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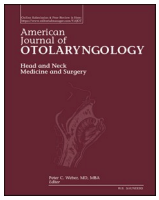

Corticosteroid nasal spray for recovery of smell sensation in COVID-19 patients: A randomized controlled trial

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ABSTRACT

Objectives: To evaluate the role of the topical corticosteroid, mometasone furoate, nasal spray in the treatment of post COVID-19 anosmia.

Methods: A prospective, randomized, controlled trial was conducted among patients with post COVID-19 anosmia. One hundred patients were randomly assigned to two groups; group I included 50 patients received mometasone furoate nasal spray in an appropriate dose of 2 puff (100 μg) once daily in each nostril for 3 weeks with olfactory training, group II included 50 patients were advised to keep on olfactory training only. The assessment of smell was done using (Visual Analog Scale from 0 to 10). All patients were initially evaluated after their recovery from COVID-19 and followed up for 3 weeks. The smell scores were recorded weekly and the duration of smell loss was recorded from the onset of anosmia till the full recovery.

Results: In both groups, the smell scores significantly improved by the end of the third week ($P < 0.001$). By comparing smell scores between both groups after 1 week, 2 weeks, and 3 weeks of treatment, there were no statistically significant differences between both groups. In group I, (62%) of patients completely recovered their sense of smell after 3 weeks of treatment, compared to (52%) of patients in group II ($P = 0.31$).

Conclusion: The results suggested that using mometasone furoate nasal spray as a topical corticosteroid in the treatment of post COVID-19 anosmia offers no superiority benefits over the olfactory training, regarding smell scores, duration of anosmia, and recovery rates.

Trial registration: ClinicalTrials.gov ID: NCT04484493

1. Introduction

In December 2019, there was an infectious outbreak in Wuhan in the Hubei Province of China. The etiology for this outbreak was a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was responsible for the Corona Virus Disease 2019 (COVID-19) [1]. Globally, as of 5 November 2020, more than 47 million cases have been reported across 188 countries and territories, resulting in more than 1.2 million deaths, reported to WHO [2].

Patients with COVID-19 infection mainly present by symptoms of the lower respiratory tract such as fever, cough, dyspnea, and chest tightness [3], some patients may present with upper respiratory symptoms such as sore throat, nasal congestion, rhinorrhea, and olfactory dysfunction [4].

ENTUK (British Association of Otorhinolaryngology-Head and Neck Surgery) released an update in April 2020 that they remain confident during the current COVID-19 pandemic, a patient presenting with new-onset anosmia, in the absence of a head injury or nasal obstruction, should be considered likely to have COVID-19 infection [5]. Also, ERS (European Rhinologic Society) released a recommendation about "loss of smell", as a significant part of COVID-19 patient symptoms (20–60%). In COVID-19 patients, loss of smell can be the presenting symptom before others (coughing, fever, and dyspnea). Patients with sudden onset loss of smell should be considered to be COVID-19 positive [6].

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; rRT-PCR, real-time reverse transcription-polymerase chain reaction; IQR, inter-quartile range; DM, diabetes mellitus; HTN, hypertension; VAS, visual analog scale.

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The olfactory dysfunction affects the quality of life of patients. Individuals with olfactory dysfunction may encounter some problems with cooking, personal hygiene, social relationships, and emotional problems such as depression. The smell has an important role in detecting warnings of dangerous hazards in daily life such as gas and chemicals [7]. Post-viral olfactory dysfunction is one of the most common causes of olfactory loss. Based on the available evidence, olfactory training is the recommendation for the treatment of post-viral olfactory dysfunction [8].

Besides the anti-inflammatory mechanism of action, local corticosteroids have been hypothesized to improve olfactory function by modulating the function of olfactory receptor neurons through effects on the olfactory Na-K-ATPase [9]. In 2004, Heilmann et al. [10] studied the effects of systemic and topical administration of corticosteroids in patients with olfactory loss in a comparative study, they found improvement of the sense of smell after local administration of mometasone nasal spray. The improvement of olfactory function is found with different causes of olfactory dysfunction; idiopathic, upper respiratory tract infections, sinonasal disease, or posttraumatic.

Although there is no evidence-based indication for intranasal corticosteroid for treatment of COVID-19 hyposmia or anosmia, Vroegop et al. [11] based on expert opinion, recommended the use of intranasal corticosteroids, with a preference for spray formulation over gel or drops.

