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Olfactory mucosa steroid injection in treatment of post-COVID-19 olfactory dysfunction: a randomized control trial

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Abstract

Background Olfactory dysfunction can be a troublesome condition affecting the quality of life of the patient. Post-viral olfactory dysfunction is the most common cause attributing to up to 40% of anosmia. COVID-19 infection commonly causes anosmia in 30–66% of patients. The long-term effect of post-COVID olfactory dysfunction is reported to be increasing in incidence. Steroids are usually used in the treatment of olfactory dysfunction and most commonly used locally in the form of nasal steroid sprays, rinses, or drops. Oral systemic steroids are sometimes used; however, they have several known side effects. Other treatments experimented include giving vitamins, minerals, antioxidants, antivirals, and monoclonal antibodies, in addition to olfactory training, counseling, and acupuncture. In this study, the effect of intranasal steroid injection is studied in post-COVID olfactory dysfunction.

Results Forty patients with olfactory dysfunction post-COVID-19 for more than 3 months were randomly divided into 2 groups. Group A patients received 8 doses of dexamethasone over 2 months (twice weekly) injected near the olfactory mucosa in the nasal septum and middle turbinate, compared to group B who received saline injected in the same way as placebo. Numerically, nasal injection of corticosteroids in group A showed more subjective improvement using the questionnaire of olfactory disorders-negative statement QOD-NS than the control patients in group B but this improvement was statistically insignificant.

Conclusion The use of intranasal corticosteroids injection should be considered in the treatment of post-COVID anosmia.

Keywords COVID-19, Corticosteroids, Intranasal injection, Olfactory dysfunction

Background

Olfactory dysfunction can be an annoying condition that is often difficult to manage. Change in the smell function as anosmia or hyposmia significantly dulls interpretation of the world. Spoiled food is less likely to be detected. Taste can be affected resulting in decreased food enjoyment, missed meals, and nutritional deficits. This is shown to have a negative impact on quality of life and mood up to higher rates of depression. Post-viral olfactory dysfunction is the most common cause of olfactory dysfunction [1].

Loss of the sense of smell as a consequence of COVID-19 infection was first recognized in March 2020 [2]. This usually takes the form of complete or partial loss of olfactory function (anosmia and hyposmia respectively) [3].

Olfactory dysfunction was reported to range from 30 to 66% in hospitalized cases and up to 85% in mild cases not requiring hospital admission [4].

It remains unclear why some individuals experience longer-lasting olfactory deficits. This may be due to different mechanisms for olfactory loss [5].

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Although a method for the treatment of olfactory loss after upper respiratory infection has not been established, steroid has usually been used for patients [6].

While the British Rhinology Society ENT UK guidelines recommended that olfactory training and intranasal corticosteroids were recommended in the treatment of loss of smell of more than 2 weeks onset; the administration of oral steroids was recommended against if symptoms of COVID persisted and was optional in the cases where other symptoms subsided. Also, intranasal corticosteroid drops were considered optional too [7].

The steroid nasal drop method has the advantage of requiring only a small amount of steroids. It is quite difficult to direct the steroid solution to the olfactory cleft and patients must administer the drops themselves every day. So, the steroid dose depends on the patient and is imprecise. On the other hand, when steroids are administered orally, the patients are guaranteed a steroid effect. But patients must take a relatively high dose and it can be problematic for patients with a gastric ulcer or another complication [6].

Injecting the steroid into the nasal mucosa near the olfactory cleft should be slowly spread in the nasal mucosa near the olfactory cleft, thus being effective at the local area. In Japan, it was found that there was an improvement in half of the patients with anosmia within the onset of 1 year [8].

Methods

This study was approved by the research committee of the ENT department of the Faculty of Medicine, Cairo University, under approval number of 211001R on 18.10.21.

Consent to participate: written consent to participate in this study was provided by all participants.

Forty patients presented with olfactory dysfunction after being diagnosed with COVID-19 for more than 3 months. Patients were subjected to full ENT examination including detailed history taking and nasal endoscopy.

Inclusion criteria are as follows:

- Patients presenting with isolated olfactory dysfunction whether anosmia, hyposmia, or parosmia after they have been diagnosed as COVID since more than 12 weeks with no other persistent symptoms, i.e., after complete recovery from COVID-19

Exclusion criteria are as follows:

- Patients under 18 years old
- Patients with any other persistent symptoms of COVID-19 as cough, sore throat, or fever
- Patients with mucormycosis
- Patients with sinonasal polyposis or any local ENT disease which might be the cause of conductive olfactory dysfunction

Written consent was taken from all patients enrolled in the study. Questionnaire of olfactory disorder-negative statement (QOD-NS) (Figs. 1 and 2) which was also translated into Arabic by Alsayid et al. in 2021 [9] was filled out by the patients before starting treatment.

