Therapeutic Effect of Combined Oral Vitamin A and Corticosteroid Nasal Spray in Recovery of Smell Sensation in Covid-19 Patients

Original Article

Ayman Abdelaal Mohamady, Bassem Fouad Michael, Mohamed El desoky and Islam Farid Abu Shady*

Department of Otolaryngology, Faculty of Medicine, Benha University, Benha, Egypt.

ABSTRACT

Background: Inspired air is guided by the nose's structure to the olfactory epithelium. The turbulent airflow that delivers odorants to the olfactory epithelium more effectively in the nose is initiated by sniffing, marking the beginning of the physical detection of odorants. Post viral olfactory impairment specially associated with COVID-19 is a condition with limited established treatments, and despite various ongoing studies.

Aim: To determine the impact of oral vitamin A combined with nasal steroid spray in the recovery of olfactory dysfunction (OD) in COVID-19 cases.

Patients and Methods: This randomized controlled trial was done in Otolaryngology department, Faculty of Medicine, Benha University on 120 patients diagnosed with COVID-19 infection & have olfactory dysfunction.

Results: Smell scores were significantly greater among study group I contrasted with controls after 3 weeks (8.25 ± 0.438 vs 7.45 ± 1.25) and 2 months (9.78 ± 0.261 vs 8.33 ± 1.48, *P-value < 0.001*). There was a significant increase in smell scores after patients discharge till 2 months in both groups, but the smell recovery was better in group I contrasted with group II (*p-value<0.001*). Patients achieved complete smell recovery was greater among group I contrasted with group II without significant difference.

Conclusion: The use of oral vitamin A combined with nasal steroid spray can reduce the period of post-COVID-19 anosmia/hyposmia. However, compared to olfactory training alone over four weeks, no significant smell score improvement is seen. Younger age, non-diabetic, shorter COVID-19 duration, milder severity, were discovered to be significantly correlated factors with better smell recovery.

Key Words: Anosmia, COVID-19, olfaction, olfactory dysfunction, oral Vitamin A.

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Corresponding Author: Mohamed El desoky, MSc, Department of Otolaryngology, Faculty of Medicine, Benha University, Benha, Egypt. **Tel.:** 01091154799, **E-mail**: mohamedaldisuqi@gmail.com

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INTRODUCTION

The olfactory epithelium, which is positioned high in the nasal cavity, is where inspired air is intended to be directed by the nose. Initiating the turbulent airflow that transports odorants to the olfactory epithelium located higher in the nose, sniffing signifies the start of the physical detection process. The olfactory nerve (cranial nerve I) and the trigeminal nerve (cranial nerve V) work together to provide for chemosensory perception in the nose[1].

Multiple nerve fibers and rootlets from the receptor cells make up the olfactory nerve. There must be no compromise in the whole network of cells, nerves, the bulb, the tract, the striae, and the cortex involved in smelling[2].

Multiple systems are affected by the 2019 COVID-19 illness, that is induced by the coronavirus 2 subtype that causes the severe acute respiratory syndrome. Interest in OD in asymptomatic individuals has been sparked by reports of its occurrence, which may serve as an early signal of SARS-CoV-2 infection. Intranasal inoculation of SARS-CoV-2 into the olfactory neuronal circuitry is hypothesized to be the causative cause in cases of SARS-CoV-2-related anosmia, suggesting the existence of a novel viral disease specific to COVID-19[3].

OD brought on by COVID-19 may go better on its own without any therapy at all. Nevertheless, therapy should be sought when damage lasts longer than two weeks. Lines of therapy may include olfactory training comprises repetition and purposeful smelling of a group of odorants. Patients with postinfectious OD have been treated with oral and intranasal corticosteroids to rule out an inflammatory component. Furthermore, intranasal sodium citrate, which has the potential to regulate olfactory receptor transduction cascades, intranasal vitamin A, which may stimulate olfactory neurogenesis, and intranasal vitamin C have exhibited potential as therapeutic interventions for postinfectious OD[4].