We aimed in this study to evaluate the role of the topical corticosteroid, mometasone furoate, nasal spray in the treatment of anosmia/hyposmia in patients recently recovered from COVID-19 infection.

2. Patients and methods

2.1. Study design and patients

This was a prospective, randomized, controlled trial conducted at Benha University Hospital, Benha faculty of medicine, Benha, Egypt; during the period between August and November 2020. This study was submitted on patients who recently recovered from proven COVID-19 infection and complaining of anosmia or hyposmia. The proven COVID-19 infection was based on a positive real-time reverse transcription-polymerase chain reaction (rRT-PCR) with samples obtained by a nasopharyngeal swab. The recovery was defined as 2 consecutive negative (rRT-PCR) samples.

Adults 18 years or older patients were included in the study if; a confirmed case (positive PCR), recovered/discharged (2 negative PCR), suffering from sudden recent anosmia or hyposmia with or without loss of taste, and was either hospitalized or managed as home isolated. We excluded patients from the study if; a patient is already on a nasal steroid or with previous chronic rhinological pathologies, patients on a systemic steroid for a previous systemic disease, patients with anosmia improved before COVID-19 recovery, pregnancy, or patients who did not complete the follow up period.

All patients signed their written informed consent to participate. The study was performed in accordance with the Helsinki Declaration of 1975 and its amendments, the study protocol was approved by the Research Ethics Committee at Faculty of Medicine, Benha University (REC-FOMBU), Egypt with approval number RC4.7.2020.

2.2. Initial assessment and evaluation

Complete medical history was taken including; age, sex, duration, severity of COVID-19 illness, and place of isolation. Also, we recorded the risk factors such as diabetes mellitus (DM), hypertension (HTN), and if the patient had received systemic steroids during the treatment course. Essential clinical assessment and examination with an appropriate protective measures were performed for all participants.

2.3. Lines of treatment

The participants in this study were randomly assigned to two groups (simple 1:1 randomization); in group I (study group), 50 patients received topical corticosteroid nasal spray (mometasone furoate nasal spray) in an appropriate dose of 2 puff (100 μg) once daily in each nostril for 3 weeks with olfactory training. Olfactory training, as recommended by Whitcroft and Hummel [12], was advised in the form of sniffing of rose, lemon, and clove for 20 seconds each, twice a day. The other 50 patients, who were assigned to group II (control group) did not receive topical corticosteroid nasal spray but only the olfactory training.

2.4. Follow up

As regards the assessment of smell, the patient assessed his smell sensation with "a visual analog scale (VAS)-smell score" using familiar substances with a distinctive odor, with caution to avoid any irritants like bleach or ammonia. We recommended some substances like; mint, coffee, and garlic. The patient reported the degree of anosmia/hyposmia subjectively with a visual analog scale (VAS) from 0 to 10 (0 means total loss of smell and 10 refers to completely normal smell sensation). The assessment of smell was done initially after recovery/discharge, after 1 week, after 2 weeks, and after 3 weeks for all patients. The duration of smell loss was recorded from the onset of anosmia/hyposmia till full recovery of the sensation.

2.5. Statistical analysis

Obtained data were statistically analyzed using SPSS version 16 software (SPSS Inc., Chicago, IL, USA). "Chi-square" test was used to analyze categorical data. While "Mann-Whitney U" test, was used to analyze quantitative data. The "Wilcoxon signed-rank" test is used to compare repeated measurements on a single sample. Spearman's "Rho" test as a non-parametric test used to measure the association between two variables, where $r = 1$ means a perfect positive correlation and $r = -1$ means a perfect negative correlation. P-value ≤ 0.05 was considered the accepted level of significance in this work.

3. Results

A total of 108 patients were enrolled in the study and were randomly allocated in the two groups, 4 patients in each group were lost and excluded during the follow up period, and 50 patients in each group were analyzed [Fig. 1].

Among the total included and analyzed 100 adult patients, 46 patients were male (46%) and 54 were female (54%). Patient ages ranged from 18 to 61 years, the median age was 29.0 years (IQR 21.75–38.0). 31 patients (31%) were managed in hospital while 69 patients (69%) were home isolated. According to COVID-19 illness severity; 70 patients (70%) were mild, 24 patients (24%) were moderate and 6 patients (6%) had suffered severe illness. The study included 16 diabetic patients (16%) and 14 patients (14%) were hypertensive. 13 patients (13%) had received systemic steroids during the course of treatment of COVID-19 illness and stopped it with the recovery/discharge.

