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Clinical Trial to Assess Efficacy of Fluticasone Nasal Spray and Smell Retraining Therapy on Post COVID-19 Anosmia in Suez Canal University Hospital

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Abstract

***Background*: Most COVID-19 patients experience loss of smell, a symptom considered a hallmark of the disease. Olfactory training improves olfactory function through frequent sniffing of strong odors. Although oral corticosteroids can sometimes enhance olfactory function, their effects are frequently transient and dissipate when the medication is stopped. Intranasal steroids, however, have been associated with long-term improvement. *Aim*: To assess the efficacy of Fluticasone nasal spray and smell retraining therapy on post-COVID-19 anosmia. *Methods*: This randomized clinical trial was carried out in Suez Canal University Hospital at the ENT department from February 2022 to July 2022. Patients used Fluticasone nasal spray once daily,2 puffs per nostril (200mcg) for 3 months. Smell retraining therapy involved repeat sniffing a set of odorants (commonly lemon, rose, cloves, and eucalyptus) for 20 seconds each at least twice a day for 3 months. Patients were tested 1 month, 2 months, and 3 months from the start of treatment, and they were offered a yes or no questionnaire if they could identify various smells. History and examination were carried out in person using the questionnaire. *Results*: There was a statistically significant negative correlation between age and olfactory improvement. There was a statistically significant difference between the presence of chronic disease and olfactory improvement. There was a statistically significant positive correlation between the duration of smell loss and the start of improvement. *Conclusion*: Olfactory training and fluticasone nasal spray are effective for treating post-COVID-19 anosmia.**

Keywords: Anosmia, Olfactory Training, Steroids, Odorants.

Introduction

Olfaction is the sensation of smell. It is one of the five main human senses. The quality of life of patients is impacted by olfactory impairment. Olfactory dysfunction patients may struggle with cooking, personal cleanliness, forming social connections, and mental issues including depression. It plays a significant part in spotting danger signs associated with everyday risks like gas and chemicals[1]. Complete loss of smell is called anosmia. Numerous respiratory viral infections, particularly COVID-19 infection, are linked to this illness. The symptoms of this illness range

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from a low fever, lethargy, and cough to severe breathing difficulties and respiratory failure[2]. Since December 2019, this virus has been spreading exponentially over the entire planet. Anosmia is thought to arise in COVID-19 individuals, and in a small number of cases, it could even be the initial symptom. However, only a small number of studies evaluated a sample of lab-confirmed patients and carried out quantitative scent testing. There is little data on the occurrence, severity, and duration of anosmia in COVID-19 patients. The effectiveness of using steroids in the treatment of COVID-19-related anosmia has been demonstrated in several investigations. However, no therapy has been developed[3]. Local corticosteroids have been proposed to enhance olfactory function in addition to their anti-inflammatory actions via altering the activity of olfactory receptor neurons through effects on the olfactory Na-K-ATPase[4]. Fluticasone nasal spray significantly improved individuals with COVID-19 anosmia, according to a Singh et al.[3] study on the subject. In individuals with olfactory loss, research by Heilmann et al.[5] on the effects of topical corticosteroid treatment (mometasone nasal spray) revealed little to no impact. Numerous studies have shown that olfactory training improves olfaction in people with postinfectious olfactory impairment. Patients with chronic COVID-19-related olfactory impairment may be candidates for olfactory training because of the low cost and few side effects of this treatment[6]. This study aims to assess the efficacy of fluticasone nasal spray and smell retraining therapy on post-COVID-19 anosmia.

Patients and Methods

This study was a randomized clinical trial evaluating the efficacy of Fluticasone nasal spray and smell retraining therapy on post-COVID-19 anosmia, conducted at Suez Canal University Hospital at the ENT outpatient clinic. Patients were selected by simple random sampling technique from COVID-19 patients presented to Suez Canal University Hospital at the ENT outpatient clinic with post-COVID-19 anosmia. The study included Patients complaining of anosmia for more than 3 weeks after PCR-positive COVID-19 infection in the age range (18-50) (olfactory function deterioration starts in the fifth decade of life in healthy humans)[7]. Patients were excluded from the study if they had sino nasal disease, a history of head or nasal trauma. previous surgery for nasal polyposis or nasal neoplasms. Based on a previous placebo-controlled trial[3] in which the prevalence of the patients that restored their smell after using Fluticasone nasal spray was 93.3%, by sample size calculation,96 patients were required. However, after accounting for a 10% drop-out rate, the total required sample size will be 104 patients.

