Different modalities in the management of post-COVID-19 olfactory dysfunction.

Eslam Farid Abu Shady[1], Ahmed Shehata El Sayed Saleh[1], Aymen Abdel-Aal Mohammady[1], and Moustafa Goma[1]

[1]Benha University Faculty of Medicine

July 5, 2023

Abstract

Objectives: to evaluate the effectiveness of treatment options for post-COVID-19 olfactory dysfunction. *Design:* This is a retrospective cohort study. *Setting:* ..... *Participants*: 120 patients between January 2020 and December 2022 with post-COVID-19 olfactory dysfunction (anosmia or hyposmia). *Main outcome measures:* Initial smell scores and on weeks 1,2,3,4 of treatment regimens. *Results:* 43.3% of patients were males and 56.6% were females aged from 18 to 62 years (median age was 38.5 years). 38 patients (36.3%) were hospitalized while 82 patients (68.3%) managed at home. There was a significant difference in the average time for complete recovery in group B was 25.7 ± 9.20 days and group C was 24.8± 6.67 days and group D was 23.5± 7.13 days compared to 28.97 ± 4.29 days in control group A *(P = 0.02*)*. There is no significant association between age, sex, place of management, severity of COVID-19 illness, obesity, and the duration of COVID-19 illness with smell scores and the duration of anosmia/hyposmia but there was a highly significant association with diabetes, hypertension, smoking, and asthma *(P-Value=<0.001***). Conclusion:* This study suggests that combining the usage of topical mometasone furoate or topical vitamin A or intranasal theophylline with olfactory training shortens the duration of post-COVID- 19 anosmia/hyposmia but offers no superiority regarding smell scores over olfactory training alone after 4 weeks.

Different modalities in the management of post-COVID-19 olfactory dysfunction.

Abstract

Objectives: to evaluate the effectiveness of treatment options for post-COVID-19 olfactory dysfunction.

Design: This is a retrospective cohort study.

Setting: .....

Participants : 120 patients between January 2020 and December 2022 with post-COVID-19 olfactory dysfunction (anosmia or hyposmia).

Main outcome measures: Initial smell scores and on weeks 1,2,3,4 of treatment regimens.

Results: 43.3% of patients were males and 56.6% were females aged from 18 to 62 years (median age was 38.5 years). 38 patients (36.3%) were hospitalized while 82 patients (68.3%) managed at home. There was a significant difference in the average time for complete recovery in group B was 25.7 ± 9.20 days and group C was 24.8± 6.67 days and group D was 23.5± 7.13 days compared to 28.97 ± 4.29 days in control group A (P = 0.02*) . There is no significant association between age, sex, place of management, severity of COVID-19 illness, obesity, and the duration of COVID-19 illness with smell scores and the duration of anosmia/hyposmia but there was a highly significant association with diabetes, hypertension, smoking, and asthma (P-Value=<0.001***) .

Conclusion: This study suggests that combining the usage of topical mometasone furoate or topical vitamin A or intranasal theophylline with olfactory training shortens the duration of post-COVID- 19 anosmia/hyposmia but offers no superiority regarding smell scores over olfactory training alone after 4 weeks.

Keywords: COVID-19, SARS-CoV-2, anosmia, olfaction, olfactory dysfunction.

Key points:

- Olfactory dysfunctions affect the quality of life as patients encounter problems with cooking, decreased appetite, personal hygiene, social relationships.
- The pathophysiological mechanism of anosmia and olfactory dysfunction in COVID-19 remains not fully understood.
- There is currently very little evidence for treatments, specifically for COVID-19-related olfactory dysfunction.
- This study evaluates the effectiveness of treatment options for post COVID-19 olfactory dysfunction with nasal steroid, nasal vitamin A and intranasal theophylline.
- Combining the usage of topical mometasone furoate or topical vitamin A or intranasal theophylline with olfactory training shortens the duration of post-COVID- 19 anosmia/hyposmia.

Introduction:

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2) infection. COVID-19 has wrought on public health and economic systems worldwide since January 2020. The typical clinical symptoms of COVID-19 are fever, cough, fatigue, headache, myalgia, joint pain, sore throat, olfactory dysfunction (OD), gustatory dysfunction (GD), and diarrhea **(1)**

In March 2020, Prof C. Hopkins, as President of the British Rhinological Society, published a letter describing "the loss of sense of smell as a marker of COVID-19 infection" **(2)** . The European Rhinologic Society also suggested a recommendation about "loss of smell", as a significant part of COVID-19 patient symptoms (20-60%). Loss of smell can be the presenting symptom before others (coughing, fever, and dyspnea). Patients with sudden onset olfactory loss should be aware of COVID-19 positive **(3)** .