Regarding age and sex, both groups were matched with non-significant differences. As shown in [Table 1], there were no statistically significant differences between both groups as regards prognostic factors such as; severity of COVID-19 illness, diabetes, hypertension, and receiving systemic steroids during treatment of COVID-19. Also, there were no statistically significant differences between group I and group II as regards the duration of COVID-19 illness and the duration of anosmia/hyposmia before recovery/discharge ($P > 0.05$).

As shown in [Table 1], as regards smell scores at recovery/discharge at the initial assessment, there was no statistically significant difference between both groups, the median score was 2.0 (IQR 0.5–5.0) in both groups ($P = 0.47$). By comparing smell scores between both groups after

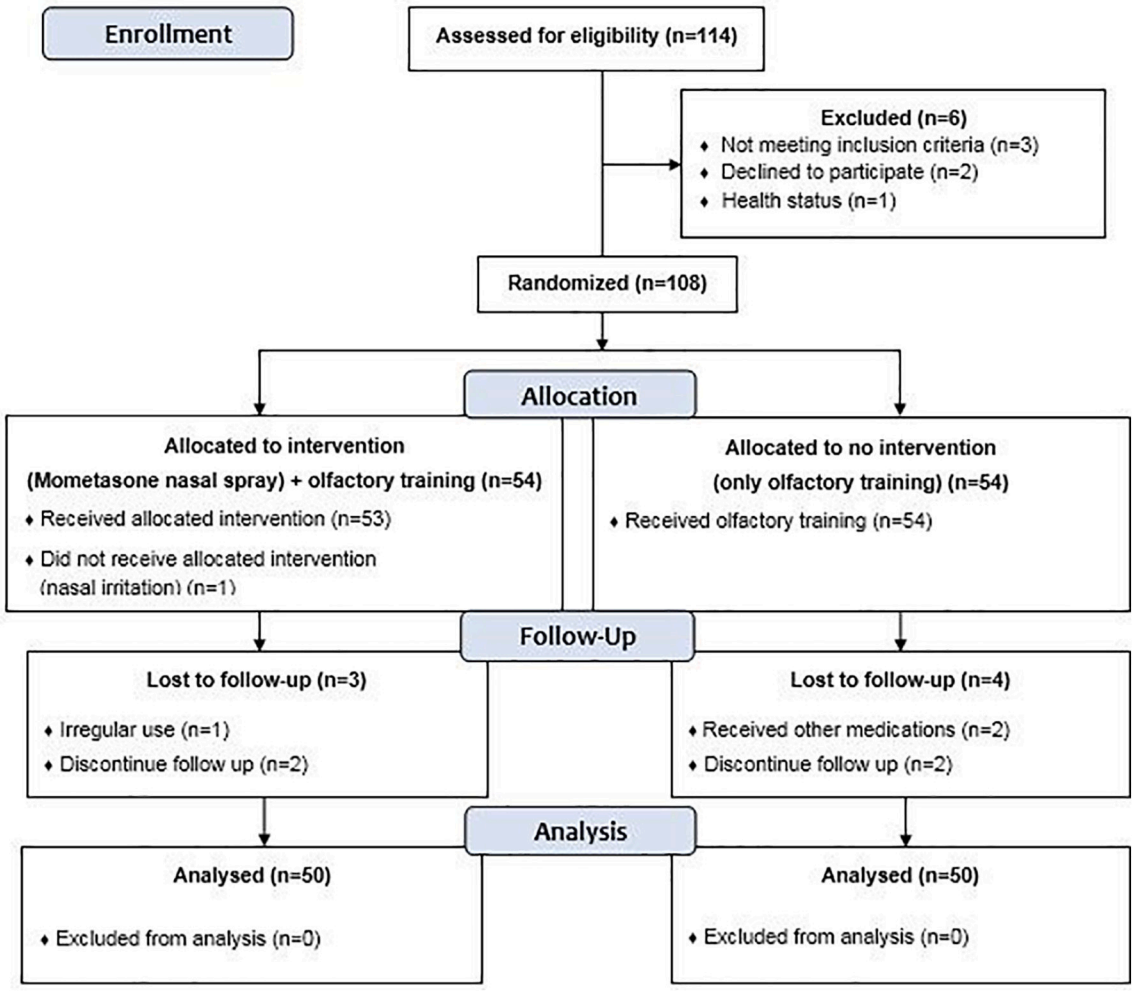

Fig. 1. CONSORT flow diagram.