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Vitamin A could offer improvement of Covid-19 OD. The commenced dose was oral 25,000 IU daily for two weeks[5]. There has been no known link between diabetes and vitamin A[6]. However, serum vitamin A was positively and significantly correlated with both diastolic & systolic blood pressure[7].

This investigation aimed to determine the impact of combining oral vitamin A with nasal steroid spray for the recovery of Covid 19 OD cases.

PATIENTS AND METHODS:

2.1. Study Design and patients:

This study was an RCT done on 120 patients attended Otolaryngology outpatient clinics at Benha university hospitals who had COVID-19 infection and presented with OD (anosmia or hyposmia) persistent after recovery from this viral infection. The study was conducted From January 2023 to July 2023.

This research was approved by the Benha Faculty of Medicine's Ethical Committee (REC-FOMBU), Egypt. The committee granted approval for the study protocol with the identification number Ms-3-11-2022.

The cases were simply randomized (through card method) into 2 groups (Fig .1): Group I: 60 cases were subjected to oral vitamin A (25,000 IU soft gels prescribed daily for three weeks) combined with nasal steroid spray (Mometasone furoate nasal spray, formulated with an optimal dose of 2 bursts (100 µg) per nostril, once per day for a period of three weeks). In Group II, sixty patients underwent olfactory training exclusively, which consisted of twice-daily inhaling of lemon, rose, and clove essential oils for 20 seconds each.

Inclusion criteria:

Age amongst 18 and 60 years, verified diagnosis with COVID-19 infection based on clinical, radiological findings, along with real-time polymerase chain reaction (RT-PCR) results and correlated OD (Hyposmia or anosmia, with or without taste loss) persisted after recovery from COVID-19 infection (confirmed by negative PCR).

Exclusion criteria:

Age beyond the previous age range, Patients commenced on nasal steroid spray or systemic steroids, patients with OD enhanced prior to recovery from COVID-19 infection, patients with chronic nasal or sinus problems, pregnancy, patients lost at follow up and hypertensive patients.

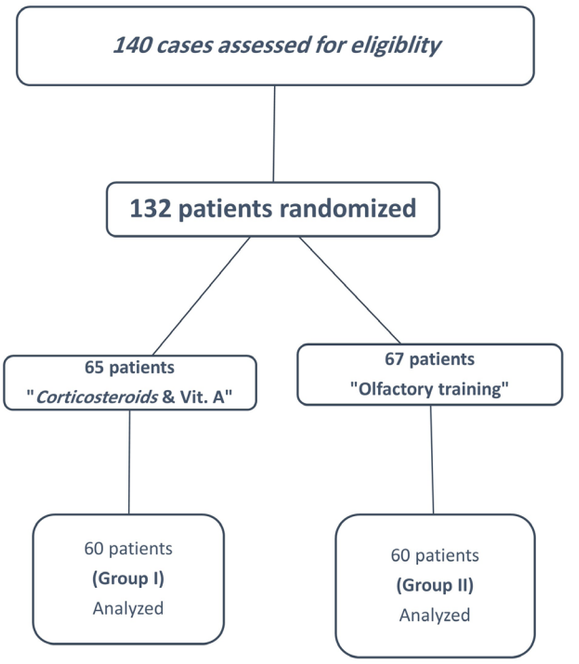

Fig. 1: Flow chart of patient selection

2.2. All patients were subjected all the following:

Complete history taking along with the duration COVID-19 infection, presence of taste disorder, manifestations of COVID-19 infection, current systemic comorbidities and review of other systems.

Complete physical examinations including Vital signs (Temperature, Heart rate, Blood pressure, Respiratory rate) & symptoms of COVID-19 complications. Complete ENT Examination. CSF rhinorrhea and sinonasal polyposis.

Olfactory function evaluation (normal smell, anosmia, hyposmia) based on patient subjective senses, smell score, visual analog scale (VAS). This was used with familiar nonirritant substances that have a detectable odor like mint, garlic, and coffee. Score from 0 to 10, 0 means do not recognize it at all (absolute lack of smell) and 10 means fully recognize it (complete normal smell). The assessment of smell was done initially after recovery/discharge, after 1 week, after 3 weeks, and after 2 months for all patients.

