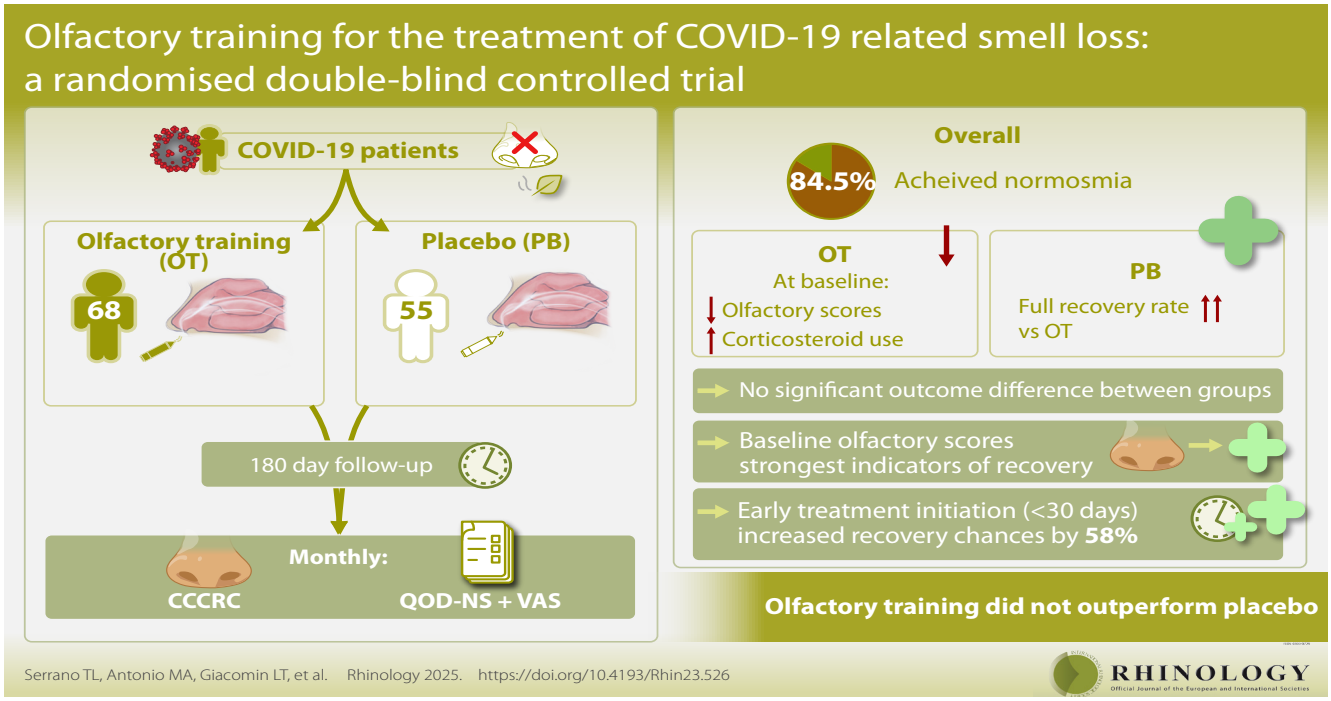
Rhinology 63: 3, 325 - 333, 2025
https://doi.org/10.4193/Rhin24.081



Abstract

Background: Olfactory training is the most widely recommended treatment for smell loss; however, there are no randomised placebo-controlled trials evaluating its effectiveness in COVID-19. We aimed to evaluate the efficacy of isolated training and factors associated to olfactory recovery.

Methods: This is a prospective randomised double-blind controlled trial, using standard olfactory training (OT) and placebo (PB) in COVID-19 patients experiencing smell loss. They were followed up for 180 days and assessed with the Connecticut olfactory test (CCCRC) and with subjective methods on a monthly basis.

Results: A total of 123 participants completed follow-up: 68 in the OT group and 55 in the PB group. Overall, 84.5% achieved normosmia, with full recovery (FR) significantly higher in PB. At baseline, OT had lower olfactory scores and higher corticosteroid use. Multivariate analysis showed no significant differences in outcomes between groups. Baseline olfactory test scores were the strongest predictors of recovery. Exploratory analyses stratified participants by time to treatment initiation (early ≤ 30 days; late > 30 days), showing a 58% higher chance of FR in the early group for similar CCCRC scores, regardless of management type.

Conclusions: OT is not superior to PB for treating COVID-19-related smell loss. Better results of first evaluation indicate great chance of full recovery and the use of systemic corticosteroid, in persistent olfactory loss, has not affected outcome.