The patients were divided randomly by sealed envelopes into 2 groups: group A—20 patients were injected dexamethasone 8 mg 8 times over 2 months (twice weekly) into the nasal mucosa near the olfactory cleft in the upper part of the nasal septum and the upper part of anterior end of the middle turbinate guided by the nasal endoscope after applying local anesthesia office based [6], while the 20 patients enrolled in group B were injected with saline as a placebo with the same intervals. Patients in both groups underwent olfactory training during treatment.

Olfactory function was reassessed subjectively by the olfactory disorder questionnaire after 4 weeks of the treatment. QOD-NS is a validated instrument analyzing multiple aspects of how changes in olfaction impact an individual's daily life. It consists of 17 statements for olfactory function, and each statement has a scale containing four statements: I agree, I agree partially, I disagree partially, and I disagree. The answers were assigned a score of 3, 2, 1, and 0, respectively.

Scores are from 0 to 51. QOD-NS score cut-off of 38.5 has been previously reported that stratifies QOD-NS scores in patient with normal vs. abnormal olfaction on objective psychophysical testing (hyposmia and anosmia). This cut-off score of 38.5 was calculated using a QOD-NS scoring method where high scores reflected poor QOL and low scores reflected good QOL. As such, we used the numerical inverse of 38.5 to obtain a cut-off score of 12.5 in order to reflect normal vs abnormal scores [10].

QOD-NS measures important aspects of olfactory-specific QOL: *Factor 1* contains a large number of social-related questions which may illustrate how olfactory dysfunction might lead to social isolation, and impairment of interpersonal relationships. *Factor 2* eating-related problems as food, drinks, and restaurant enjoyment. *Factor 3* gives insight into how olfactory impairment might increase a patient's stress level or cause impairment in mental health. *Factor 4* contains fear-related question; it also helps inform our understanding of how frequently olfaction changes can affect QOL and how bothersome these changes can be to patients.

I disagree	I disagree partly	I agree partly	I agree	English Statements
				Because of the changes in my sense of smell, I go to restaurants less often than I used to.
				I am always aware of the changes in my sense of smell.
				Because of the changes in my sense of smell, I don't enjoy drinks or food as much as I used to.
				I am worried that I will never get used to changes in my sense of smell
				Because of changes in my sense of smell, I feel more anxious than I used to feel.
				The changes in my sense of smell cause most of my problems.
				The changes in my sense of smell annoy me when I am eating.
				Because of changes in my sense of smell I visit friends, relatives, or neighbors less often.
				Because of changes in my sense of smell, I try harder to relax.
				Because of changes in my sense of smell I have weight problems.
				The changes in my sense of smell make me feel isolated.
				Because of changes in my sense of smell I avoid groups of people.
				Because of changes in my sense of smell I eat less than I used to or more than I used to.
				Because of the difficulties with smelling, I am scared of getting exposed to certain dangers (e.g., gas, rotten food).
				Because of changes in my sense of smell I have problems with taking part in activities of daily life.
				The changes in my sense of smell make me feel angry.
				Because of changes in my sense of smell, my relationship with my wife/ husband/ partner is affected.

Fig. 1 Version 1; the first version of the questionnaire. Scoring system: I disagree = 0, I disagree partly = 1, I agree partly = 2, I agree = 3 [9]

Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. For comparison of serial measurements (before and after) within each patient, the non-parametric Wilcoxon signed-rank test was used [11].

For comparing categorical data, the chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5 [12]. *P*-values less than 0.05 were considered statistically significant.

Results

The patients' ages ranged from 21 to 56 years with a mean of 32.9 ± 10.07 years in group A and 31.85 ± 8.22 years in group B. Eighteen cases were males (45%) and twenty-two were females (55%). Among the 40 cases presented with olfactory dysfunction in this study, 32 (80%) had post-COVID anosmia and 8 (20%) complained of hyposmia.

Twenty-nine (72.5%) out of the 40 cases included in this study showed improvement and regained normal olfaction whether by local corticosteroids injection or saline injection. Seven (17.5%) cases suffered hyposmia while 4 (10%) cases remained anosmic (Table 1).

Both groups showed statistically significant improvement in the scores of the QOD-NS and the improvement of the symptom of complaint (Table 2).