In contrast to reports on infection by other viruses, olfactory dysfunction is associated with a relatively good prognosis in COVID-19, which suggests distinct pathological mechanisms that require further clarification **(4)** .

Olfactory dysfunctions affect the quality of life as patients with olfactory dysfunction encounter problems with cooking, decreased appetite, personal hygiene, social relationships, and emotional problems such as depression, and feeling unsafe as smell also has an important role in detecting warning of dangerous hazards in daily life such as gas, combustion smoke, and chemicals. Women are more likely to experience emotional issues such as depression, anxiety related to olfactory impairment **(5)** .

The occurrence of post-viral olfactory dysfunction is not new, most commonly occurring with rhinovirus, parainfluenza, Epstein-Barr virus, and some coronaviruses. Many viruses may lead to Olfactory dysfunctions through an inflammatory reaction of the nasal mucosa and further development of rhinorrhea. Follow-up of postviral olfactory loss revealed that over 80% of the patients reported subjective recovery after one year with 35-67% of spontaneous improvement **(6)** .

Although there is a large number of studies, the underlying pathophysiological mechanism of anosmia and olfactory dysfunction in COVID-19 remains not fully understood **(7)** .

It is hypothesized that the SARS-CoV-2 causes loss of smell by entering the supporting neural cells in the olfactory epithelium through the ACE2 receptor **(3)** .

In response, a rapid autoimmune response activates lymphocytes and macrophages and causes the release of cytokines. This autoimmune response can differ greatly between patients and may explain long-term

olfactory disorders. This inflammatory response during COVID-19 is also seen in certain brain areas, along the olfactory pathway **(8)** .

There are few established interventions for postviral olfactory dysfunction and, although several studies are being conducted, there is currently very little evidence for treatments, specifically for COVID-19-related olfactory dysfunction **(7)** .

One of the therapeutic options for olfactory disorders in COVID-19 is olfactory training. During it, the patient sniffs a set of known odors daily. Olfactory training may speed up and increase the extent of smell recovery **(9)** ; however, effects seem limited As the persistent loss of smell is thought to be caused by an inflammatory response. Corticosteroids might be a treatment option. Some studies assessed corticosteroids in nasal spray, without beneficial effect **(10)** .

Previous studies have investigated the utility of vitamin A in the treatment of olfactory dysfunction, with varying results. The first of these, a case series reported by Duncan and Briggs **(11)** , reported beneficial effect with high-dose systemic therapy**(12)** .

Vitamin A could be administered topically and this way should theoretically produce higher localized concentrations at the level of the olfactory epithelium than would be seen with the equivalent dose of systemic therapy **(12)** .

Effective treatment to correct loss of smell and taste can be established, a biochemical basis for the cause of these symptoms is decreased secretion of several growth factors (cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP)) in the saliva and nasal mucus. Growth factors act on stem cells in taste buds and olfactory epithelial cells to generate the elegant repertoire of cellular components in these sensory organs **(13)** .

Successful treatment with oral theophylline that increased nasal mucus levels of cAMP and cGMP required increased theophylline doses, duration, and endurance of adverse effects, including restlessness, gastrointestinal tract discomfort, sleep difficulties, tachycardia, and other unwanted symptoms. Theophylline treatment also required regular determinations of blood theophylline levels to ensure adequate drug absorption and lack of toxic effects. These efforts limited the use of this orally administered drug **(13)** .

Efforts to improve therapeutic efficacy and reduce adverse effects of oral theophylline administration made it logical to administer the drug intranasally. So it can affect olfactory receptors more directly without causing the systemic adverse effects associated with oral therapy**(14)** .

This study evaluates the effectiveness of treatment options for post COVID-19 olfactory dysfunction with nasal steroid, nasal vitamin A and intranasal theophylline.

Patient and methods:

This is a retrospective cohort study of 120 patients at .....