Key words: anosmia, COVID-19, olfactory training, smell

Introduction

SARS-CoV-2 infection was first identified at the end of 2019 in China and characterised as a pandemic by the World Health Organization as early as March 2020 [1]. With the rapid spread of the virus, there were an increasing number of reports of smell loss as a warning symptom of COVID-19. Studies using psychophysical and/or subjective tests have shown different prevalence rates, ranging 19.4-98% [2–8]. A meta-analysis with 1,627 individuals showed a prevalence of olfactory impairment of 52.7% and heterogeneity of 98.8% [9].

Olfactory dysfunction duration and olfactory recovery in COVID-19 patients remain uncertain. Studies using subjective methods have shown approximately 50% of full and 40% of partial recovery within a period of 15 to 80 days [10–12]. Similarly, articles using psychophysical tests have shown that olfactory disturbances persisted in 40-77% of patients 30 days after the clinical onset and in 50% after 3 months [13–15].

Olfactory training (OT) is the most commonly recommended treatment by American and European medical organizations, such as the British Rhinological Society (BRS) and the Clinical Olfactory Working Group (COWoG), based on evidence of its effectiveness in treating post-viral olfactory dysfunction [16–21]. This therapy is easy to administrate and has low cost and minimal adverse effects [22,23].

Hwang et al. [24] and Asvapoositkul et al. [25], in their meta-analyses of OT in COVID-19 patients, concluded that OT yielded positive results in the pre- and post-treatment comparison but pointed out that the studies included were heterogeneous, had a small sample size, and lacked placebo-controlled trials to assess the effect of isolated OT. This is one of the reasons why it cannot be concluded that improvements in the patients' sense of smell are caused by the intervention and not by natural recovery over time.

Therefore, given the small body of evidence, our main objective was to evaluate the efficacy of isolated OT after COVID-19 compared with placebo (PB), using a psychophysical olfactory test and subjective measures, such as the Visual Analogue Scale (VAS) and a quality of life questionnaire. In addition, in a secondary analysis, we assessed correlated variables that could have an impact on olfactory recovery and evaluated time-to-treatment initiation as an impact factor on recovery.

Materials and methods

A prospective randomised double-blind trial was carried out in a tertiary referral hospital after the approval of the National Ethics Committee (number 32195020.5.0000.5404).

Selection criteria

COVID-19 patients with a confirmed positive RT-PCR test and notified by the university health centre were invited to participate via text message. The inclusion criteria were: 18 years and older, perception of sudden smell loss during SARS-CoV-2 infection, and disease onset no later than December 2020. Patients with complaints of smell loss prior to COVID-19, with nose and sinus disorders, with history of head and neck radiotherapy, with neurodegenerative or psychiatric diseases, and with a normal olfactory test were excluded.

Data collection

Participants underwent a teleconsultation to collect data on demographics, comorbidities, olfactory patterns, and therapies used at the time of consultation. A face-to-face consultation was scheduled to carry out the Connecticut olfactory test (CCCRC) and to apply a quality-of-life questionnaire (brief version of the QOD-NS) [26] and VAS for smell discomfort. Qualitative smell disorders, such as parosmia and phantosmia, were not assessed. Teleconsultation and face-to-face procedures were always carried out by the main researcher.

CCCRC was conducted in a ventilated room, with an indoor air temperature of 23ºC. The participant remained blindfolded and left and right nostrils were tested separately. The test was divided into two parts: odour detection threshold and odour identification, both with results ranging between 0 and 7. In part 1, olfactory threshold was tested using different concentrations of butanol in vials numbered 1 (more concentrated) to 7 (more diluted), to be compared with a vial with distilled water. The objective was to determine the lowest concentration of butanol that the participant was able to detect with systematic responses. In part 2, the participant was asked to identify 7 odorants [chocolate, coffee, cinnamon, mothballs, paçoca (peanut fudge), baby powder, and soap] in a maximum of 2 attempts. A table displayed the pictures and names of these substances as well as 13 distractors, which could be used to help identification. Ultimately, the averages of parts 1 and 2 and the left and right nostrils were used to calculate the final results: anosmia (0-1.75), hyposmia [severe (2-3.75); moderate (4-4.75) and mild (5-5.75)] normosmia (6-7).

The quality of life questionnaire used was a short version of the Questionnaire of Olfactory Disorders-Negative Statements, a summarized version of the Questionnaire of Olfactory Disorders (QOD) [27]. It includes 7 statements with a 4-point response scale. Results range from 0 to 21 points, where lower scores represent greater impact of loss of smell on quality of life.