1 week, 2 weeks and 3 weeks of treatment, there were no statistically significant differences between both groups, *P*-values were (0.10, 0.08 and 0.16) respectively. As regards duration of anosmia/hyposmia till complete recovery, the comparison between both groups showed no statistically significant difference as the average time (Mean ± SD) for complete recovery of smell in group I was 26.41 ± 7.99 days and was 26.15 ± 5.07 days among group II ($P = 0.88$). In group I, 31 out of 50 patients (62%) had their sense of smell completely recovered by the end of the third week, compared to 26 out of 50 patients (52%) in group II ($P = 0.31$). Totally the average time for complete recovery of smell was 26.29 ± 6.76 days and the recovery rate was (57%) by the end of the third week.

[Table 2] summarized the comparison between smell scores in each group over the period of the study; in both groups, there were significant improvements over the period of the study. In group I, the median of smell scores was 2.0 (IQR 0.5–5.0) initially and by the end of the third week it improved to 10.0 (IQR 9.0–10.0) ($P < 0.001$). In group II, the median of smell scores was 2.0 (IQR 0.5–5.0) initially and improved to 10.0 (IQR 5.0–10.0) by the end of the third week ($P < 0.001$).

For the all 100 patients analyzed in the study, we studied some prognostic factors which may affect anosmia/hyposmia caused by COVID-19. As shown in [Fig. 2], there was a statistically significant positive correlation between age and only the duration of anosmia/hyposmia ($P = 0.004$), and not the degree of smell loss (smell scores over the period of study). Also, there was a statistically significant positive correlation between the duration of COVID-19 illness and the duration of anosmia/hyposmia ($P < 0.001$).

There were no significant differences between males and females as regards smell loss scores and duration of anosmia/hyposmia [Table 3]. Diabetes significantly affect the duration of anosmia till complete recovery, 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 ($P = 0.006$). Receiving systemic steroids during the treatment course of COVID-19 illness seemed not significantly affecting either scores of smell loss or the duration of anosmia/hyposmia.

4. Discussion

Olfactory function as a part of the chemosensory system is important for digestive behavior as it helps to detect and enjoy food, and important for social communication besides the detection of environmental hazards [13]. Post-viral anosmia is one of the main causes of olfactory dysfunction in adults (40% of cases of anosmia). Common cold or upper respiratory viral infections are well-known causes of post-infectious smell loss [14].

Olfactory dysfunction is a characteristic finding of COVID-19 patients, which can be the only symptom or with other symptoms, but its pathogenesis is still not well understood. It may result from viral-induced olfactory nerve damage, local inflammation of the nasal cavity, or both [15].

Prescribing corticosteroids in COVID-19 olfactory dysfunction is still in question [16]. As for the treatment, until now experts and the first reports suggest recovery of anosmia, but data are still limited. Administering topical nasal corticosteroids in post COVID-19 anosmia remains

Table 1
Comparison between the studied groups.

Variant	Group I N (50)	Group II N (50)	*P* Value
Sex N (%)			0.69
Male	24 (48.0)	22 (44.0)	
Female	26 (52.0)	28 (56.0)	
Age, year Median (IQR)	28.0 (20.5–38.0)	30.0 (22.5–39.0)	0.71
Isolation place N (%)			0.52
Hospital	17 (34.0)	14 (28.0)	
Home	33 (66.0)	36 (72.0)	
Severity of COVID-19 illness N (%)			0.36
Mild	32 (64.0)	38 (76.0)	
Moderate	15 (30.0)	9 (18.0)	
Severe	3 (6.0)	3 (6.0)	
DM N (%)	8 (16.0)	8 (16.0)	1.0
HTN N (%)	6 (12.0)	8 (16.0)	1.0
Received systemic steroids N (%)	5 (10.0)	8 (16.0)	1.0
Duration of COVID-19 illness, day Median (IQR)	16.0 (11.5–22.0)	14.0 (12.0–20.5)	0.57
Duration of anosmia/hyposmia before recovery/discharge, day Median (IQR)	12.0 (10.0–16.0)	11.0 (9.0–15.5)	0.38
Initial smell score Median (IQR)	2.0 (0.5–5.0)	2.0 (0.5–5.0)	0.47
Smell score after 1 week Median (IQR)	5.0 (2.0–5.0)	2.0 (1.0–5.0)	0.10
Smell score after 2 weeks Median (IQR)	7.0 (5.0–10.0)	5.0 (2.0–8.0)	0.08
Smell score after 3 weeks Median (IQR)	10.0 (9.0–10.0)	10.0 (5.0–10.0)	0.16
Duration of anosmia/hyposmia till complete recovery, day Mean ± SD	26.41 ± 7.99	26.15 ± 5.07	0.88
Patients completely recovered the smell after 3 weeks N (%)			
NO	19 (38.0)	24 (48.0)	0.31
YES	31 (62.0)	26 (52.0)	