Data collection

Patients were given a yes-or-no questionnaire to see if they could identify different odors.

I. Procedures:

From February 2022 through July 2022, Suez Canal University Hospital hosted this clinical experiment. The study comprised 104 recruited individuals with impaired olfactory function for more than 3 weeks following COVID-19 infection as determined by a PCR test[8].

For three months, patients applied two 200mcg puffs of Fluticasone nasal spray once daily to each nostril[9]. A series of odorants (often lemon, rose, cloves, and eucalyptus) must be repeatedly sniffed for 20 seconds at a time, at least twice dai-

ly for three months[6]. Patients underwent testing after 1, 2, and 3 months of therapy. Patients were given a yes-or-no questionnaire to see if they could identify different odors. Smells to be tested: 1) Musky (perfume), 2) vinegar, 3) Floral (jasmine/ roses), 4) Mint.

II. Method of testing

The University of Pennsylvania smell identification test, the Sniffin Stick test, and the smell magnitude test are not available in Egypt. Instead, we used a smell identification test developed by Singh et al. to evaluate olfactory function. The test used four smells (mint, rose, musk, and vinegar). The basic substance was mixed with 5 ml of water and stored in glass bottles. For testing, paper strips containing a few drops of the scent solution were given to patients[3].

Ethical Approval

All participants' patients or family members gave their written informed consent. Each patient received a straightforward explanation of the study's purpose from the research team. Any patient received care according to best practices. All information was regarded as private and will not be shared outside of this study without the consent of the participants or their family members. Any means of communication between the researcher and the patients or their loved ones, inviting them to come back at any moment for an explanation. Each participant in this study and his family had access to the study's findings. All patients or their family members had the freedom to decline study participation or to leave the trial at any time without having to give a reason.

Statistical Analysis

The acquired data were statistically analysed using SPSS statistics for Windows (Statistical Package for the Social Sciences), version 26 (IBM, Armonk, NY, USA). The Shapiro-Wilk test was employed to determine if the data distribution was normal. Every test was run with a 95% confidence level. A P value of 0.05 or below was regarded as statistically significant. The SPSS chart builder and Microsoft Excel for Windows 2019 were used to create the charts. While categorical variables were reported as frequency and percentage, quantitative variables were expressed as mean and standard deviation. For inter-group (between participants) comparison of parametric and non-parametric continuous data without follow-up readings, independent sample T and Mann Whitney tests, respectively, were utilised. Using the cross tabs tool, the Fisher exact and Chi square tests were employed to compare nominal data between groups. We performed both univariate and multivariate regression analyses.

Results

Table 1 describes the baseline characteristics of the patients with a mean age of (34.06 ± 9.262 years) ranging from 19 to 50 years (Figure 1). The majority of participants were females 61 (63.5%) while 35 (36.5%) were males (Figure 2). majority of participants 71 (74%) had no chronic diseases, 13 (13.5%) were diabetics, 6 (6.3%) were hypertensive, and 6 (6.3%) were hypertensive and diabetics. Figure 3 shows a relevant medical history of the studied sample. The mean duration of smell loss at presentation time (6.25 ± 6.579 months) ranged from 1 to 24 months. (Figure 4). Table 2 shows that the baseline smell assessment, only 1 (1%) patient can identify vinegar, and 1 (1%) patient can identify mint. In follow-up after 1 month, it was found that 54 (56.3%) could identify

vinegar, 52 (54.2%) could identify mint,50 (52.1%) could identify musky perfume, and 44 (45.8%) could identify jasmine roses. In follow-up after 2 months, it was found that 13 (13.5%) could identify vinegar, 11 (11.5%) could identify mint,15 (15.6%) could identify musky perfume, and 13 (13.5%) could identify jasmine roses. In follow-up after 3 months, it was found that 7 (7.3%) could identify vinegar, 5 (5.2%) could identify mint, 11 (11.5%) could identify musky perfume, and 5 (5.2%) could identify jasmine roses. Table 3 demonstrated that there was statistically significant difference between the mean duration of start of improvement for each smell ($p< 0.001$).