Participants were randomised into a group treated with OT and a group receiving PB by another researcher in a 1:1 ratio, using a randomised sequence list in Microsoft Excel®. They were assigned to the groups sequentially throughout the study time. All patients received 4 vials labelled with the odour name: clove, lemon, eucalyptus, and rose. The PB group, however, received vials without essential oils. They were instructed to perform the exercise for 5 minutes twice daily, rotating odours after 15 seconds, as proposed by Hummel et al. [16]. They were further

instructed to write down their perceptions and sensations on a diary provided by the researchers to monitor progress and encourage compliance. The participants were also advised not to share their training kits and not to allow family members to handle them.

Follow-up

Participants were evaluated by the same researcher on a monthly basis. They were submitted to CCCRC, completed the sv-QOD-NS and VAS scales, and were followed up on treatment compliance by answering the question: "In percentage, how much of the recommended olfactory training did you do?" An answer of 100% meant that the OT was performed twice daily and 0% represented no training performed.

Additionally, participants were followed up for 180 days or until olfactory test results returned to normal values and VAS score indicated no or mild discomfort. There was no exchange between previously randomised groups and the researcher had no access to the patient's treatment group. At every visit, the vials were replaced to maintain odour intensity and avoid any possible contamination.

Statistical analysis

Statistical analyses were carried out using the IBM-SPSS® software platform. Categorical variables are expressed as numbers and percentages of the total. Descriptive statistics for quantitative variables are given as median and interquartile range. Chi-squared, Fisher's exact, and Fisher-Freeman-Halton exact tests were used to compare qualitative variables. Quantitative analyses were performed using Mann-Whitney, Wilcoxon, Kruskal-Wallis, and Friedman tests.

Treatment effect over time was assessed using Kaplan-Meier survival curves and Log Rank tests. Cox regression was used for multivariate analysis, adopting the forward stepwise Wald method to select variables, with p-inclusion of 0.05 and p-exclusion of 0.10. Variables with a $p < 0.20$ were also included as they could act as a confounding factor. The significance level was set at 5%, reflecting a 95% confidence interval.

Results

Sample

A total of 182 COVID-19 patients were assessed between June and December 2020. Thirty-three participants had a normal sense of smell according to CCCRC scores. A total of 149 participants started treatment: 75 in the OT group and 74 in the PB group. Twenty-four patients withdrew from research and 2 had their follow-ups interrupted: 1 due to pregnancy and 1 due to adverse effect (headache). Follow-up was completed by 123 patients: 68 in the OT group and 55 in the PB group (Figure 1). All participants had non-severe COVID-19 according to the WHO classification [28].

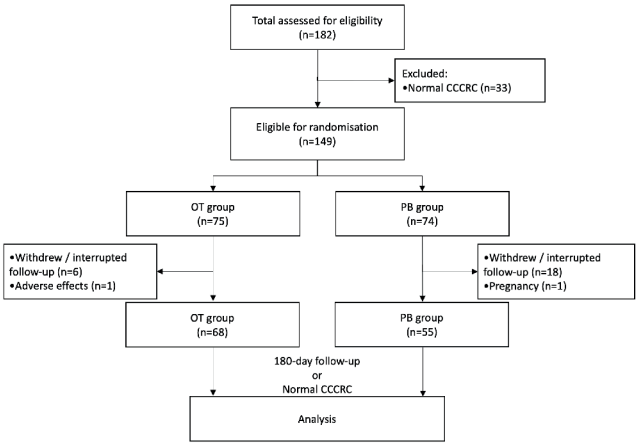


Figure 1. Flow-chart. CCCRC = Connecticut olfactory test; OT = Olfactory Training; PB= Placebo.

Comparison between groups

The median age of participants was 36 years old, and 74.8% were female. When analysing similarity between groups, it could be observed that the use of systemic corticosteroids during COVID-19 was higher in the OT group (OT: 78.9% vs. PB: 21.1%; p=0.024). The first olfactory test also showed a difference between groups, with a significantly lower score in the OT group (OT: 2.75 [IQR: 1.81-3.5] vs. PB: 3.5 [IQR: 2.75-4.25]; p=0.001). No differences were observed for other variables, as shown in Table 1.

Treatment compliance

Treatment compliance was evaluated at all follow-up reassessment sessions and showed no difference between groups. We rated it as satisfactory when more than 50% of recommended training had been carried out. At the first reassessment session, 66 (97%) OT participants and 52 (94.5%) PB participants showed satisfactory treatment compliance (p=0.400) and the score was maintained in the subsequent sessions. We considered a global satisfactory score when the participant showed satisfactory values in more than 50% of reassessment session. In our study, 62 (91.1%) OT participants and 45 (87.2%) PB participants showed satisfactory compliance (p=0.484).

