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ORIGINAL ARTICLE

Anosmia and/or Ageusia in Coronavirus Disease 2019-Infected Patients: Role of Early Corticosteroids and Timeline

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Abstract

Aim: **An increasing number of coronavirus disease 2019 (COVID-19) cases have started to experience unusual symptoms to the virus such as olfactory and gustatory dysfunctions. The study aimed to compare the effects of early corticosteroids (CS) administration versus no administration in the time-to-recovery from olfactory dysfunction in COVID-19.**

Patients and methods: **This comparative, nonrandomized study has been conducted at Benha University Hospital and another Primary Health Center in Cairo, Egypt, from January 2021 to June 2021. A total of 83 patients who have met the inclusion criteria were assigned into two groups: early-CS group (41 cases) and no-CS group (42 cases).**

Results: **Both groups were comparable regarding age, BMI, and sex. Females constituted 65.9 and 59.5% of cases in the early-CS group and the no-CS group, respectively. At presentation, regarding the severity of anosmia, both groups were comparable ($P = 0.302$). Complete anosmia was reported in 80.5 and 78.6% of the early-CS group and the no-CS group, respectively. The mean duration for anosmia onset was 3.7 ± 1 and 4.1 ± 1.8 days in the early-CS group and the no-CS group, respectively ($P = 0.204$).**

Time-to-recovery from anosmia was significantly less in the early-CS group, with a median (interquartile range) of 7 (9) days than in the no-CS group, with 14 (10) days ($P < 0.001$). Approximately 95.1% of cases in the early-CS group recovered in the first 2 weeks versus only 66.7% in the no-CS group.

Conclusion: **Unless contraindicated, early administration of systemic CSs reduces the time needed to recover from COVID-19 olfactory dysfunction.**

Keywords: Anosmia, Corticosteroids, Coronavirus disease 2019, Olfactory dysfunction

1. Introduction

Since the appearance of the coronavirus disease 2019 (COVID-19) pandemic in December 2019, when the disease was first reported, the number of cases has dramatically increased. As of May 18, 2021, globally, more than 163 312 429 confirmed cases of COVID-19 − caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection − including 3 386 825 deaths, have been reported by the WHO. In Egypt, 246 909 confirmed cases of COVID-19, including 14 388 death cases, have been reported by the WHO [1].

People of all age groups are at risk for infection and severe disease. However, older people more than or equal to 60 years and those with chronic comorbid medical conditions are at a higher risk for serious COVID-19. In an analysis of more than 1.3 million confirmed COVID-19 cases, 14% were hospitalized and 5% died [2].

The symptoms of COVID-19 are many, with presence of fever, cough, or shortness of breath in 70% of cases, myalgia in 36%, and headaches in

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34%. Other reported symptoms were rhinorrhea, anosmia, dysgeusia, sore throat, diarrhea, dizziness, abdominal pain, anorexia, and vomiting [2].

Primarily, COVID-19 is a respiratory disease; however, it also leads to cardiovascular, hematological, dermatologic, hepatic, renal, neurological, and other complications [3–11].

Olfactory and gustatory dysfunctions, unusual symptoms, started to be reported in an increasing number of COVID-19 cases [12,13]. This was reported in several research studies all over the world. In Italy, changes in smell and taste have been reported in more than a third of COVID-19 cases [14]. Moreover, in South Korea, anosmia has been reported in 30% of mild COVID-19 cases as the main sign of infection [12]. In addition, anosmia has been reported in other studies in Germany (>60% of cases with COVID-19) and Brazil (>80% of COVID-19 cases) [12,14]. Thus, sudden changes in olfaction have been reported as initial signs of COVID-19, even in the absence of nasal congestion or rhinorrhea [15–20].

However, despite being very prevalent symptoms in patients with COVID-19, the timeline of these symptoms and the management strategy have not been well established. Therefore, the rationale intended for this study was to investigate the timeline of these symptoms and the effect of early corticosteroids (CS) and vitamin B complex on the recovery in patients diagnosed with COVID-19.

2. Patients and methods

This pilot nonrandomized controlled, interventional study was conducted at Benha University Hospital and another primary healthcare center in Cairo, Egypt, upon 81 individuals diagnosed as COVID-19 cases and confirmed by PCR during the period from January 2021 to June 2021. The ethical review committee approved the study. The purpose of this study was clearly explained to all patients. An informed consent was signed and obtained from every patient. We invited all patients aged 18 years or more who came to the centers with confirmed COVID-19 and had a loss of smell and/or taste to participate. For inclusion in the study, all of the following criteria were to be fulfilled: age 18 years or more and patients with PCR-confirmed COVID-19. Exclusion criteria included pregnancy or lactation, uncontrolled diabetes mellitus, immunocompromised cases, active bacterial infection, peptic ulcer disease, glaucoma, recent live-attenuated vaccine, psychotic disorder, refusal to participate, or participation in another study.