Table 2
Improvements of smell scores in each group over the period of the study.

Groups	Initial smell score median (IQR)	Smell score after 1 week median (IQR)	Smell score after 2 weeks median (IQR)	Smell score after 3 weeks median (IQR)
Group I N (50)	2.0 (0.5–5.0)	5.0 (2.0–5.0)	7.0 (5.0–10.0)	10.0 (9.0–10.0)
$Z1_{Wilcoxon}$ (*p*1)		2.82 (0.005)	4.03 (< 0.001)	4.39 (< 0.001)
$Z2_{Wilcoxon}$ (*p*2)			3.85 (< 0.001)	4.22 (< 0.001)
$Z3_{Wilcoxon}$ (*p*3)				3.65 (< 0.001)
Group II N (50)	2.0 (0.5–5.0)	2.0 (1.0–5.0)	5.0 (2.0–8.0)	10.0 (5.0–10.0)
$Z1_{Wilcoxon}$ (*p*1)		2.21 (0.027)	4.14 (<0.001)	4.39 (< 0.001)
$Z2_{Wilcoxon}$ (*p*2)			3.96 (<0.001)	4.13 (<0.001)
$Z3_{Wilcoxon}$ (*p*3)				3.84 (<0.001)
All cases N (100)	2.0 (0.75–5.0)	3.5 (1.0–5.0)	5.0 (2.75–9.0)	10.0 (8.0–10.0)
$Z1_{Wilcoxon}$ (*p*1)		3.56 (<0.001)	5.74 (<0.001)	6.17 (<0.001)
$Z2_{Wilcoxon}$ (*p*2)			5.49 (<0.001)	5.87 (<0.001)
$Z3_{Wilcoxon}$ (*p*3)				5.26 (<0.001)

controversial [11].

The steady increase in the number of COVID-19 infected cases leads to an increase in the prevalence of post COVID-19 anosmia. This necessitates seeking to find an effective treatment to avoid the psychological impact and the negative impact on quality of life. There is no good evidence suggesting the use of topical corticosteroids in the treatment of post COVID-19 olfactory dysfunction, therefore we conducted this study as a clinical trial evaluating the role of topical corticosteroids as mometasone furoate nasal spray in the improvement of patients with post COVID-19 anosmia.

This randomized clinical trial included 100 patients, 50 patients in each group, all patients suffered from post COVID-19 olfactory dysfunction (anosmia/hyposmia), on studying the demographic criteria of our patients, it was noticed that the ages of the patients were of a wide range from 18 years to 61 years, male to female ratio was 46/54, this matches with the study of Sakalli et al. [17], in which male to female ratio was 44/44 among patients had a loss of sense of smell related to SARS-CoV-2 infection. However, Lee et al. reported a higher prevalence in females; 152/336 [18].

By following the improvements in both arms of the study, both groups in this study showed significant improvements over the period of the study by comparing the weekly smell scores in each group. However, by comparing the smell scores between both groups, there was no advantage or superiority for the study group (group I) of topical mometasone nasal spray, over the control group (group II) as the comparison of smell scores between both groups after 1 week, 2 weeks and 3 weeks of treatment, showed no statistically significant differences between both groups, *P*-values were (0.10, 0.08 and 0.16) respectively. This mismatches with Scangaset al. [19], who stated that topical steroid treatment has been reported to improve the recovery in post-infectious olfactory dysfunction patients. Also, this mismatches with Heilmannet al. [10], who found improvement of olfactory function after local administration of mometasone nasal spray for olfactory dysfunction caused by upper respiratory tract infections. But the aetiological viral infection in those two previous studies was not the new coronavirus which we have no much information about its pathogenesis in anosmia.

