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Olfactory Training in the Treatment of COVID-19–Related Olfactory Disorders

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Abstract

Background. Loss of smell can impair quality of life. Olfactory disorders (ODs) are often caused by viral infections, such as coronavirus disease 2019 (COVID-19). The aim of the study was to evaluate the effectiveness of olfactory training in patients with post-COVID OD. **Materials and methods.** The entire group consisted of 75 subjects (15 men and 60 women). They were randomly divided into two groups. Patients in both groups received pharmacological treatment (intranasal corticosteroids and vitamin A), salt irrigations, and elements of speech therapy olfactory training (SOT). Participants in the study group additionally carried out classical olfactory training (OT) using applicators with 4 scents twice a day. Olfactory function was assessed using the Sniffin Sticks' Test (SST). **Results.** For total SST score, the mean change before and after intervention in the study group was 7.9 points ($p < 0.001$). In the control group, the mean change was 2.8 points ($p = 0.006$). **Conclusions.** Classical OT appears to improve the recovery from post-COVID OD compared to pharmacological therapy with SOT elements alone. The use of intranasal corticosteroids, topical vitamin A, and saline nasal irrigation in our therapy seemed to help in improving olfaction. It is thought that the multidisciplinary team used here – doctor, speech therapist, and psychologist – may have also contributed to the effectiveness of the therapy.

Keywords: olfactory; olfactory training; COVID

1. Introduction

Loss of smell can impair quality of life [1]. It can cause anxiety in social situations ("I won't know if I'm sweating"); anxiety surrounding an inability to identify danger (e.g. a fire or gas leak); discomfort in preparing and eating shared meals; and ruling out certain professions (e.g., being a cook). In all these situations it can lead to anxiety and lack of self-confidence.

Olfactory disorders (ODs) are often caused by viral infections [2]. The incidence of OD in coronavirus disease 2019 (COVID-19) is estimated at 41–67%, depending on the method of investigation (self-assessment or smell test) and the population studied [3–5]. The incidence of OD also depends on the strain of the SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2) predominating at any given time – the Alpha and Delta variants cause OD much more frequently than the Omicron variety [6,7]. In the majority of cases, olfactory function eventually improves spontaneously, but in about 7–20% of patients, OD persists after other COVID-19 symptoms have resolved [5,8,9].

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COVID-19–associated OD (post-COVID OD) is mainly associated with damage to the olfactory epithelium (OE). When SARS-CoV-2 penetrates the supporting cells of the OE, it can trigger a massive inflammatory response. Damage to these cells leads to dysfunction and subsequent atrophy of olfactory neurons within the OE, resulting in conductive OD [10]. In addition, penetration of SARS-CoV-2 into the central nervous system causes sensory–nervous OD [11,12]. The results of olfactory tests indicate that post-COVID OD is more peripheral than central [13–15]. It is likely that the greater the epithelial damage, the longer the duration of the olfactory impairment.

Currently, there is no known effective pharmacological treatments for post-COVID OD. Guidelines in the European position paper on olfactory dysfunction (EPPOD) primarily recommend the use of olfactory training (OT) for a minimum of 12 weeks [16]. In addition to the OT used by ear, nose, and throat (ENT) specialists, there is also the olfactory training used by speech therapists (SOT), which is based on improving the detectability of odors found in everyday life [17]. The aim of this study was to evaluate the effectiveness of OT in patients with post-COVID OD.

2. Materials and Methods

This paper presents the results of a prospective, single-centre study. The study protocol, the consent forms for participation in the study and processing of personal data, and patient leaflet were approved by the Bioethics Committee of the Institute of Physiology and Pathology of Hearing (No. KB.IFPS 7/2021) and were in accordance with the World Medical Association's Declaration of Helsinki. Participation in the study was voluntary and free of charge. An outline of the study is shown in Figure 1.