While comparing between both groups, although the use of intranasal corticosteroid injection in group A patients showed more improvement regarding their complaint, however, there was no statistically significant difference between studied groups regarding the improvement in the olfaction as group A showed 17 cases regained their olfaction and 2 cases had hyposmia

I disagree	I disagree partly	I agree partly	I agree	English Statements
				I am worried that I will never get used to changes in my sense of smell.
				The changes in my sense of smell annoy me when I am eating.
				Because of changes in my sense of smell I eat less than I used to or more than I used to.
				Because of changes in my sense of smell, I try harder to relax.
				Because of the difficulties with smelling, I am scared of getting exposed to certain dangers (e.g., gas, rotten food).
				I am always aware of the changes in my sense of smell.
				Because of changes in my sense of smell I avoid groups of people.
				The changes in my sense of smell make me feel isolated.
				Because of changes in my sense of smell, my relationship with my wife/ husband/ partner is affected.
				Because of the changes in my sense of smell, I don't enjoy drinks or food as much as I used to.
				The changes in my sense of smell make me feel angry.
				Because of changes in my sense of smell I have problems with taking part in activities of daily life.
				The changes in my sense of smell cause most of my problems.
				Because of the changes in my sense of smell, I go to restaurants less often than I used to.
				Because of changes in my sense of smell I have weight problems.
				Because of changes in my sense of smell I visit friends, relatives, or neighbors less often.
				Because of changes in my sense of smell, I feel more anxious than I used to feel.

Fig. 2 Version 2; the second version of the questionnaire. Same questions but rearranged in different order. Scoring system: I disagree = 0, I disagree partly = 1, I agree partly = 2, I agree = 3 [9]

and only one case had anosmia while in group B, 12 cases regained olfaction and 5 cases had hyposmia and 3 cases had anosmia (Table 3).

Regarding the olfactory disorders questionnaire assessment, there was no statistically significant difference between both groups. However, group A showed slight improvement than group B. Group A showed a pre-injection mean score 40.5 ± 3.3 that improved to be 7.6 ± 8.91 post-injection while group B showed a pre-injection mean score 38.5 ± 6.5 that improved to be 12.4 ± 12 post-injection (Fig. 3).

The process of intranasal injection done in an office-based manner under local anesthesia was not free of minor complications as controllable bleeding that occurred in 7 patients (5 in group A and 2 in group B) and local pain of moderate severity that occurred in 3 patients (1 in group A and 2 in B) that did not allow us to continue the injection session of the whole amount of drug. Both complications were not of statistical significance between the groups (Table 3).

Discussion

Most COVID-19 patients that experienced Olfactory dysfunction had complete recovery of their sense of smell by 2 weeks to up to 40 days. A smaller percentage of patients had persistent olfactory dysfunction with the disappearance of all other COVID-19-related symptoms. This encouraged researchers to try different forms of treatments to treat this condition that may be related to the extent or mechanism of damage of olfactory epithelium. The aim of this study was to assess the use of intranasal corticosteroids injection in treating this condition especially since it was experimented before in other patients with olfactory dysfunction; however, it was not done in a blind manner on COVID-19 olfactory dysfunction patients [13]. Current evidence supports olfactory training as a first-line intervention. However, there has been no consensus on appropriate pharmacotherapy for treatment of post-COVID olfactory dysfunction and there is very limited evidence available comparing the efficacy and harms of further

Table 1 Description of the whole sample

		Count	%
Sex	**Male**	18	45.0%
	Female	22	55.0%
Complain	**Anosmia**	32	80.0%
	Hyposmia	8	20.0%
Effect	**Anosmia**	4	10.0%
	Hyposmia	7	17.5%
	Normosmia	29	72.5%
Complications	**Bleeding**	7	17.5%
	Pain	3	7.5%
	No	30	75.0%

interventions for persistent olfactory dysfunction following COVID-19 infection [14, 15].

Therefore, the aim of the present study was to study the effect of olfactory mucosal injection of steroids in the treatment of post-COVID olfactory dysfunction.

The comparison between the studied groups regarding the effect of each treatment revealed a statistically significant improvement of the olfactory dysfunction symptoms in both groups. And although there was a non-statistically significant improvement in patients among group A (85%) than in group B (60%) (*P* value is 0.25), still the patients who had the local injection with steroids had more improvement than those injected by saline (placebo).

Similarly, a systemic review by Yuan et al. [16] indicated that olfactory function in patients with postviral olfactory dysfunction was effectively improved through direct steroid administration in the olfactory cleft, classical olfactory training, or modification of classical olfactory training.

This may mean that the patients improve eventually over time helped by olfactory training and that the olfactory mucosa injection of steroids aided to accelerate the recovery of olfactory dysfunction symptom.