Eligibility criteria:

The time periods sampled were 'pandemic' (1 January 2020 to 5 may 2022) and 'post-pandemic'(6 may 2022 to 31 December 2022) with post-COVID-19 olfactory dysfunction (anosmia or hyposmia) who have none of the below-mentioned exclusion criteria.[**Table 1**]

This study was approved by ....., which approved the study protocol with the approval number RC-17-1-2023. The study was carried out in compliance with the Helsinki Declaration of 1975 and its amendments. A written informed consent form was obtained.

Inclusion and exclusion criteria: shown in [**Table 1**]

Table 1:Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
The age of patients ranged between 18 and 40 years.	Endoscopic or radiological evidence of nasal polypo
Patients with COVID-19 ¡ 12 weeks.	Corticosteroid use (nasal, oral, or intravenous) sinc
Negative Polymerase Chain Reaction (PCR)	Pregnant or breast-feeding females.
Patients presented with loss of smell with or without taste $>$ 4 weeks.	History of neurodegenerative disease (ie. Alzheimer
	History of an allergic reaction to theophylline or vi
	Patients with vitamin A, steroid and theophylline c

Data collection:

Patients were identified from the regional multidisciplinary team (MDT) database, which includes all patients recovered from COVID-19 infection.

Recovery of COVID-19 infection confirmed by 2 consecutive negative polymerase chain reaction (PCR) swabs. All patients were submitted for detailed endoscopic nasal examination.

The study depended on baseline visits at the outpatient clinic of ENT and follow up for 4 weeks. Patients age, sex, olfactory dysfunction onset and duration, severity of COVID infection, isolation place, hospitalization, medication used, medical history, date of confirmed positive and negative COVID swabs and potential risk factors as obesity, hypertension, diabetes mellitus, tobacco smoking and asthma were taken in consideration.

Patients allocated into four groups each group 30 patients:

- **1st group (group A)**: Control group- received isotonic saline nasal irrigation in each nostril twice daily.
- **2nd group (group B)**: received mometazone furoate nasal spray 2 puff 100mg per each nostril once daily.
- **3rd group (group C)**: received vitamin A nasal drops 2drops 10.000IU per each nostril once daily (vi-tadral, Aristo pharma Gmbh, Berlin, Germany).
- **4th group (group D)**: received nasal theophylline 400mg theophylline tablet diluted in 240 mL isotonic nasal saline in sinus rinse bottle, irrigation per each nostril twice daily.

All enrolled participants received medications for 4 weeks in addition to olfactory training in the form of sniffing of 4 different scents typically phenylethyl alcohol (rose), citronella (lemon), eugenol(clove) and eucalyptol (eucalyptus), each odorant for 15 seconds, with10 seconds rest between odorant twice daily for one month.

Olfactory function evaluation (normal smell, anosmia, hyposmia) based on patient subjective senses, visual analog scale (VAS)-smell score. This was used with familiar nonirritant substances with a distinctive odor like mint, coffee, and garlic. Score from 0 to 10, 0 means do not recognize it at all (total loss of smell) and 10 means fully recognize it (complete normal smell). This test was done before starting medications and every week for one month for all participants.

Smell loss duration was considered from the onset of olfactory dysfunction to complete recovery of the smell sensation.

Statistical analysis:

The data were recorded on an "Investigation report form". These data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 26. Descriptive statistics were calculated for the data in the form of mean and standard deviation (±SD), Median and interquartile range (IQR) and Number and percent. In the statistical comparison between the different groups, the significance of difference was tested using student's t -test to compare between mean of two groups of numerical data, for continuous non- parametric data, Mann-Whitney U- test was used for inter-group analysis, Anova to compare between mean of more than two groups of numerical data, for continuous non- parametric

data, Kruskal Wallis test was used for inter-group analysis Inter-group comparison of categorical data was performed by using chi square test (X^2- value). P value <0.05 was considered statistically significant.

Results:

Patient characteristics:

A total of 120 patients met the iclusion criteria of the study allocated into four groups of 30 patients. Among the total included and analyzed 120 adult patients, 52 patients were male (43.3%) and 68 were female (56.6%). Patient ages ranged from 18 to 62 years; the median age was 38.5 years (IQR 24.75). 38 patients (36.3%) were managed in hospital while 82 patients (68.3%) were home isolated. severity: to COVID-19 illness severity; 87 patients (72.5%) were mild, 25 patients (20.83%) were moderate, and 8 patients (6.67%) suffered severe illness. The study included 23 diabetic patients (19.1%) and 41 patients (34.2%) were hypertensive. 20 patients (16.7%) were suffering from obesity and 18 patients (15%) were asthmatic and 37 patients (30.8%) were smokers.