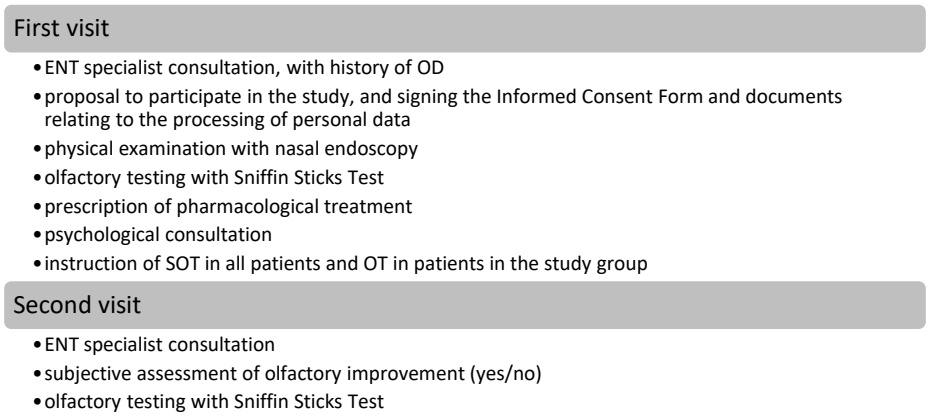

Figure 1. Outline of the present study. Each subject visited the clinic twice at an interval of about 12 weeks.

2.1. Subjects

The entire group consisted of 75 subjects (15 men and 60 women) aged between 18 and 73 years; the mean age was 42.3 years (SD = 14.1). They were randomly divided into two groups: a study group made up of 40 women and 10 men aged from 18 to 73 years (M = 42.9; SD = 13.7) and a control group comprised of 20 women and 5 men ranging in age from 18 to 68 years (M = 40.9; SD =15.0). All of them had presented to the Institute of Physiology and Pathology of Hearing for subjective OD associated with COVID-19.

2.2. Inclusion and Exclusion Criteria

The main inclusion criterion for the study was experiencing an OD that occurred during COVID-19 and lasted at least 1 month after the acute symptoms had resolved. Only patients with a positive SARS-CoV-2 virus test during acute infection were included. Patients who did not have a COVID-19 test performed at the time of OD or who had a negative test result were excluded. Patients in whom subjective OD existed before COVID-19 were also excluded. A further exclusion criterion were

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conditions or diseases that may affect normal olfactory function (based on medical history and physical examination) and pregnancy. Following the olfactory test, patients with results within normal limits or those who cooperated poorly with the investigator during the test were excluded.

2.3. Study Group and Control Group

The participants were randomly divided into a study group and a control group. All subjects underwent the same olfactory test, ENT specialist consultation, and psychological consultation, after which they received identical recommendations for pharmacological treatment and instructions for SOT using odours present in everyday life. Patients in the study group additionally received a set of therapeutic applicators for OT containing four specific odours and strict instructions for their use.

2.4. Olfactory Testing

After reviewing the literature of available olfactory tests, the researchers selected the Sniffin Sticks Test (SST), because it allows assessment of an olfactory threshold, the ability to discriminate and identify odors, is low cost, and can be used repeatedly [18]. The SST was developed in 1997 and a Polish adaptation was published in 2014 [19,20]. SST is made of 4 markers soaked in fragrances dissolved in a solution of propylene glycol (Figure 2). During the test, the tip of the stick is held approximately 2 cm from the nostrils for 3 seconds (s). The test is divided into three parts: a threshold test, a discrimination test, and an identification test. The threshold test consists of 16 sticks: 4 different fragrances, each one at 4 different concentrations and soaked in either n-butanol, 2-phenylethanol (PEG), or two unscented. The patient needs to indicate which stick carries the odour. The discrimination test consists of 16 sets of sticks: two with the same odour and one with a different odour. The patient indicates the stick with the different odour. The identification test consists of 16 sticks and the patient names the odour using four prompts. A maximum of 16 points can be obtained in each part of the test, and a total of 48 points can be obtained in the whole test. A score above 30 indicates normosmia, between 15 and 30 indicates hyposmia, and below 16 indicates anosmia [21]. The SST tests were only conducted in the clinic, but the sticks themselves were given to the participants for OT training.

2.5. ENT Consultation

During the ENT consultation, a medical history was taken, primarily concerning the OD: its onset, temporal relationship to COVID-19 history (confirmed by a test), subjective nature of the disorder (weakness/complete loss), and the patient's other complaints and diseases. Each patient then underwent a thorough physical examination, including nasal endoscopy. The ENT specialist recommended to all patients the use of mometasone furoate (an intranasal corticosteroid, INCS, taken as 2 doses of 50 μg into each nostril once per day, for a total dose of 200 μg per day), a nasal ointment containing vitamin A (1 g per 10 g of ointment [22], Table 1), and saline irrigations.

Table 1. Compounding nasal ointment formula.