Anosmia duration counted from the onset of olfactory dysfunction till recovery of all olfactory function.

2.3. Statistical Analysis:

The statistical software for social sciences, version 24.0 (produced by SPSS Inc. in Chicago, Illinois, USA), was utilized in order to do the analysis on the data that was recorded. The mean, the standard deviation (SD), and the range were the three different ways that quantitative data

was expressed. The frequency and percentage of occurrence were utilized to convey the qualitative data. The arithmetic mean () and the standard deviation (SD) were utilized in order to compile a summary of the data. The following statistical analyses were utilized for the comparison: the student t-test, the Mann Whitney test, the Chi-square test (X2), the Z-test for percentage, and the odds ratio (OR).

RESULTS:

There is no significant variance among the groups concerning demographic data (age, BMI and gender). In group I the mean age was 47.76 ± 9.85 years, there were 34 (56.7%) females. In group II the mean age was 48.1 ± 7.65 years & there were 30 (50%) females. There was no significant distinction among the groups concerning demographic data. (Table 1)

There was no significant variance among the groups concerning comorbidities. (Figure 2)

There was no significant variance among the groups concerning Severity of COVID-19. (Figure 3)

There was no significant variance among the groups concerning heart rate, RR, SBP, and DBP. (Table 2)

Our study results showed no significant variance among the groups concerning COVID-19 duration and anosmia/hyposmia duration before recovery. In group I, the mean COVID-19 duration was 9.5 ± 5.63 days and the mean anosmia/hyposmia duration before discharge was 8.27 ± 2.83 days. In group II, the mean COVID-19 duration was 9.16 ± 5.82 days and the mean anosmia/hyposmia duration before discharge was 7.93 ± 2.48 days. There was no significant variance among the groups concerning COVID-19 duration and anosmia/hyposmia duration before recovery. (Table 3)

Our results showed that visual analogue score (VAS) after 3 weeks and 2 months was significantly greater among group I contrasted with group II. In group 1 VAS score initially after discharge was 2.54 ± 0.747, after 1 week was 5.63 ± 0.562, after 3 weeks was 8.25 ± 0.438 and after 2 months was 9.78 ± 0.261. In group 2 VAS score initially after discharge was 2.71 ± 0.763, after 1 week was 5.47 ± 0.607, after 3 weeks was 7.45 ± 1.25 and after 2 months was 8.33 ± 1.48. Moreover, there was a significant increase in smell VAS from discharge till 2 months after in both groups, but Recovery was more favorable in group I compared to group II. VAS after 3 weeks and 2 months was significantly greater among group I contrasted with group II. Moreover, there was a significant increase in smell VAS from discharge till 2 months after in both groups, but the recovery was improved in group I compared to group II. (Table 4)

Anosmia/hyposmia duration till recovery was significantly greater among group I contrasted with group II. However, percentage of patients achieved complete smell recovery was superior among group I contrasted with group II but without statistically significant variance. (Table 5)

Younger age, non-diabetic, small COVID-19 duration, mild severity, and vitamin A administration were discovered to be significantly correlated factors with smell recovery. (Table 6)

Table 1: Demographic distribution between the two studied groups.

		Group I (n=60)	Group II (n=60)	t/$\square^2$	*P*
Age (years) Mean ± SD		47.76 ± 9.85	48.1 ± 7.65	.211	*.833*
BMI (kg/m^2) Mean ± SD		27.45 ± 2.73	27.12 ± 2.96	.634	*.527*
Gender	Female	34 (56.7%)	30 (50%)	.536	*.464*
	Male	26 (43.3%)	30 (50%)		

Table 2: Vital sings distribution between the two studied groups.