Olfactory outcomes

The first olfactory test revealed that 8 (6.5%) participants had mild hyposmia, 23 (18.7%) moderate hyposmia, 68 (55.3%) severe hyposmia, and 24 (19.5%) anosmia. At the end of follow-up, 104 (84.5%) participants achieved normosmia and some participants still showed some degree of smell loss: 6 (4.9%) mild hyposmia, 6 (4.9%) moderate hyposmia, 6 (4.9%) severe hyposmia, and 1 (0.8%) anosmia. The comparison between the results of the first and last olfactory tests is displayed in Figure 2.

Table 1. Comparison of variables between the groups treated with Olfactory Training and Placebo.

	Total (n=123)	OT (n=68)	PB (n=55)	p-value
Age, median (IQR), years	36,0 (31.8-45.5)	36,5 (31.6-46.0)	35,9 (32.4-43.1)	NS[a]
Male, No. (%) Female, No. (%)	31 (25.2) 92 (74.8)	21 (67.7) 47 (51.1)	10 (32.3) 45 (48.9)	NS[b]
HS/Technician, No. (%) Incomplete University Degree, No. (%) Complete University Degree, No. (%) Post-graduation, No. (%)	35 (28.5) 12 (9.7) 62 (50.4) 14 (11.4)	14 (40.0) 7 (58.3) 36 (58.1) 11 (78.6)	21 (60.0) 5 (41.7) 26 (41.9) 3 (21.4)	NS[b]
DM, No. (%)	6 (4.8)	4 (66.7)	2 (33.3)	NS[c]
Rhinitis, No. (%)	37 (30.1)	18 (48.6)	19 (51.4)	NS[b]
Smoker, No. (%) Former Smoker, No. (%)	5 (4.1) 12 (9.7)	2 (40) 6 (50)	3 (60) 6 (50)	NS[d]
Systemic Corticosteroid, No. (%)	19 (15.4)	15 (78.9)	4 (21.1)	0.024[b]
Topic Corticosteroid, No. (%)	7 (5.7)	4 (57,1)	3 (42.9)	NS[c]
Time-to-treatment initiation, median (IQR), days	44 (28-58)	42.5 (26.25-57.75)	49 (36-58)	NS[a]
First CCCRC, median (IQR)	3.25 (2-4)	2.75 (1.81-3.5)	3.5 (2.75-4.25)	0.001[a]
sv - QOL-NS, median (IQR)	17 (10-21)	15.5 (10-21)	18 (9-21)	NS[a]
Global Adherence, No. (%)	110 (89.4)	62 (91.2)	48 (87.3)	NS[b]

OT = Olfactory Training; PB = Placebo; IQR = interquartile range; NS = not significant; [a] = Mann-Whitney test; No. = number; HS = High School; [b] = chi-squared test; DM = diabetes mellitus; [c] = Fisher´s exact test; [d] = Fisher-Freeman-Halton exact test; CCCRC = Connecticut olfactory test; sv-QOD-NS = brief version of the Questionnaire of Olfactory Disorders – Negative Statements.