Regarding age and sex, all groups showed non-significant differences. There were no statistically significant differences between all groups as regards prognostic factors such as place of management, severity of COVID-19 illness, obesity as shown in **(15)** .

We found a high signigant association between other prognostic factors as; diabetes (P-Value=<0.001***) , hypertension(P-Value=<0.001***) , smoking (P-Value=<0.001***) , and asthma (P-Value=<0.001***) as shown in **(15)** .

Also, there were no statistically significant differences between the studied groups as regards the duration of COVID-19 illness (P-Value =0.5) and the duration of anosmia/hyposmia before recovery/discharge (P-Value =0.2) . There is signigant difference between the studied groups as regards Duration of anosmia/hyposmia till complete recovery (P-Value=<0.02*) . [**Table 2**]

Duration of anosmia/hyposmia and smell scores of the studied groups:

As regards duration of anosmia/hyposmia till complete recovery, the comparison between studied groups showed statistically significant difference as the average time (Mean ± SD) for complete recovery of smell in group A was 28.97± 4.29 days and was 25.70± 9.20 days among group B and 24.80±6.67among group C and was 23.50± 7.13 days among group D (P value <0.02*) . [**Table 2**]

Recovery of anosmia/hyposmia:

Regarding smell scores at recovery/discharge at the initial assessment, there was no statistically significant difference between the studied groups, (P value = 0.2) . On comparing smell scores after1 week, 2 weeks and 3 weeks of treatment, there were high statistically significant differences between the studied groups (P-values <0.001*) . But there is no significant difference after the fourth week of treatment (p value =0.6) as shown in [**Table 3**].

In group A, 17 out of 30 patients (56.6%) had their sense of smell completely recovered by the end of the fourth week, compared to 18 out of 30 patients (60%) in group B and 21 out of 30 patients (70%) in groups C and D.

Table 2 : Comparison between the studied groups.

Variant	Variant
Age (year) Mean (±SD)	Age (year) Mean (±SD
Sex NO. (%)	**Female**
	Male
Isolation place	**Home**
	Hospital
Severity	**Mild**

Variant	Variant
	Moderate **Severe**
Duration of COVID-19 illness (days) Mean (±SD)	Duration of COVID-19
Duration of anosmia/hyposmia before discharge, recovery of COVID19 illness (days) Mean (±SD)	Duration of anosmia/h
Duration of anosmia/hyposmia till complete recovery (days) Mean (±SD)	Duration of anosmia/h

Table 3: Improvements of smell scores in each group over the period of the study.

Variant	Group A	Group A	Group B	Group B	Group C	Group C	Group D	Group D	*P-va*
Initial smell score median (IQR)	5	0-5	5	0-5	0	0-5	2.5	0-5	0.2
Smell score after 1 week median (IQR)	0	0-1.25	5	0-5	2.5	0-5	5	5-5	**<0**
Smell score after 2 weeks median (IQR)	5	0-5	5	5-5	5	5-10	10	5-10	**<0**
Smell score after 3 weeks median (IQR)	5	5-10	5	5-5	10	5-10	10	5-10	**<0**
Smell score after 4 weeks median (IQR)	10	5-10	10	5-10	10	5-10	10	5-10	0.6

Table 4: Potential risk factors as prognostic factors and smell loss in total studied patients.

Variant	DM (21)	Hypertension (32)	Obesity (17)	Smok
	Yes NO 23 97	Yes NO 41 79	Yes NO 20 100	Yes N
Initial smell scores	0.002*	0.9	0.7	0.7
Smell score after 4 weeks	0.71	0.9	0.9	0.9
Duration of anosmia or hyposmia	0.3	0.3	0.6	0.3
No. of patients with complete recovery of smell after 4 weeks	**<0.001***	**<0.001***	0.4	**<0.0**

Table 5: Sex as a prognostic factor.