Table 1: Patients' characteristics

All patients (n= 96)	Mean & SD	Median	Range	IQR
Age (years)	34.06 ± 9.262	32.00	19, 50	26.25, 41.00
Duration of smell loss at time of presentation (Months)	6.25 ± 6.579	3.25	1, 24	1.50, 9.75
Gender (Freq./ %)	**Male**	35	36.5%	
	Female	61	63.5%	
Chronic illness (Freq./ %)	**Absent**	71	74.0%	
	DM	13	13.5%	
	DM & HTN	6	6.3%	
	HTN	6	6.3%	

Table 4 demonstrated that there was statistically significant positive correlation between the duration of smell loss and start of musky improvement ($r= 0.246$, $p = 0.040$), the start of rose improvement ($r= 0.304$, $p = 0.011$), and the start of mint improvement ($r= 0.271$, $p = 0.023$). Table 5 demonstrated that there was a statistically significant negative correlation between age and improvement. Table 6 demonstrated that there was no statistically significant difference between gender distribution and outcome, there was a statistically significant difference between the presence of chronic disease and final outcome.

Discussion

The quality of life for COVID-19 patients who have lost their sense of smell has significantly declined. Their diminished sense of smell mostly interferes with daily activities related to olfactory functioning[10]. Studies have shown that the predominance of loss of smell in COVID-19 patients ranges from 59% to 86%[11]. So, randomized clinical trial was conducted at the ENT department of Suez Canal University Hospital to determine the effectiveness of Fluticasone nasal spray and smell retraining therapy in treating post-COVID-19 anosmia. 72.9% of the 96 patients (70 participants) who had lost their sense of smell for longer than 3 weeks following COVID-19 infection had recovered by the conclusion of the research. We used a test previously used by Singh et al for olfactory function assessment in which four odours were used (mint, rose, musk, vinegar) for testing, the basic substance was mixed with 5 ml water and kept in glass bottles.

Table 2: Baseline, after 1 month, after 2 months and after 3 months of smell assessment in the studied patients:

		Frequency	Percentage
Baseline	*Musky perfume*	0	0%
	Vinegar	1	1.0%
	Jasmine roses	0	0%
	Mint	1	1.0%
After 1 month	*Musky perfume*	50	52.1
	Vinegar	54	56.3
	Jasmine roses	44	45.8
	Mint	52	54.2
After 2 months	*Musky perfume*	13	13.5%
	Vinegar	11	11.5%
	Jasmine roses	15	15.6%
	Mint	13	13.5%
After 3 months	*Musky perfume*	7	7.3%
	Vinegar	5	5.2%
	Jasmine roses	11	11.5%
	Mint	5	5.2%

Data is expressed as percentage and frequency.

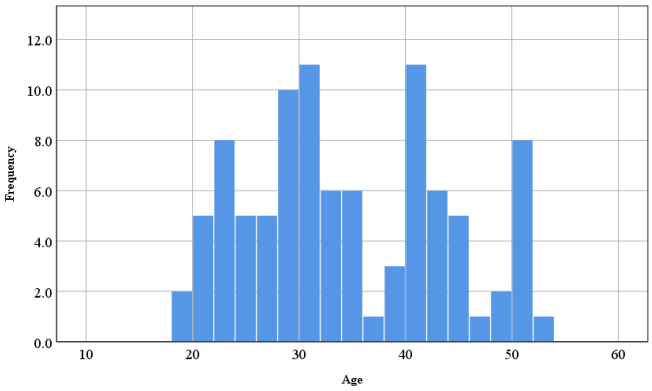

Figure 1: Age distribution of the studied sample.

The Sniffin Stick test, University of Pennsylvania smell identification test, and smell magnitude test are not available in Egypt. For testing, paper strips containing a few drops of the scent solution were given to patients[3]. Patients with impaired smell sense without a history of sinonasal illness, prior surgery for nasal polyposis, tumour, or nasal or head trauma were included in this research. All research participants' nasal endoscopies were normal. This is crucial to make sure that the therapy of the underlying sinonasal condition does not interfere with any improvement in olfactory function brought on by steroid nasal spray. A study by Fleiner et al.[12] found that combining OT with topical corticosteroid spray improved olfactory function compared to OT alone, but it was different from this study in that it also considered other causes of olfactory dysfunction, such as sinonasal diseases, post-traumatic stress disorder, and idiopathic causes. The majority of participants in the current study—61 (63.5%)—were female, whereas 35 (36.5%) were men, according to the gender distribution. Rashid et al.[13] studied 276 individuals with COVID-19 who

reported smell or taste abnormality and found that females (71%) demonstrated olfactory and taste problems more frequently than men (29%), confirming earlier research findings of a female preponderance.