	Group I (n=60)	Group II (n=60)	t	*P*
Heart rate (beat/min) Mean ± SD	87.42 ± 12.96	84.66 ± 11.47	1.24	*.219*
Respiratory rate (breath/min) Mean ± SD	16.5 ± 2.96	17.13 ± 3.24	1.11	*.268*
SBP (mmHg) Mean ± SD	121.7 ± 10.23	120.5 ± 9.53	.665	*.508*
DBP (mmHg) Mean ± SD	73.3 ± 6.89	71.87 ± 6.63	1.16	*.249*

Table 3: Clinical characteristics distribution between the two studied groups.

	Group I (n=60)	Group II (n=60)	MW	*P*
COVID-19 duration (days) Mean ± SD	9.5 ± 5.63	9.16 ± 5.82	425	*.756*
Anosmia/hyposmia duration before discharge (days) Mean ± SD	8.27 ± 2.83	7.93 ± 2.48	866	*.454*

Table 4: Smell visual analog scale distribution between the two studied groups.

	Group I (n=60)	Group II (n=60)	t	*P*
Initially after discharge Mean ± SD	2.54 ± 0.747	2.71 ± 0.763	1.23	*.220*
After one week Mean ± SD	5.63 ± 0.562	5.47 ± 0.607	1.48	*.140*
After 3 weeks Mean ± SD	8.25 ± 0.438	7.45 ± 1.25	4.68	*<0.001*
After 2 months Mean ± SD	9.78 ± 0.261	8.33 ± 1.48	7.47	*<0.001*

Table 5: Follow up clinical characteristics between the two studied groups.

	Group I (n=60)	Group II (n=60)	t/□²	*P*
Rate of smell recovery				
Yes	39 (65%)	31 (51.7%)	2.19	*.139*
No	21 (35%)	29 (48.3%)		
Anosmia/hyposmia duration till recovery (days) Mean ± SD	32.49 ± 8.75	36.26 ± 9.66	2.24	*.027*

Table 6: Multivariate regression analysis to determine the potential factors affecting/associated with smell recovery.

	OR	S.E.	Sig.	95% Confidence Interval for OR
Age	1.063	.152	.015	1.021 - 1.122
Male gender	2.264	.089	.164	.649 – 4.164
No DM	.913	.062	.003	.716 - .943
No Smoking	2.046	.043	.466	.837 – 7.232
COVID-19 duration	2.233	.046	.024	.495 – 3.642
COVID-19 severity	3.641	.072	.002	1.326 – 7.161
Anosmia/hyposmia duration	2.014	.018	.096	.730 - 3.193
Vitamin A	1.134	.153	.017	.854 - 1.644

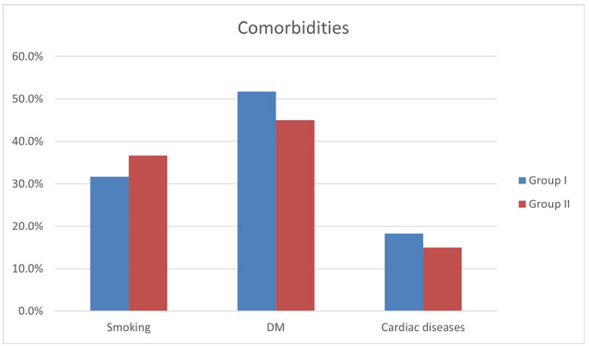

Fig. 2: Comorbidities distribution between the two studied groups.

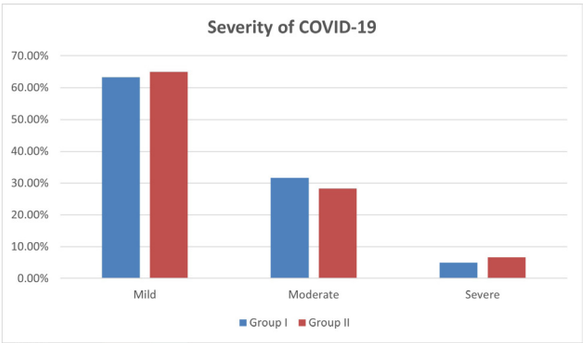

Fig. 3: Severity of COVID-19.