As regards the duration of anosmia/hyposmia and the recovery rates, there were no benefits of the mometasone furoate nasal spray as the comparison between both groups showed no statistically significant differences as the average time for complete recovery in the study group was 26.41 ± 7.99 days compared to 26.15 ± 5.07 days in the control group ($P = 0.88$). In the study group, (62%, 31/50) of patients completely recovered their sense of smell compared to (52%, 26/50) of patients in the control group ($P = 0.31$).

To our knowledge, there is a lack of studies in the treatment of post COVID-19 olfactory dysfunction, but there is a case report of Touisserkani and Ayatollahi [20]; a female patient with COVID-19 anosmia did not recover after 2 weeks of its onset and for 10 days on the topical nasal steroid without improvement. Then oral prednisolone was prescribed and after 6 days of consuming prednisolone, her anosmia reversed.

From our results, the local corticosteroid nasal spray in the form of mometasone furoate shows no advantages in the treatment of anosmia/hyposmia in patients recovered from COVID-19 infection. Despite the negative results of the study, we believed that it can make way for further positive results. Based on the negative findings, future researches can be directed to try other lines of treatment for COVID-19 olfactory dysfunction.

The results of our study suggest that the pathogenesis is neurological rather than local nasal inflammation, therefore further trials are recommended to evaluate the role of systemic steroids in post COVID-19 anosmia and olfactory dysfunction.

In our study, the total average time for complete recovery of smell was 26.29 ± 6.76 days. (57%, 57/100) of patients were completely recovered their sense of smell by the end of the third week. This goes in line with the study of Dell'Era et al. [21], in which (49.5%) of patients reported a full regaining of smell sense after 14 days since the beginning

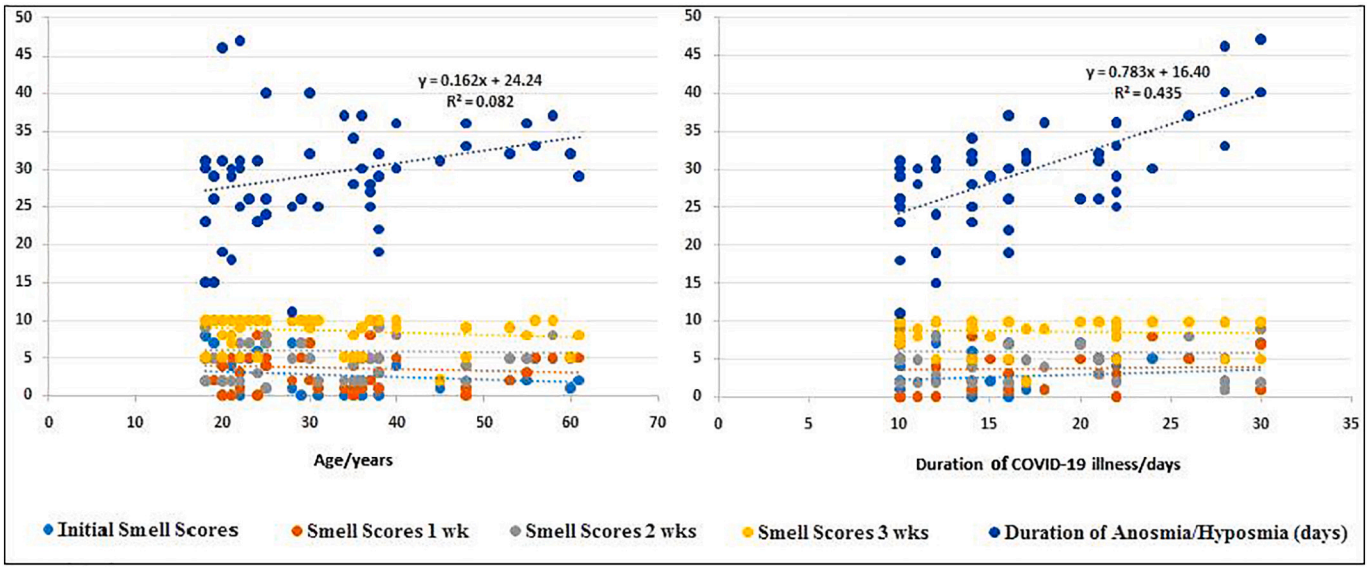

Fig. 2. Correlation between age and duration of COVID-19 illness as prognostic factors and duration of smell loss in total studied cases.