Formula	Dosage
Liquid vitamin A 1,0 g Lanoline 3,0 g Liquid paraffin 3,0 g Vaseline 3,0 g Mixed into an ointment	2 times a day into both nasal cavities

2.6. Psychological Consultation

The aim of the psychological consultations was to diagnose the patient's psychological state, measure the intensity of the OD condition, and establish an intervention plan, including a course of OT and SOT. During the consultation, an interview was also conducted about the patient's previous

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olfactory conditions, ability to recognise odours, and taste and smell preferences. Information was gathered about the patient's methods of coping with OD: what resources they drew on and what obstacles they faced. Patients were asked to carry out OT and SOT in conditions of relative calm and tranquility, with no time pressure. Advice on stress reduction and sleep hygiene was also delivered.

2.7. Speech Therapy Olfactory Training (SOT)

It was recommended to the patients that the sense of smell should be stimulated with different olfactory substances present in their environment, such as spices, fruit, flowers, or perfume. In addition to odour stimulation itself, patients were asked to introduce exercises involving guessing and naming odours and to exercise olfactory memory. SOT should be carried out daily, although no frequency was imposed. Patients were encouraged to use their other senses (taste, touch, sight) and to trigger memories and associations related to smell.

2.8. Olfactory Training (OT)

Applicators soaked in the following fragrances were used to perform OT: lemon, clove, eucalyptus, and rose (Figure 2). The applicators were placed close to one nostril and sniffed for about 15 s, and then repeated for the other nostril. During a single session, all the sticks (one for each odour) needed to be applied, and this process was performed twice per day. It was recommended that other senses be used during the training session (sight, taste, or touch) and that memories associated with the sniffed odour be recalled. The applicators were manufactured on behalf of the Institute of Hearing Physiology and Pathology and had medical device status.

Figure 2. Set of olfactory training applicators used by the patient. Odours used (from left): eucalyptus, lemon, rose, clove.

2.9. Statistical Analysis

The demographic and clinical characteristics of the study and control groups were examined using descriptive statistics and percentages. A Kolmogorov–Smirnov test was used to check the assumption of normality of variables. Differences across groups were assessed through a $\chi 2$ test and

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Mann–Whitney U-test. The relationship between variables was evaluated with a rho-Spearman correlation coefficient. A mixed-design ANOVA was used to evaluate the change in olfactory sensitivity before and after intervention in the study and control groups. Statistical significance was specified as a p-value less than 0.05. Data analysis was conducted using IBM SPSS Statistics v. 24.

3. Results

3.1. Characteristics of Participants

Patients presented to the ENT specialist at different times after the onset of the COVID-19–associated OD. In the study group the time between the onset of OD and presentation to the doctor ranged from 2 to 20 months (M = 8.7; SD = 5.1); in the control group it was between 4 and 20 months (M = 8.1; SD = 3.8). There were 5 smokers and 45 non-smokers in the study group and 2 smokers and 23 non-smokers in the control group.

3.2. Change in the Sniffin' Sticks Test before and after Intervention

Table 2 gathers SST results obtained in the clinic from the participants from the study group and the control group.

Table 2. Descriptive statistics for Sniffin' Sticks test scores obtained by the study and control groups before and after intervention. M, mean; SD, standard deviation.

	Study group (n = 50)				Control group (n = 25)			
	Pre		Post		Pre		Post	
	M	SD	M	SD	M	SD	M	SD
Thresholds	1.87	2.34	5.11	3.98	1.41	1.55	3.04	3.03
Discrimination	9.28	3.14	11.30	2.55	9.52	2.80	10.28	3.05
Identification	8.74	2.94	11.54	3.35	9.12	3.29	9.40	3.33
Total score	19.91	6.57	27.85	8.22	20.05	5.97	22.80	6.84

The intervention effect was statistically significant for all analyzed variables. For thresholds ($F = 48.6$, $p < 0.001$, $\eta2 = 0.40$); for discrimination ($F = 18.4$, $p < 0.001$, $\eta2 = 0.20$); for identification ($F = 21.5$, $p < 0.001$, $\eta2 = 0.23$); and for total score ($F = 80.3$, $p < 0.001$, $\eta2 = 0.52$). The group effect was statistically non-significant for each variable.

The interaction effect (group x intervention) was statistically significant for three variables: for thresholds ($F = 5.3$, $p = 0.024$, $\eta2 = 0.07$); for identification ($F = 14.4$, $p < 0.001$, $\eta2 = 0.17$); and for total score ($F = 18.9$, $p < 0.001$, $\eta2 = 0.21$); whereas for discrimination $F = 3.8$, $p = 0.056$, $\eta2 = 0.05$. The interaction effect is illustrated in Figure 3.