	Male	Female	*P-value*
Initial smell score	1.0	1.0	0.4
Score after 4weeks	6.0	6.5	0.2
Duration	28.7	28.1	0.06
N of complete recovery after 4 weeks	35from 52	41 from 68	0.1

Discussion:

Olfactory dysfunction is known to affect the quality of life as patients with olfactory dysfunction report difficulties with cooking, decreased appetite and challenges with maintaining personal hygiene and social relationships, fear of hazardous events **(5)** .

Post viral anosmia is one of the main reasons for smell dysfunction in adults (40% of cases of anosmia). Common cold viruses or upper respiratory tract infections are well known to cause post-infectious smell loss. The previously described coronaviruses are assumed to account for 10-15% of cases. So that, the COVID-19 virus supposed also to be able to cause anosmia in infected patients and if it occurs, it is not a specific finding **(16)** .

Olfactory dysfunction in COVID-19 patients, which can be the only presenting symptom or with other symptoms, but its pathogenesis is still not fully understood. It may result from viral-induced olfactory nerve damage, local inflammation of the nasal passage, or both **(17)** .

In Kanjanaumporn et al. **(3)** study, short-term smell and taste recovery rate was approximately 44-74%, which is higher than previous reports of other post-viral olfactory dysfunction such as rhinovirus, influenza, respiratory syncytial virus, and other coronaviruses. Overall, 48.6–89% of COVID-19 patients with Olfactory dysfunction experience complete remission or improvement after 4 weeks of follow-up**(18)** .

Le Bon et al. **(19)** in their systematic review showed that there is no strong evidence to support using oral and topical corticosteroids in patients with post-infection olfactory dysfunction. However other studies like Kanjanaumporn et al.**(3)** stated that topical steroid treatment has improved the chance of recovery in post-infectious olfactory dysfunction.

Our results support the results of Le Bon et al. **(19)** as no statistically significant difference in improvement after topical steroid usage combined with olfactory training in group B (60%) of patients exhibited clinical improvement by the fouth week of treatement compared to 56.6% in the control group A (olfactory training alone), and this result matches with Abdealim et al. **(20)** and Hintschich et al. **(21)** studies who suggested that using topical mometasone furoate nasal spray in the treatment of post COVID- 19 anosmia offers no benefits over olfactory training.

In a retrospective cohort study by Hummel et al. **(22)** revealed a benefit from intranasal vitamin A 10000 IU per day in addition to olfactory training in the treatment of post-infectious olfactory loss for two months of treatment.

Our resuts shows minor improvement rates in group C after combining topical vitamin A with olfactory training 70 % of patients showed clinical improvement by the end of fourth week compared to 56.6 % in the control group A but this is not significantly differed from olfactory training alone or with combined topical steroid usage after 4 weeks.

Our resuts shows inconclosive improvement rates in group D combined topical theophylline with olfactory training (70%) of patients showed clinical improvement by the end of fourth week compared to 56.6 % in the control group A and this is also not superior than olfactory training alone,combined topical steroid nor combined topical vitamin A usage after 4 weeks, and this results matches the results of Gupta et al. **(23)** and Lee et al. **(24)** studies.

By following the improvements in the study, all groups showed significant improvements over the first three weeks of the study. Comparing the smell scores between the studied groups, there was superiority for the study group (group B) of topical mometasone nasal spray, and (group C) topical vitamin A and (group D) topical theophylline over the control group (group A) olfactory training alone as the comparison of smell scores between all groups after 1 week, 2 weeks and 3 weeks of treatment, showed statistically significant differences between groups, (P-values were <0.001*) but no final significant difference between smell scores between groups after the end of the fourth week (p-value= 0.6) .

Regarding the duration of anosmia/hyposmia and the recovery rates, there was a statistically significant difference as the average time for complete recovery in group B was 25.7 ± 9.20 days and group C was 24.8± 6.67 days and in group D was 23.5± 7.13 days compared to 28.97 ± 4.29 days in the control group A (P = 0.02*) . These results show that intranasal vitamin A application and topical usage of theophylline help to shorten the duration of post-COVID-19 anosmia/hyposmia.

Our study revealed no significant association between age, sex ,place of management, severity of COVID-19 illness, obesity and the duration of COVID-19 illness with smell scores and the duration of anosmia/hyposmia in the studied groups but showed a high significant association between other prognostic factors as; diabetes (P-Value=<0.001***) , hypertension (P-Value=<0.001***) , smoking (P-Value=<0.001***) , and asthma (P-Value=<0.001***) and full recovery within 4 weeks. We found a significant positive correlation between asthma and both smell scores after 4 weeks and duration of anosmia/hyposmia p-values were 0.01* and 0.03* respectively.