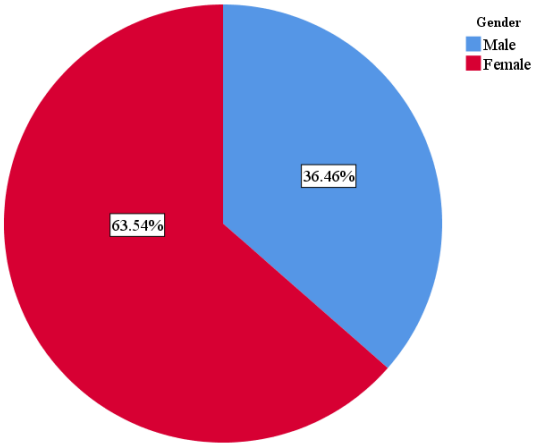

Figure (2): Gender distribution of the studied sample.

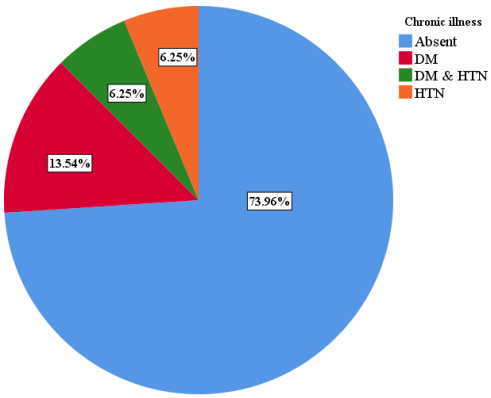

Figure (3): Relevant medical history of the studied sample.

The patients in our research had an average age of 34.06 ± 9.262 years. In the Levinson et al.[14] cohort of 42 participants with mild COVID-19, it was observed that subjects younger than 40 years showed improved olfaction more quickly than those who were older than 40 years. We found a statistically significant negative correlation between age and olfactory improvement. In the current study, there was a statistically significant difference between the presence of chronic disease and improvement in olfaction. Of the participants, 25 (26%) had chronic diseases, 13 (13.5%) were diabetics, 6 (6.3%) were hypertensive, and 6 (6.3%) were both hypertensives and diabetics. The average time for recovery of the sense of smell was 35.0 2.31 days in diabetic patients compared to 25.64 6.53 days in non-diabetic ones, according to Abdelalim et al.'s study [2], which revealed that age, diabetes, and the length of COVID-19 illness can affect the duration of anosmia/hyposmia. A statistically significant positive link between the length of scent loss and the beginning

of recovery was found in the current investigation.

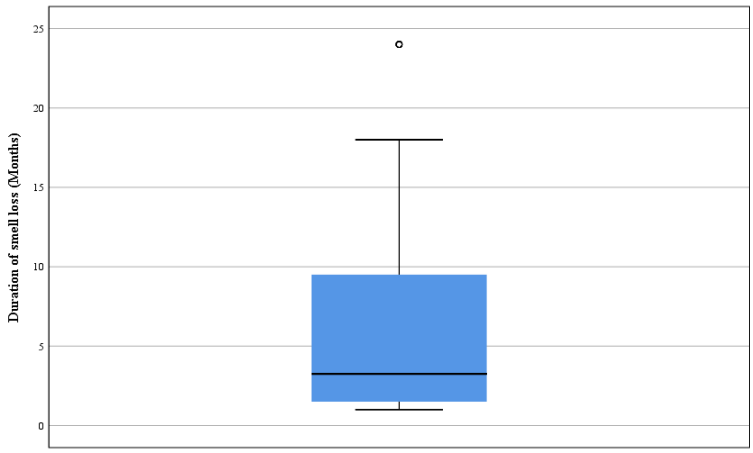

Figure 4: Box and whisker plot showing duration of smell loss at time of presentation

Table 3: The mean duration of start of improvement for each smell.		
Start of improvement (Months)	Mean ± SD	P
Start of musky improvement	1.39 ± 0.67	**< 0.001**
Start of vinegar improvement	1.30 ± 0.6	
Start of rose improvement	1.53 ± 0.76	
Start of mint improvement	1.33 ± 0.61	

P is significant when < 0.05. Test: Related samples Friedman Test.

Table 4: Relation between duration of smell loss and start of improvement.		
Duration of smell loss (Months)	Correlation coefficient	P
Start of musky improvement	0.246	**0.040**
Start of vinegar improvement	0.220	0.068
Start of rose improvement	0.304	**0.011**
Start of mint improvement	0.271	**0.023**

P is significant when < 0.05.