For odour thresholds, the mean change before and after intervention in the study group was 3.2 points and was statistically significant ($p < 0.001$); the effect size was $\eta2 = 0.47$. In the control group, the mean change was 1.6 points and was also statistically significant ($p = 0.006$), but the effect size was smaller, $\eta2 = 0.10$. For odour discrimination, the mean change before and after intervention in the study group was 2 points and was statistically significant ($p < 0.001$); the effect size was $\eta2 = 0.29$. In the control group, the mean change was 0.8 points and was statistically non-significant ($p = 0.155$). For odour identification, the mean change before and after intervention in the study group was 2.8 points and was statistically significant ($p < 0.001$); the effect size was $\eta2 = 0.42$. In the control group, the mean change was 0.3 points and was statistically non-significant ($p = 0.607$). For total SST score, the mean change before and after intervention in the study group was 7.9 points and was statistically significant ($p < 0.001$); the effect size was $\eta2 = 0.65$. In the control group, the mean change was 2.8 points and was also statistically significant ($p = 0.006$); the effect size was $\eta2 = 0.10$.

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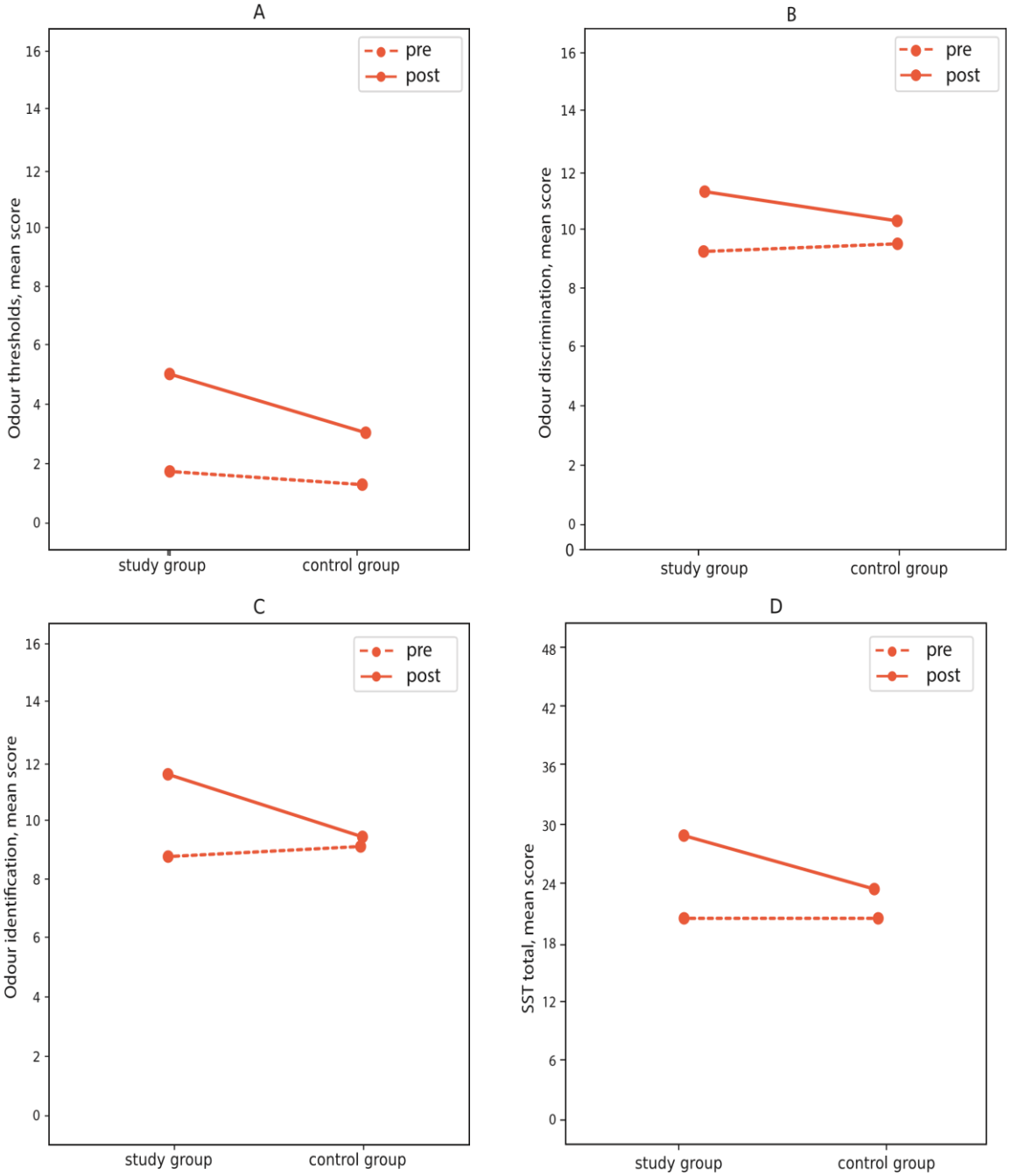