DISCUSSION

Since the initial case was identified in December 2019 in Wuhan, China, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been the causative agent of coronavirus disease 2019 (Covid-19)[8].

Patients with COVID-19 exhibited a greater impairment in olfactory function contrasted with those with upper respiratory tract infections. While the majority of patients would likely recover completely, a subset of them would presumably develop permanent post-viral olfactory dysfunction (PVOD). Patients who have upper respiratory infections as a result of viruses involving rhinovirus, parainfluenza, or other coronaviruses are already known to exhibit this characteristic[9].

The results of our study align with the objectives of Kasiri *et al*., whose aim was to evaluate the effectiveness of mometasone furoate nasal spray in promoting the recovery of patients suffering from severe microsmia or anosmia caused by COVID-19. They found no statistically significant distinctions in age or gender among the two groups[10].

Our clinical results discovered that that there was no significant variance among the Studied groups concerning comorbidities. In group 1; there 31.7% of patients were smokers, 51.7% had DM and 18.3% had cardiac disease. In group 2; there 36.7% of patients were smokers, 45% had DM and 15% had cardiac disease.

Our results are in line with Abdelalim *et al*. who stated that there were no statistically significant differences between studied groups regarding diabetes melitus[11].

Our present research shows that there was no significant distinction among the groups relating to heart rate, RR, SBP, and DBP. There was no significant difference among the groups concerning laboratory parameters (HB, TLC, PLTs, RBS, ALT, AST, serum albumin, total bilirubin, creatinine, ESR and CRP).

Our results are matching Kasiri *et al*. Results as there was no statistically significant variance among the intervention & control groups as regards HB, TLC, ESR, PLTS and CRP with P-value = (0.705, 0.854, 0.200, 0.867and 0.753) respectively[10].

Our current study showed no significant variance among studied groups concerning severity of COVID symptoms. In group 1; 63.3% with mild symptoms, 31.7% were moderate and 5% suffered severe symptoms. In group 2; 65% of patients were mild, 28.3% moderate and 6.7% had severe symptoms.

Our result supported with Abdelalim *et al*. As there was no statistically significant variances among group I & group II concerning the severity of COVID-19 symptoms throughout studied groups[11].

Our result disagrees with Rashid *et al*. who stated shorter duration of anosmia of their study group (betamethasone group) the median clinical duration of anosmia to involvement was 5 (3–6) days[12].

Our results in consistent with Kasiri *et al*. study as they showed significant statistical difference between studied momentasone and olfactory training alone regarding Smell Scores after one, two, three, and four weeks (*p: 0.318, <0.001, <0.001, <0.001,* respectively)[10].

Moreover, our result disagrees with Hosseinpoor *et al*. they reported that in the intervention group using mometasone furoate nasal spray the mean VAS score initial and following 2 weeks was 1.73 ± 1.55, VAS score initial and afterward 4 weeks was 4.66 ±2.36 and VAS score following 2 & 4 weeks was 2.27 ± 2.09. This difference was due to, there were 5.7% of their patients had DM and in our study, there were 51.7 % of patients were diabetics[13].

Furthermore, Le Bon *et al*. they stated that the olfactory score of the group that received oral steroids in conjunction with olfactory training improved significantly, surpassing the minimum clinically significant difference for subjective improvement of scent (*p-value = 0.007*). Merely through olfactory conditioning[14].

Our current study showed that regarding follow up clinical characteristics between the studied groups. Rate of smell recovery in group 1 was 39 (65%), mean anosmi/hyposmia duration till recovery was 32.49 ± 8.75 days. In group 2 Rate of smell recovery in group 1 was 31 (51.7%), mean anosmia/hyposmia duration till recovery was 36.26 ± 9.66 days, anosmia/hyposmia duration till recovery was significantly higher among group I (Patients who subjected to oral vitamin A) compared to group II (patients who subjected to olfactory training alone). However, percentage of patients achieved complete smell recovery was greater among group I contrasted group II but without statistically significant difference.