This was also noted in research by Vaira et al.[15], which showed that individuals whose symptoms lasted for more than 20 days following the commencement of OD were at a greater risk of long-lasting olfactory impairment. Following up after a month revealed in this study that 54 (56.3%) could identify vinegar, 52 (54.2%) could identify mint, 50 (52.1%), could identify musky scent, and 44 (45.8%) could identify jasmine flowers. Following up after two months revealed that 65 (67.7%) were able to identify vinegar, 65 (67.7%) were able to identify mint, 63 (65.6%) were able to identify musky scent, and 59 (61.5%) were able to identify jasmine odor. Following up after three months revealed that 70 participants (72.9%) could name the four scents. Similar findings were seen in Singh et al.'s[3] prospective interventional trial when 120 patients with anosmia due to COVID-19 were divided into intervention and control groups. Fluticasone intranasal spray was administered for anosmia by patients in the intervention group for five days. Compared to

the control group, the results demonstrated a considerable improvement in olfactory impairment. On day five, olfaction in the case group was 93.33% better for a musky scent, 91.67% better for a vinegar smell, 88.33% better for a flowery fragrance, and 90% better for a minty smell. Additionally, Nguyen and Patel[16] showed how topical nasal steroids capable of penetrating the olfactory cleft might enhance OT's efficacy. They claimed that improving olfactory function in those with loss of smell was more effective with budesonide nasal irrigation combined with OT than OT alone. The randomised controlled experiment by Abdelalim et al.[2] employed a different kind of steroid. To evaluate the effectiveness of mometasone furoate nasal spray on anosmia, 100 patients who had recovered from COVID-19 according to RT-PCR negative findings were included. Olfactory training was combined with a topical mometasone nasal spray (100 mcg daily) in Group 1. The other group was instructed to continue olfactory training for just three more weeks. The findings demonstrated that olfactory training outperformed the use of intranasal corticosteroids in terms of advantages. Additionally, during 4 weeks of the intervention, Mometasone Spray was assessed by Kasiri et al. (2021) in comparison to a placebo group for its ability to ameliorate post-COVID-19 anosmia. Their findings showed that there were no significant olfactory score differences between the two groups. In a further trial on corticosteroids by Rashid et al.[13], a total of 276 patients were randomly assigned to receive either 0.9% sodium chloride solution or betamethasone nasal drop three times per day for a maximum of one month.

Table 5: Correlation between age and improvement in outcome in the studied patients:

	Correlation coefficient	P
Musky perfume improvement	-0.344	**0.001**
Vinegar improvement	-0.344	**0.001**
Jasmine roses improvement	-0.344	**0.001**
Mint improvement	-0.344	**0.001**

Data is expressed as percentage and frequency.

A self-reported examination of the sense of smell revealed that the betamethasone nasal drop usage had no appreciable impact on the anosmia recovery period. According to recent reports by Miwa et al.[17] and Hura et al.[18], OT is helpful for enhancing olfactory function, particularly when started early and with good treatment compliance. The main drawback is that instructions must be given every day for several months. This research has several restrictions, as despite continuous follow-up, there may be disparities in patient adherence to occupational therapy (OT) and unavoidable little changes in how they carry out their OT at home. Also, it lacks a placebo trained control group to properly represent the treatment effects. The suggested training duration for OT at the time the study was designed was 12 weeks[19]. However, a multicenter follow-up research by Damm et al.[20] indicated that after a 32-week training session, olfactory performance had significantly improved. Future studies on the long-term effects of OT, which might provide insight into how it affects higher olfactory function, will be interested in this.

Table 6: Comparison of final outcome according to gender distribution					
		Male (n= 35)	**Female (n= 61)**	Odds ratio	P
Musky perfume	Not improved Improved	9 (25.7%) 26 (74.3%)	17 (27.9%) 44 (72.1%)	0.9	0.819
Vinegar	Not improved Improved	9 (25.7%) 26 (74.3%)	17 (27.9%) 44 (72.1%)	0.9	0.819
Jasmine roses	Not improved Improved	9 (25.7%) 26 (74.3%)	17 (27.9%) 44 (72.1%)	0.9	0.819
Mint	Not improved Improved	9 (25.7%) 26 (74.3%)	17 (27.9%) 44 (72.1%)	0.9	0.819
Chronic disease		**Absent (n= 71)**	**Present (n= 25)**	**Odds ratio**	**P**
Musky perfume	Not improved Improved	13 (18.3%) 58 (81.7%)	13 (52.0%) 12 (48.0%)	0.21	**0.001**
Vinegar	Not improved Improved	13 (18.3%) 58 (81.7%)	13 (52.0%) 12 (48.0%)	0.21	**0.001**
Jasmine roses	Not improved Improved	13 (18.3%) 58 (81.7%)	13 (52.0%) 12 (48.0%)	0.21	**0.001**
Mint	Not improved Improved	13 (18.3%) 58 (81.7%)	13 (52.0%) 12 (48.0%)	0.21	**0.001**

Conclusion

Fluticasone nasal spray and olfactory training can be considered as an effective treatment for post-COVID-19 anosmia.