Figure 3. Mean levels of odour thresholds (A), discrimination (B), identification (C), and total Sniffin Sticks Test score (D) before (dashed lines) and after (solid lines) intervention for the study and control groups.

3.3. Subjective Improvement and Clinically Significant Improvement in Olfactory Sensitivity

In the study group there were 37 patients (74%) who said they had improved while 13 patients reported no improvement. In the control group, improvement was reported by 12 patients (48%) and lack of improvement by 13 patients. The difference between the groups was statistically significant ($\chi 2 = 4.97$; $p = 0.026$).

According to Gudziol et al. [23], a clinically significant improvement in SST is an improvement of at least 5.5 points. In our study there were 33 patients (66%) in the study group and 6 patients (24%) in the control group whose SST improved by more than 5.5 points. The difference between the groups was statistically significant ($\chi 2 = 11.78$; $p = 0.001$).

3.4. Improvement in Olfactory Sensitivity in Terms of Age, Gender, Smoking, and Delay in Presentation

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The change in the total SST score before and after intervention was taken as an indicator of improvement in olfactory sensitivity. A negative correlation between age and improvement was found (rho = −0.25, p = 0.029). The older the patients were, the less they improved, however the strength of the correlation was weak.

There was a statistically significant difference between men and women (U = 298.5, p = 0.044). The mean improvement in men (M = 8.9; SD = 1.4) was slightly higher than in women (M = 5.4; SD = 5.0).

The correlation between delay in presenting to an ENT specialist and change in the SST score was statistically non-significant (rho = 0.11, p = 0.336). The difference between smokers and non-smokers was found to be statistically non-significant (U = 207.0; p = 0.571).

4. Discussion

The results of our study indicate that classical OT, together with SOT and regular pharmacological therapy, can be helpful in post-COVID OD therapy. Based on the SST results, 66% of the patients in the study group achieved a significant improvement in olfactory function, while only 24% of patients in the control group did. The study group showed improvement in all parts of the SST, with an average of 3.2, 2.0, and 2.8 points for the threshold, discrimination, and identification tests, respectively. The control group showed less improvement, averaging 1.6, 0.8, and 0.3 points, respectively. SST total score improved by an average of 7.9 points in the study group and 2.8 points in the control group. The changes were statistically significant for all SST parameters in the study group, while they were non-significant in the control group for the discrimination and identification test. In terms of self-assessment of the sense of smell, 74% of patients in the study group experienced an improved sense of smell compared to only 48% in the control group.

This may be related to the fact that patients in the study group were given exercise applicators, which may have resulted in greater patient engagement and test regularity. The small size of applicators meant they could be used at any place and time. It has been shown that increased concentration and attention on sniffed odours increases the effectiveness of OT [24]. The OT used in our study was modelled on the training developed by Hummel et al. [25] Patients in the study group sniffed SSTs with 4 scents (rose, clove, lemon, eucalyptus) twice a day, for 15 s each. Repeated short-term exposure to odours can improve the sense of smell by increasing the number of receptors and olfactory neurons [25].

A study by Li et al. showed that the effect of OT can be increased if other senses, such as vision and hearing, are stimulated at the same time [24]. Multisensory stimulation has previously been used by speech therapists. SOT can be used not only in the course of therapy for olfactory disorders associated with diseases of the nose and paranasal sinuses, but also in the rehabilitation of patients after laryngectomy, with memory disorders, or neurodegenerative disease. In addition to stimulating the sense of smell, other senses (taste, sight, touch) are also stimulated during SOT, which activates memory traces [26]. Stimulation of this multisensory semantic network can lead to improved olfactory function if the additional stimuli reaching the senses during the training session are congruent with the odorant used [24]. Although the inclusion of speech therapists in OD therapy can be beneficial to patients, it is not common, perhaps due to the low popularity of SOT [27]. Our results show that the use of SOT alone, without imposing the amount of exercise performed during the day, has a small benefit in improving the sense of smell. Patients in the control group showed improvement mainly in the threshold component of the SST, but it cannot be excluded that this improvement was related to the use of pharmacological treatment and the improvement of nasal patency.