These results as regards the prognostic factors differ from Esquinas-Requena et al. **(25)** , who confirmed that the only prognostic factor of persistent olfactory/taste dysfunction in COVID-19 patients was the absence of fever as they studied the prognostic factors during the period of COVID-19 illness, not after patient recovery.

Conclusion :

This study suggests that combining the usage of topical mometasone furoate or topical vitamin A or intranasal theophylline with olfactory training shortens the duration of post-COVID- 19 anosmia/hyposmia but offers no superiority regarding smell scores over olfactory training alone after 4 weeks.

Age, sex, place of management, severity of COVID-19 illness, obesity and the duration of COVID-19 illness can be rolled out as discriminative prognostic factors affecting the duration of anosmia but diabetes, hypertension, smoking and asthma can affect the full recovery within four weeks.

Funding sources:

The authors did not receive any funds for performing this study.

Disclosure statement :

The authors have no conflicts of interest regarding this publication.

Ethics and consent:

This study was approved by ....., gave approval for the study protocol with the approval number RC-17-1-2023. The study was carried out in compliance with the Helsinki Declaration of 1975 and its amendments. A written informed consent form was obtained.

References:

1. Subasty J. A Study to Assess the Effectiveness of Information Booklet on Prevention of COVID19 among Adolescents at Selected Village, Coimbatore: PPG College of Nursing, Coimbatore; 2021.

2. Hopkins C, Kumar N. Loss of sense of smell as marker of COVID-19 infection. The Royal College of Surgeons of England: British Rhinological Society. 2020:1-2.

3. Kanjanaumporn J, Aeumjaturapat S, Snidvongs K, Seresirikachorn K, Chusakul S. Smell and taste dysfunction in patients with SARS-CoV-2 infection: A review of epidemiology, pathogenesis, prognosis, and treatment options. Asian Pacific Journal of Allergy and Immunology. 2020;38(2):69-77.

4. van Eijk LE, Binkhorst M, Bourgonje AR, Offringa AK, Mulder DJ, Bos EM, et al. COVID-19: immunopathology, pathophysiological mechanisms, and treatment options. The Journal of pathology. 2021;254(4):307-31.

5. Boesveldt S, Postma EM, Boak D, Welge-Luessen A, Schopf V, Mainland JD, et al. Anosmia—a clinical review. Chemical senses. 2017;42(7):513-23.

6. Lee DY, Lee WH, Wee JH, Kim J-W. Prognosis of postviral olfactory loss: follow-up study for longer than one year. American journal of rhinology & allergy. 2014;28(5):419-22.

7. Klimek L, Hagemann J, Doge J, Freudelsperger L, Cuevas M, Klimek F, et al. Olfactory and gustatory disorders in COVID-19. Allergo journal international. 2022;31(7):243-50.

8. Li J, Liu H-H, Yin X-D, Li C-C, Wang J. COVID-19 illness and autoimmune diseases: recent insights. Inflammation Research. 2021;70:407-28.

9. Di Stadio A, D'Ascanio L, Vaira LA, Cantone E, De Luca P, Cingolani C, et al. Ultramicronized palmitoylethanolamide and luteolin supplement combined with olfactory training to treat post-COVID-19 olfactory impairment: a multi-center double-blinded randomized placebo-controlled clinical trial. Current neuropharmacology. 2022;20(10):2001-12.

10. Saussez S, Vaira LA, Chiesa-Estomba CM, Le Bon SD, Horoi M, Deiana G, et al. Short-term efficacy and safety of oral and nasal corticosteroids in COVID-19 patients with olfactory dysfunction: a European multicenter study. Pathogens. 2021;10(06):698.

11. Duncan RB, Briggs M. Treatment of uncomplicated anosmia by vitamin A. Archives of otolaryngology. 1962;75(2):116-24.

12. Hummel T, Whitcroft KL, Rueter G, Haehner A. Intranasal vitamin A is beneficial in post-infectious olfactory loss. European Archives of Oto-rhino-laryngology. 2017;274:2819-25.

13. Henkin RI, Velicu I, Schmidt L. An open-label controlled trial of theophylline for treatment of patients with hyposmia. The American journal of the medical sciences. 2009;337(6):396-406.