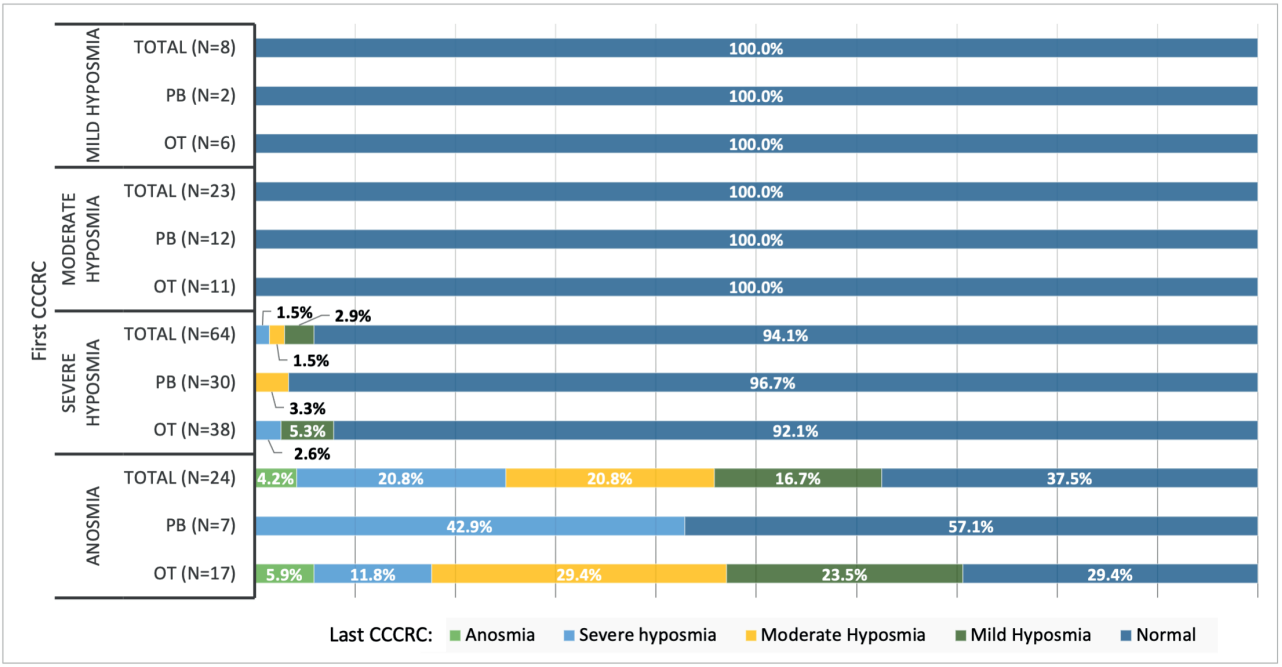


Figure 2. Olfactory evolution in first and last tests.

Olfactory training vs. placebo

Given the high percentage of participants who achieved normosmia (84.5%), we decided to dichotomise the results into partial recovery (PR) and full recovery (FR) i.e., a normal olfactory test. FR was achieved by 53 (77.9%; 95%CI: 67-86.6%) participants in the OT group and 51 (92.7%; 95%CI: 83.4-97.7%) in the PB group. The risk of FR in the OT group was 16% lower than that for the PB group (RR=0.84; 95%CI: 0.73-0.97; p=0.024). Similarly, the OT group required a median of 119 days (95%CI: 105-133) for full recovery and the PB group needed 77 days (95%CI:

Table 2. Comparison of variables between outcomes for full recovery and partial recovery.

		FR (n=104)	PR (n=19)	p-value
Age	Median (IQR), years	36 (31.8-44.1)	38.1 (28.6-48.3)	NS[a]
Sex	Female, No. (%) Male, No. (%)	81 (88) 23 (74.2)	11 (12) 8 (25.8)	NS[b]
Level of Education	HS/Technician, No. (%) Incomplete University Degree, No. (%) Complete University Degree, No. (%) Post-graduation, No. (%)	30 (87.5) 10 (83.3) 54 (87.1) 10 (71.4)	5 (14.3) 2 (16.7) 8 (12.9) 4 (28.6)	NS[c]
Rhinitis	Yes, No. (%) No, No. (%)	29 (78.4) 75 (87.2)	8 (21.6) 11 (12.8)	NS[d]
Smoking	Yes, No. (%) No, No. (%) Former, No. (%)	4 (80) 89 (84) 11 (91.7)	1 (20) 17 (16) 1 (8.3)	NS[c]
Adherence	Yes, No. (%) No, No. (%)	93 (84.5) 11 (84.6)	17 (15.5) 2 (15.4)	NS[b]
Time-to-treatment initiation	Median (IQR), days	44 (28-58)	45 (27-59)	NS[a]
First CCCRC	Median (IQR), number	3.5 (2.75-4)	1.0 (0.5-1.75)	<0.001[a]
Systemic Corticosteroid	Yes, No. (%) No, No. (%)	13 (68.4) 91 (87.5)	6 (31.6) 13 (12.5)	0.045[b]
Topic Corticosteroid	Yes, No. (%) No, No. (%)	7 (100) 97 (83.6)	0 (0.0) 19 (16.4)	NS[b]

FR = full recovery; PR = partial recovery; IQR = interquartile range; NS = not significant; [a] = Mann-Whitney test; No. = number; [b] = Fisher´s exact test; HS = High School; [c] = Fisher-Freeman-Halton exact test; [d] = chi-squared test; CCCRC = Connecticut olfactory test.