At the time of planning this study, no guidelines for the pharmacological treatment of post-COVID OD were known, so we decided to use the treatment – INCS and vitamin A ointment – described previously in studies of non-COVID post-infectious OD. Enhancement of OT by the addition of INCS may improve olfactory function in patients with post-infectious OD, especially in discrimination and odour identification [28,29]. In their studies, Abdelalim et al. showed that the use

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of INCS alone has no benefit in the treatment of post-COVID OD, while Kasiri et al. showed that post-COVID OD therapy with OT in combination with INCS (mometasone furoate was used in the study) can accelerate the return of normal olfactory function compared to OT alone [30,31]. When INCS is included in therapy, it is more beneficial to administer the drug as a rinse instead of a spray due to the possibility of more drug reaching the olfactory cleft16. Although the inclusion of INCS in OD therapy appears to be of benefit, further research is needed to establish exact treatment regimens (INCS dosage and duration of treatment) [32,33].

The olfactory system has the ability to regenerate neurons [34], in which vitamin A plays an important role. Retinoic acid, a metabolite of vitamin A, regulates transcription and thus affects tissue development during embryogenesis and the regeneration of adult neurons [35,36]. Disorders of neuronal regeneration of the olfactory system manifest clinically as OD. In a study by Reiden et al., no beneficial effect of OD treatment with oral vitamin A was observed [37], while Hummel et al. showed that intranasal vitamin A can be helpful in the treatment of post-infectious OD [38]. Patients who used OT and intranasal vitamin A in the treatment of OD had significantly better outcomes than patients using OT alone. However, this study was unable to show whether the use of intranasal vitamin A alone, without OT, improves olfactory function. Vitamin A nasal ointment moisturises the nasal mucosa, protecting it from the adverse effects of INCS (dry mucosa, scabs, nose bleeds). A complementary pharmacological treatment – nasal saline irrigations – were recommended due to their positive effects on nasal mucosa (thinning of mucous, reduction of oedema, and removal of retained debris) [39].

Patients received guidance on reducing stress in daily life, which is important because of the negative impact of stress on the treatment of olfactory disorders due to the inhibition of the process of neurogenesis [40]. Participants were also asked to perform mindfulness exercises, which consist of learning to focus on the stimuli perceived by the different senses. Meditation has beneficial effects on health, including reducing anxiety and emotional stress, lowering blood pressure, and increasing recognition and working memory; it also improves perceptual awareness and allows for increased attention [41]. Oleszkiewicz et al. asked a group of people to count the odours they perceived during the day; the test group included people with olfactory disorders, the study group included healthy people. In both groups, they observed that the perception of odours can be improved by consciously focusing on them and in this way olfactory sensitivity can be increased [42].

This study has limitations. Patients reported to the research centre only after the onset of olfactory impairment and therefore the baseline condition of their sense of smell is unknown. In case of an observed improvement, we cannot be sure whether it occurred as a result of OT or whether it occurred spontaneously. On the other hand, in the case of patients in whom no improvement was seen, we could only rely on information from the patients themselves, as we couldn't verify whether OT had been applied correctly or consistently. Studies by Haas et al. show that some patients will drop out of the recommended OT as soon as they feel an improvement in their sense of smell or when rapid improvement is lacking [43]. The creation of a tool, perhaps an app, to remind patients and assist them with OT would help improve patient compliance and monitor progress. An additional limitation is the lack of knowledge of the SARS-CoV-2 variant with which the participants were infected; only information on which variant was prevalent at the time of the illness is known.

5. Conclusions

Classical OT appears to improve the recovery from post-COVID OD compared to pharmacological therapy with SOT elements alone. Pharmacological treatment of post-COVID OD has not been systematically tried before, but using INCS, topically applied vitamin A, and nasal saline irrigations in our therapy appeared to be helpful, although this is uncertain because all subjects were given the same therapy. Of course, the degree of compliance with the therapy will also affect the degree of olfactory improvement, but in this study compliance was not measured so this remains uncertain. It is thought that the multidisciplinary team used here – doctor, speech therapist, and psychologist – may have contributed to the effectiveness of the therapy.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee at the Institute of Physiology and Pathology of Hearing (number KB.IFPS 7/2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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