A review study by Wu et al. [15] indicated that olfactory training should be initiated as soon as possible for

Table 2 Comparison between pre- and post-injection in each group

	Mean	SD	Median	Minimum	Maximum	*P* value
Group A						
Q pre	40.50	3.30	40.00	36.00	48.00	< 0.001
Q post	7.60	8.91	4.50	0.00	40.00	
Group B						
Q pre	38.50	6.50	39.50	12.00	44.00	< 0.001
Q post	12.40	12.00	7.00	2.00	40.00	

Table 3 Comparison between studied groups

		Group A		Group B		*P* value
		Count	%	Count	%	
Sex	**Male**	10	50.0%	8	40.0%	0.525
	Female	10	50.0%	12	60.0%	
Complain	**Anosmia**	14	70.0%	18	90.0%	0.235
	Hyposmia	6	30.0%	2	10.0%	
Effect	**Anosmia**	1	5.0%	3	15.0%	0.250
	Hyposmia	2	10.0%	5	25.0%	
	Normosmia	17	85.0%	12	60.0%	
Complications	**Bleeding**	5	25.0%	2	10.0%	0.542
	Pain	1	5.0%	2	10.0%	
	No	14	70.0%	16	80.0%	

	Group A					Group B					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	*P* value
Q pre	40.50	3.30	40.00	36.00	48.00	38.50	6.50	39.50	12.00	44.00	0.512
Q post	7.60	8.91	4.50	0.00	40.00	12.40	12.00	7.00	2.00	40.00	0.121

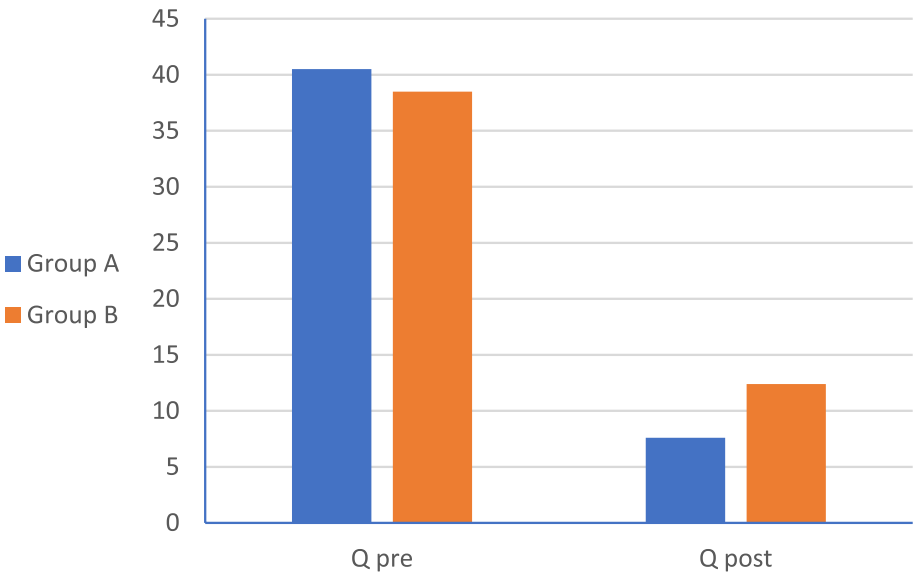

Fig. 3 Comparison of the scores of the QOD-NS pre- and post-injection in both groups

patients with post-COVID-19 olfactory dysfunction. Patients may benefit from a limited intranasal or oral corticosteroid course [15].

Furthermore, a review study by Burton et al. [17] of 18 randomized controlled trials with 2738 participants with chronic rhinosinusitis treated with intranasal steroids. A moderate benefit was seen in sinonasal symptoms, including olfactory dysfunction after treatment [17].

A previous study by Fujii et al. [18] treated olfactory dysfunction using dexamethasone injection 4 mg/0.5 mL septal mucosa every 2 weeks × 8 and indicated that olfactory dysfunction caused by head trauma can be recovered to a limited degree in some cases by the local injection of steroid within the relatively short period from the start of the therapy.

However, Abdelalim et al. [19] on patients with olfactory dysfunction who were randomly divided into two groups: one group 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, and the other group of patients were advised to keep on olfactory training only. However, 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 [19].

Although intranasal injection of corticosteroids injection was tried before to treat olfactory dysfunction, however this study can be considered to be a pioneer study when comparing the effect of intranasal injection of steroids in the olfactory mucosa to treat post-COVID-19 olfactory dysfunction against placebo injection of saline in a blind fashion.

This study is not free of weaknesses. The sample size in the current report could have been increased to increase the power of the study. As well, a comparison to oral corticosteroids could have added to the strength of this study. However, this can represent a perspective for future research for further studies.

Conclusion

The use of intranasal corticosteroids injection should be considered in the treatment of post-COVID anosmia.

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Authors' contributions
HL was responsible for the design of the work and data acquisition, and MAA was responsible for data analysis and writing of the manuscript. All authors have approved the submitted version of the manuscript.

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Availability of data and materials
The data of this study are available at the corresponding author upon request.

Declarations

Ethics approval and consent to participate
This study was approved by the research committee of the ENT department of the Faculty of Medicine, Cairo University, under approval number of 211001R on 18.10.21. Written consent to participate in this study was provided by all participants.

Consent for publication
Written informed consent to publish the patients' clinical detail information was obtained.

Competing interests
The authors declare that they have no competing interests.

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