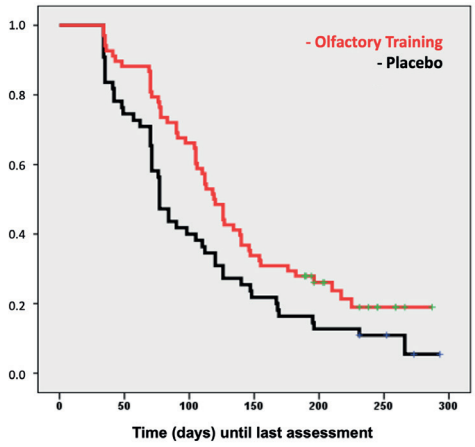


Figure 3. Kaplan-Meier survival curve demonstrating temporal evolution of olfactory recovery for the groups treated with Olfactory Training and Placebo.

69-85). The Kaplan-Meier survival curve (Figure 3) demonstrates this difference (p=0.018).

Variables associated to outcomes

In view of the results obtained, we analysed factors that could have affected outcome. The first CCCRC was lower among participants with PR (FR: 3.3±1.1 vs. PR: 1.2±1.0; p<0.001) and a higher number of participants with FR did not use systemic corticosteroids (87.5% vs. 68.4%; p=0.045). The other variables assessed (sex, age, level of education, rhinitis, smoking, treatment compliance, time-to-treatment initiation, and use of corticosteroids) were similar between groups, as shown in Table 2.

A multivariate analysis was carried out including the following variables: treatment group (p=0.021), sex (p=0.189), use of systemic corticosteroids (p=0.037), and first CCCRC (p<0.001). The forward stepwise Wald method demonstrated that the only factor affecting outcome was the first CCCRC result (HR: 1.94; 95%CI: 1.63-2.30; p<0.001), showing that full recovery is 94% higher for every point in the first olfactory test result.

Time-to-treatment initiation

We performed a sub-analysis of the data, categorizing time-to-treatment initiation into two groups: early (≤ 30 days) and late (> 30 days). A total of 37 participants initiated treatment early (OT: 26 vs. PB: 11), while 86 initiated treatment later (OT: 42 vs. PB: 44). No statistically significant difference in outcomes was observed between early and late management groups (early: 83.8% vs. late: 84.9%; p = 0.877). When comparing treatment groups within the early management cohort, no significant difference in outcomes was observed (OT: 80.8% vs. PB: 90.9%; p = 0.410). However, among participants who initiated treatment late, the PB group had a higher proportion of participants achieving full recovery (OT: 76.2% vs. PB: 93.2%; p = 0.028). Additionally, within the early management cohort, the PB group had a median time to full recovery of 76 days, compared to 105 days

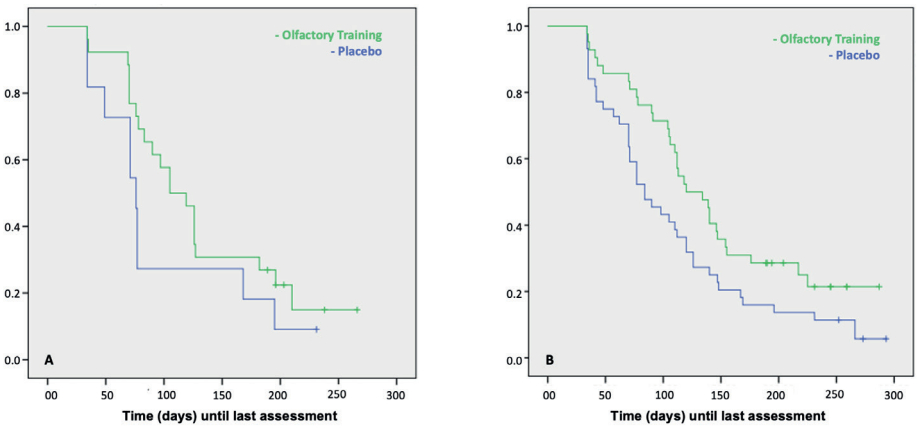


Figure 4. Kaplan-Meier survival curve comparing temporal evolution of olfactory recovery between groups (Olfactory Training and Placebo) and time-to-treatment initiation (Early and Late). A: Early treatment (<30 days); B: Late treatment (≥30 days).

for the OT group (p = 0.182). For those who initiated treatment later, a significant difference was observed (p = 0.037), with OT participants requiring a median of 120 days to achieve full recovery, compared to 84 days in the PB group (Figure 4).

The multivariate analysis, performed using Cox regression, included variables used in previous model in addition to the variable time-to-treatment initiation. In the final model, only time-to-treatment initiation and first CCCRC results remained as significant predictors. When comparing two participants with the same first CCCRC score, the risk of FR was 58% higher in the early management group, regardless of the treatment type (PB or OT). Additionally, for each unit increase in the first CCCRC, there was a two-fold increase in the likelihood of achieving FR.