Table 3
Sex, DM and receiving systemic steroids as prognostic factors and smell loss in total studied cases.

Total cases	Sex			DM			Received systemic steroids		
	Male (46)	Female (54)	P	Yes (16)	No (84)	P	Yes (13)	No (87)	P
Initial smell score Median (IQR)	2.0 (1.0–5.0)	2.0 (0.0–5.0)	0.78	2.0 (1.0–4.75)	2.0 (0.0–5.0)	0.96	1.0 (1.0–5.0)	2.0 (0.0–5.0)	0.81
Smell score after 1 week Median (IQR)	4.0 (1.0–5.0)	2.0 (1.0–5.0)	0.61	5.0 (1.5–5.0)	3.0 (1.0–5.0)	0.79	2.0 (1.0–5.0)	4.0 (2.0–5.0)	0.47
Smell score after 2 weeks Median (IQR)	5.0 (4.0–9.0)	5.0 (2.0–9.0)	0.72	6.5 (4.25–8.0)	5.0 (2.0–9.25)	0.77	5.0 (4.0–8.0)	5.0 (2.0–9.0)	0.90
Smell score after 3 weeks Median (IQR)	9.0 (8.0–10.0)	10.0 (8.0–10.0)	0.27	8.5 (5.75–9.75)	10.0 (8.0–10.0)	0.10	9.0 (5.0–10.0)	10.0 (8.0–10.0)	0.32
Duration of anosmia/hyposmia, day Mean ±SD	25.63±6.92	26.71±6.72	0.56	35.0±2.31	25.64±6.53	0.006	30.66±7.2	25.78±6.59	0.09
Patients completely recovered the smell after 3 weeks N (%)	22 (47.8)	35 (64.8)	0.09	4 (25.0)	53 (63.1)	0.004	6 (46.1)	51(58.6)	0.39

of the symptoms and this percentage improved to 62.9% after 23 days. But our results differ from results of Sakalli et al. [17], who reported improvement of anosmia in (78.4%, 69/88) within 20 days, and the average time for recovery was 8.02 ± 6.41 days. This difference can be explained by our exclusion of the cases with olfactory dysfunction improved before recovery from COVID-19 illness.

Our study revealed that age, diabetes and the duration of COVID-19 illness can affect the duration of anosmia/hyposmia as there was a statistically significant positive correlation between age and the duration of anosmia/hyposmia ($P = 0.004$), 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 ($P = 0.006$). There was a statistically significant positive correlation between the duration of COVID-19 illness and the duration of anosmia ($P < 0.001$). Our results as regards the prognostic factors differ from Lovato et al. [22], who stated that the absence of fever was the only prognostic factor of persistent olfactory/taste dysfunction in COVID-19 patients as they studied the prognostic factors during the period of COVID-19 illness, not after recovery.

5. Conclusion

The results of our study suggest that using mometasone furoate nasal spray as a topical corticosteroid therapy in the treatment of post COVID-19 anosmia offers no benefits over the olfactory training. This topical corticosteroid nasal spray shows no superiority regarding the smell scores over the period of the study, the duration of anosmia/hyposmia, and the recovery rates. Till now there is no good evidence suggesting the use of topical corticosteroid in the treatment of post COVID-19 olfactory dysfunction, and according to our results, the olfactory training can be the advice for anosmia in patients recovered from COVID-19 infection.

Age, diabetes, and the duration of COVID-19 illness can be stood out as discriminative prognostic factors affecting the duration of anosmia.

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The authors declare no financial support or interest to this study.

Ethics and consent

The study was performed in accordance with the Helsinki Declaration of 1975 and its amendments, the study protocol was approved by the Research Ethics Committee at Faculty of Medicine, Benha University (REC-FOMBU), Egypt with approval number RC4.7.2020. All patients signed their written informed consent to participate in the study.

Availability of data and material

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

Declaration of competing interest

The authors declare no conflict of interest.

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