Hopkins *et al*. said that while alpha lipoic acid was not advised, olfactory training was suggested for all cases who experienced prolonged loss of scent for a duration exceeding two weeks[15].

Our current study showed that younger age, non-diabetic, shorter COVID-19 duration, milder symptoms and vitamin A administration were observed to be significantly correlated factors with smell recovery.

Our results consistent with Rashid *et al*. who stated that in betamethasone group, age is a critical differentiating element that impacts the duration of recovery (*P-value = 0.001*)[12].

Moreover, our results disagree with Reden *et al*. who reported that vitamin A had no specific influence on regeneration of olfactory function contrasted with placebo[16].

CONCLUSION

The utilization of oral vitamin A combined with nasal steroid spray can reduce the period of post-COVID-19 anosmia/hyposmia. However, compared to olfactory training alone over four weeks, no significant smell score improvement is seen. Younger age, non-diabetic, shorter COVID-19 duration, milder severity, were observed to be significantly related factors with better smell recovery. Further studies with larger inclusion numbers are needed to asses our study results.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Patel RM, Pinto JM. Olfaction: anatomy, physiology, and disease. Clin Anat. 2014; 27:54-60.

2. Crespo C, Liberia T, Blasco-Ibáñez JM, Nácher J, Varea E. Cranial Pair I: The Olfactory Nerve. Anat Rec (Hoboken). 2019;302:405-27.

3. Han AY, Mukdad L, Long JL, Lopez IA. Anosmia in COVID-19: Mechanisms and Significance. Chem Senses. 2020.

4. Whitcroft KL, Hummel T. Olfactory Dysfunction in COVID-19: Diagnosis and Management. Jama. 2020;323:2512-4.

5. Chen M, Reed RR, Lane AP. Chronic Inflammation Directs an Olfactory Stem Cell Functional Switch from Neuroregeneration to Immune Defense. Cell Stem Cell. 2019;25:501-13.e5.

6. Trasino SE, Gudas LJ. Vitamin A: a missing link in diabetes? Diabetes Manag (Lond). 2015; 5:359-67.

7. Chen J, He J, Hamm L, Batuman V, Whelton PK. Serum antioxidant vitamins and blood pressure in the United States population. Hypertension. 2002;40:810-6.

8. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020;55:105924.

9. Huart C, Philpott CM, Altundag A, Fjaeldstad AW, Frasnelli J, Gane S, *et al*. Systemic corticosteroids in coronavirus disease 2019 (COVID-19)-related smell dysfunction: an international view. Int Forum Allergy Rhinol. 2021;11:1041-6.

10. Kasiri H, Rouhani N, Salehifar E, Ghazaeian M, Fallah S. Mometasone furoate nasal spray in the treatment of patients with COVID-19 olfactory dysfunction: A randomized, double blind clinical trial. Int Immunopharmacol. 2021;98:107871.

11. 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. Am J Otolaryngol. 2021;42:102884.

12. 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 Otolaryngol. 2021;42:103033.

13. Hosseinpoor M, Kabiri M, Rajati Haghi M, Ghadam Soltani T, Rezaei A, Faghfouri A, *et al*. Intranasal Corticosteroid Treatment on Recovery of Long-Term Olfactory Dysfunction Due to COVID-19. Laryngoscope. 2022;132:2209-16.

14. Le Bon SD, 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. Eur Arch Otorhinolaryngol. 2021;278:3113-7.

15. Hopkins C, Alanin M, Philpott C, Harries P, Whitcroft K, Qureishi A, *et al*. Management of new onset loss of sense of smell during the COVID-19 pandemic - BRS Consensus Guidelines. Clin Otolaryngol. 2021;46:16-22.

16. Reden J, Lill K, Zahnert T, Haehner A, Hummel T. Olfactory function in patients with postinfectious and posttraumatic smell disorders before and after treatment with vitamin A: a double-blind, placebo-controlled, randomized clinical trial. Laryngoscope. 2012;122:1906-9.