14. Henkin RI, Schultz M, Minnick-Poppe L. Intranasal theophylline treatment of hyposmia and hypogeusia: a pilot study. Archives of Otolaryngology–Head & Neck Surgery. 2012;138(11):1064-70.

15. Addison AB, Wong B, Ahmed T, Macchi A, Konstantinidis I, Huart C, et al. Clinical Olfactory Working Group consensus statement on the treatment of postinfectious olfactory dysfunction. Journal of Allergy and Clinical Immunology. 2021;147(5):1704-19.

16. El-Anwar MW, Elzayat S, Fouad YA. ENT manifestation in COVID-19 patients. Auris Nasus Larynx. 2020;47(4):559-64.

17. Luers J, Rokohl A, Loreck N, Wawer Matos P, Augustin M, Dewald F. Olfactory and gustatory dysfunction in coronavirus disease 19 (COVID-19) Clin Infect Dis. 2020;(May) doi: 10.1093/cid/ciaa525. Published online[Europe PMC free article][Abstract][CrossRef][Google Scholar].

18. Lv H, Zhang W, Zhu Z, Xiong Q, Xiang R, Wang Y, et al. Prevalence and recovery time of olfactory and gustatory dysfunction in hospitalized patients with COVID-19 in Wuhan, China. International Journal of Infectious Diseases. 2020;100:507-12.

19. Le Bon S-D, Konopnicki D, Pisarski N, Prunier L, Lechien JR, Horoi M. Efficacy and safety of oral corticosteroids and olfactory training in the management of COVID-19-related loss of smell. European Archives of Oto-rhino-laryngology. 2021;278:3113-7.

20. Abdelalim AA, Mohamady AA, Elsayed RA, Elawady MA, Ghallab AF. Corticosteroid nasal spray for recovery of smell sensation in COVID-19 patients: a randomized controlled trial. American journal of otolaryngology. 2021;42(2):102884.

21. Hintschich CA, Dietz M, Haehner A, Hummel T. Topical administration of mometasone is not helpful in post-COVID-19 olfactory dysfunction. Life. 2022;12(10):1483.

22. Hummel T, Whitcroft KL, Rueter G, Haehner A. Intranasal vitamin A is beneficial in post-infectious olfactory loss. European Archives of Oto-Rhino-Laryngology. 2017;274(7):2819-25.

23. Gupta S, Lee JJ, Perrin A, Khan A, Smith HJ, Farrell N, et al. Efficacy and safety of saline nasal irrigation plus theophylline for treatment of COVID-19–related olfactory dysfunction: the SCENT2 phase 2 randomized clinical trial. JAMA Otolaryngology–Head & Neck Surgery. 2022;148(9):830-7.

24. Lee JJ, Peterson AM, Kallogjeri D, Jiramongkolchai P, Kukuljan S, Schneider JS, et al. Smell Changes and Efficacy of Nasal Theophylline (SCENT) irrigation: A randomized controlled trial for treatment of post-viral olfactory dysfunction. American journal of otolaryngology. 2022;43(2):103299.

25. Esquinas-Requena JL, Lozoya-Moreno S, Garcia-Nogueras I, Atienzar-Nunez P, Sanchez-Jurado PM, Abizanda P. La anemia aumenta el riesgo de mortalidad debido a fragilidad y discapacidad en mayores: Estudio FRADEA. Atencion primaria. 2020;52(7):452-61.

Hosted file

`table 1.docx` available at https://authorea.com/users/635955/articles/653114-different-modalities-in-the-management-of-post-covid-19-olfactory-dysfunction

Hosted file

`table 2.docx` available at https://authorea.com/users/635955/articles/653114-different-modalities-in-the-management-of-post-covid-19-olfactory-dysfunction

Hosted file

`table 3.docx` available at https://authorea.com/users/635955/articles/653114-different-modalities-in-the-management-of-post-covid-19-olfactory-dysfunction

Hosted file

`table 4.docx` available at https://authorea.com/users/635955/articles/653114-different-modalities-in-the-management-of-post-covid-19-olfactory-dysfunction

Hosted file

`table 5.docx` available at https://authorea.com/users/635955/articles/653114-different-modalities-in-the-management-of-post-covid-19-olfactory-dysfunction