Discussion

Smell loss is a feared sequela of COVID-19 due to its impact on the individual's quality of life: it can negatively affect the pleasure of eating and interpersonal relationship as well as impair self-care and safety from harmful agents [29].

To our knowledge, this is the first study to compare COVID-19 patients with smell loss treated with olfactory training and placebo. In the systematic review on therapeutic options for post-COVID-19 olfactory dysfunction [25], the authors highlight that the lack of studies with a control group to assess the effects of isolated OT is one of the reasons why it cannot be concluded that olfactory improvement was caused by the intervention and not by the natural progression of the disease.

The group of participants can be considered homogeneous due to the following points: the analysed variables were sex, age, level of education, comorbidities, and time-to-treatment initiation; all participants had non-severe COVID-19 according to WHO classification [28]; and the study was carried out with people infected during the first wave of SARS-CoV-2 infection in Brazil. This data enables a reliable comparison between groups, since there is no influence of different levels of severity and variants; however our results may not be generalized to other variants. Studies show that olfactory dysfunction is more severe in wild-type variants, which is probably the variant that infected our participants. Conversely, Alpha, Delta, and Omicron variants are likely to have less impact on olfaction due to host factors, such as antibodies formation in the saliva and nasal secretions after previous infections or vaccination [30], as well as due to viral mutations [31]. Our sample had no re-infected patients and, at the time of the study, there were no vaccines available. In our study, olfactory impairment was probably greater than that caused by other variants and after vaccination. Likewise, in other phases of the pandemic, spontaneous recovery could be more effective and more often, thus, changing olfactory results.

Prospective studies evaluating treatments for olfactory dysfunction in COVID-19 included a sample size ranging from 12 to 152 participants [29,32–37]. Although our sample size may be small in comparison with the large number of olfactory impaired patients during the COVID-19 pandemic, it is in accordance with the literature on the topic. This study can provide knowledge on the efficacy of olfactory training in post-COVID-19 patients. Based on thorough literature review, there is no prior research comparing OT with participants receiving placebo.

We observed a significant improvement in sense of smell, with full recovery in 84.5% of participants and only 15.5% remaining with some degree of smell loss. Recovery rate was higher than that observed in a study published in 2023 [38], which showed a prevalence of smell loss in 24.2% of participants at 6 months and 17.9% at 12 months. Differences may be explained because the cited article used only an olfactory identification test and included patients with different levels of COVID-19 disease severity, which clearly showed various degrees of olfactory impairment and of recovery.

CCCRC assesses olfactory threshold and odour identification. Some researchers maintain that olfactory threshold is the most affected ability by SARS-CoV-2 [14] and OT has a major impact on

threshold, little influence on identification, and no influence on discrimination [29]. On the other hand, a meta-analysis published in 2016 [18] analysed OT effectiveness across different abilities. The authors found that OT has a significant effect on identification but small-to-moderate effect on odour detection threshold. Therefore, various modalities of olfactory analyses are essential for monitoring OT outcome in COVID-19. Different tests may explain the differences found here in comparison with the literature, which mostly reports the use of isolated identification tests. Likewise, time-to-treatment initiation could be another conflicting point, since, in our study, some patients initiated training prematurely and full recovery may have been caused by the natural history of the disease.

Unlike the study conducted by Damm et al. [39], which reported a better response among individuals who underwent OT with a high concentration of odours, the analysis of our results showed that OT in COVID-19 did not accelerate recovery and performed similarly to PB. This difference can be explained by the SARS-CoV-2 agent, which has a greater spontaneous recovery compared with other aetiologies. A further explanation can be the fact that sniffing itself may have positive effects on recovery. For postinfectious olfactory dysfunction other than COVID-19, it was demonstrated that patients submitted to low-concentration OT had higher improvement rates compared with spontaneous remission rates in the literature [39].

We observed that the probability of progression to full recovery is closely related to the first olfactory test, which is 94% higher for each point in the first test. Therefore, the high recovery rate observed in PB was possibly an effect of higher scores in the first CCCRC. It may have influenced the results and can be considered as a bias in our study, since the first olfactory score was the main variable that influenced the outcome in the multivariate analysis.

Lechner et al. [40] carried out a similar study, comparing isolated OT with a control group who only received safety information, with no use of placebos. The authors maintain that the training can be helpful, but their sample of 51 participants with persistent smell loss for over 4 weeks produced inconclusive findings. Our study was carried out over a longer period, with a larger sample and using olfactory tests that assessed both threshold and identification, which may explain such conflicting results.