Conflict of interest statement
The authors affirm that they do not have any competing interests.

Authors contribution
All authors contribute equally.

References

1. Kollndorfer K, Reichert JL, Brückler B, et al. Self-esteem as an important factor in quality of life and depressive symptoms in anosmia: A pilot study. Clin Otolaryngol. 2017 Dec;42(6):1229-34.
2. Abdelalim AA, Mohamady AA, Elsayed RA, et al. Corticosteroid nasal spray for recovery of smell sensation in COVID-19 patients: A randomized controlled trial. Am J Otolaryngol. 2021 Mar 1;42(2):102884.
3. Singh CV, Jain S, Parveen S. The outcome of fluticasone nasal spray on anosmia and triamcinolone oral paste in dysgeusia in COVID-19 patients. Am J Otolaryngol. 2021 May 1;42(3):102892.
4. Catana IV, Chirila M, Negoias S, et al. Effects of corticosteroids on hyposmia in persistent allergic rhinitis. Clujul Medical. 2013;86(2):117.
5. Heilmann S, Huettenbrink KB, Hummel T. Local and systemic administration of corticosteroids in the treatment of olfactory loss. Am J Rhinol. 2004 Jan;18(1):29-33.
6. Whitcroft KL, Hummel T. Olfactory

dysfunction in COVID-19: diagnosis and management. Jama. 2020 Jun 23;323(24):2512-4.
7. Zhang C, Wang X. Initiation of the age-related decline of odor identification in humans: a meta-analysis. Ageing Res Rev. 2017 Nov 1;40:45-50.
8. Lee Y, Min P, Lee S, et al. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J Korean Med Sci 2020 May 11;35(18).
9. Mandl M, Nolop K, Lutsky B, Participants in the 194-079 Study Group. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. Ann Allergy, Asthma & Immunol. 1997 Oct 1;79(4):370-8.
10. Elkholi SM, Abdelwahab MK, Abdelhafeez M. Impact of the smell loss on the quality of life and adopted coping strategies in COVID-19 patients. Euro Arch Oto-Rhino-Laryngol. 2021 Sep 1:1-8.
11. Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. 2020 Sep;288(3):335-44.
12. Fleiner F, Lau L, Göktas Ö. Active olfactory training for the treatment of smelling disorders. Ear, Nose & Throat Journal. 2012 May;91(5):198-215.
13. Rashid RA, Zgair A, Al-Ani RM. Effect of nasal corticosteroid in the treatment of anosmia due to COVID-19: A randomised double-blind placebo-controlled study. Am J of Otolaryngol. 2021 Sep 1;42(5):103033.
14. Levinson R, Elbaz M, Ben-Ami R, et al. Time course of anosmia and dysgeusia in patients with mild SARS-CoV-2 infection. Infect Dis. 2020 Aug 2;52(8):600-2.
15. Vaira LA, Hopkins C, Petrocelli M, et al. Smell and taste recovery in coronavirus disease 2019 patients: a 60-day objective and prospective study. J Laryngol & Otology. 2020 Aug;134(8):703-9.
16. Nguyen TP, Patel ZM. Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss. Int Forum Allergy Rhinol. 2018 Sep;8(9):977-981.
17. Miwa T, Ikeda K, Ishibashi T, et al. Clinical practice guidelines for the management of olfactory dysfunction—secondary publication. Auris Nasus Larynx, 46(5), pp.653-662.
18. Hura N, Xie DX, Choby GW, et al. Treatment of post-viral olfactory dysfunction: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2020 Sep;10(9):1065-1086
19. Hummel T, Rissom K, Reden J, et al. Effects of olfactory training in patients with olfactory loss. The Laryngoscope. 2009 Mar;119(3):496-9.
20. Damm M, Pikart LK, Reimann H, et al. Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. The Laryngoscope. 2014 Apr;124(4):826-31.