We chose to include patients with olfactory impairment of different lengths of time after being released from isolation. Proposedly, the earlier a treatment begins, the better the result will be [13,22,41]. The analysis of early and late treatment showed that improvement in late treatment results was explained by higher first CCCRC scores. When comparing two participants with the same initial CCCRC result, the risk of full recovery (FR) was 58% higher in the early treatment group, a finding consistent with the existing literature. Studies report that patients with anosmia needed about 8 more days to improve their sense of smell, compared with patients with hyposmia [42]. Therefore, in our study, it was observed that for each additional unit in the first test result, there was a two-fold increase in chances of full recovery.

Female predominance (75%) can be explained by a greater olfactory sensitivity and higher treatment compliance, as observed in other studies [43,44]. The average age corroborates the hypothesis that young patients have a better localised immune response, which produces a greater local inflammatory response [43].

Corticosteroids, a widespread drug used to treat olfactory disorders, are not recommended for COVID-19. Two meta-analyses reported no significant differences between psychophysical olfactory tests and frequency of recovered patients [45,46]. In line with the literature [47], systemic corticosteroids did not promote an improvement in olfactory function, which is demonstrated by a higher FR rate among patients who did not use them. In our study, it is worth mentioning that a limited number of participants used systemic corticosteroids (n=19), given the uncertainties about this class of drugs in the first period of the pandemic as well as the lack of standardisation and doses used.

Compliance to olfactory training is a much-discussed topic, as rates are not very high and can influence results. Studies have shown rates of around 50% [29,34], with a trend towards better results with full compliance but with no correlation with test results or with subjective improvement. We considered a rate of 50% as satisfactory, which is in agreement with the average rates observed in the literature. In all monthly reassessment sessions, more than 75% of participants showed satisfactory score. This outcome may have been influenced by the hand-outs with instructions and a diary to keep track of the training, which eventually stimulated self-improvement. Other factors that may have encouraged compliance were the insecurity about the natural progression of a novel disease and the fear of developing sequelae, which could considerably impact quality of life. Admittedly, outcomes may have improved if all patients had fully adhered to treatment.

The olfactory training with placebo was a challenging procedure, as most of our patients were hyposmic and inquired about a possible absence of odorant in the vials. At first, the researcher explained that the lower perceived odour intensity might be caused by their impaired olfactory function and sniffing could have a positive effect on recovery, according to the literature. Next, he pointed out that we were at the beginning of the pandemic, little was known about smell loss and recovery in COVID-19, and there was no well-established treatment available. These arguments encouraged the patients to participate, to trust the study design, and to maintain compliance, without asking too many questions about the procedures.

There is no consensus on the duration of OT in the literature. Hummel et al. [17] suggest a minimum of 8 weeks; our study had a longer treatment duration compared with some studies that

used OT periods between 3 to 12 weeks [32–37,40,42]. We detected an average full recovery time of 101 days, which may be a bias in these studies with short periods of treatment. The monthly serial assessment is also unprecedented, allowing for a more accurate analysis of both the influence of training on recovery time and the natural course of the disease.

Some limitations can be observed and are, therefore, a source of impetus for further studies. Our sample included participants exclusively from the university environment following notification from the university's health service and did not include patients with severe and critical forms of COVID-19, which could have led to different results for olfactory recovery. Also, our participants were infected by the first SARS-CoV-2 variant, which limits outcomes extrapolation to other variants. Ultimately, the follow-up duration to assess recovery could be expanded and new research should focus on qualitative changes in sense of smell.

Conclusion

OT has not proved to be superior to PB for treating smell loss in COVID-19. Most of the participants showed full recovery, which may be the result of the natural progression of the disease. The major factor associated with better outcome was the first olfactory test: better results indicate greater chances of full recovery. The use of systemic corticosteroids has not affected outcome to patients with persistent hyposmia.

Acknowledgements

None.

Authorship contribution

TLIS: study design, search, study selection, data collection, data analysis, drafting of the articles, and final approval of the version to be published; MAA: study selection and final approval of the version to be published; LTG: study selection and final approval of the version to be published; AMM: data analysis and final approval of the version to be published; JDR and ES: Critical revision of the article and final approval of the version to be published.

Conflict of interest

The authors declare they have no conflict of interests.

Funding

No funding was received for conducting this study.

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Rhinology 63: 3, 325 - 333, 2025
https://doi.org/10.4193/Rhin24.081

Received for publication:
February 21, 2024
Accepted: March 8, 2025

Associate Editor:
Basile Landis