Detailed medical history was taken from all cases. All patients were subjected to clinical examination and laboratory investigations in the form of erythrocyte sedimentation rate, C-reactive protein, complete blood count, and ferritin. At presentation, each patient was asked to rate the severity of their olfactory dysfunction (OD) on a Likert scale from 0 to 5, where 0 means no anosmia, and 5 means complete loss of smell. They all were asked about the onset of their symptoms in general and the onset of OD. The patients were categorized into two groups: the early-CS group, where CSs were used early within 72 h from their presentation, and the no-CS group. The dosage of CS was guided by their condition and inflammatory markers. In mild cases, dexamethasone 8 mg intramuscular injections once daily was used for 5 days and then prednisolone 10 mg oral once daily for 2 weeks, which were then decreased gradually by 5 mg/week. In moderate to severe cases, dexamethasone 8 mg intramuscular injections once daily for 5 days and then methylprednisolone 30 mg oral once daily for 2 weeks, which were then reduced gradually by 5 mg every week. Metformin 500 mg oral tablets twice daily, spironolactone 50 mg oral tablet once daily, and famotidine 40 mg oral tablet once daily were used during the period of receiving CSs to avoid any potential adverse effects of the medication. All patients of the two groups were followed until improvement. Participants were informed about the potential adverse effects of CSs (such as sugar craving, sleeplessness, stomach upset, and blood pressure increase). Management of COVID-19 was made according to local guidelines in cooperation with an internist.

A convenient sampling of 83 cases was used as a sampling technique in this study. The primary outcome measure was the time-to-recovery from anosmia. A P value of less than 0.05 was considered statistically significant. SPSS software (Statistical Package for the Social Sciences, version 24.0; SSPS Inc., Chicago, Illinois, USA) was used for analysis. Quantitative parametric data were presented as mean and SD. Quantitative nonparametric data were presented as median and interquartile range (IQR). Qualitative data were presented as numbers and proportions. Comparisons between groups were made using the χ^2 test or Fisher exact test for categorical variables and the independent t test or Mann–Whitney test for continuous variables.

3. Results

A total of 83 patients who met the inclusion criteria were assigned into two groups: the early-CS group (41 cases) and the no-CS group (42 cases).

There was no significant difference between the two study groups regarding age ($P = 0.691$) and BMI ($P = 0.459$). The mean age was 40.7 ± 14.5 and 39.5 ± 12.4 years for the early-CS group and the no-CS group, respectively. The mean BMI was 30.6 ± 7.1 and 29.4 ± 7.2 kg/m^2 for the early-CS group and the no-CS group, respectively.

Moreover, there was no significant difference between the two study groups regarding sex ($P = 0.551$). Females constituted 65.9 and 59.5% of cases in the early-CS group and the no-CS group, respectively. In addition, both groups are comparable regarding smoking, alcohol abuse, diabetes mellitus, hypertension, and morbid obesity ($P > 0.05$), as shown in Table 1.

At presentation, regarding the severity of anosmia, both groups were comparable ($P = 0.302$), as shown in Table 2. Complete anosmia was reported in 80.5 and 78.6% of the early-CS group and the no-CS group, respectively. The mean duration for anosmia onset was 3.7 ± 1 and 4.1 ± 1.8 days in the early-CS group and the no-CS group, respectively ($P = 0.204$).

Cacosmia was reported in 14.6 and 4.8% of the early-CS group and the no-CS group, respectively ($P = 0.156$). Moreover, dysgeusia was seen in 87.8 and 83.3% of the early-CS group and the no-CS group, respectively ($P = 0.562$).

Other reported symptoms at presentation were comparable between the two groups, as shown in Table 3. The most frequent symptoms were cough and fatigue/malaise, as reported in 80.5 and 75.6%, and 71.4 and 73.8% of the early-CS group and the no-CS group, respectively ($P = 0.335$ and 0.85, respectively).

Time-to-recovery from anosmia was significantly less in the early-CS group, with median (IQR) = 7 (9) days, than in the no-CS group, with median 14 (10) days ($P < 0.001$), as shown in Fig. 1 and in Table 4. Overall, 95.1% of cases in the early-CS group recovered in the first 2 weeks versus only 66.7% in the no-CS group.

Table 1. Baseline characteristics.

	Early-CS group		No-CS group		
	$N = 41$		$N = 42$		P value
Sex					
Male	14	34.1%	17	40.5%	0.551
Female	27	65.9%	25	59.5%	
Smoker	8	19.5%	7	16.7%	0.184
Alcoholic	1	2.4%	1	2.4%	0.747
DM	2	4.9%	2	4.8%	0.98
Hypertension	9	22.0%	9	21.4%	0.954
Morbid obesity	3	7.3%	2	4.8%	0.676

CS, corticosteroid; DM, diabetes mellitus.

Table 2. Anosmia severity at presentation.

Anosmia severity score	Early-CS group		No-CS group		
	$N = 41$		$N = 42$		P value
1 = mild	2	4.9%	0	0.0%	0.302
2	3	7.3%	2	4.8%	
3	2	4.9%	2	4.8%	
4	1	2.4%	5	11.9%	
5 = complete anosmia	33	80.5%	33	78.6%	

CS, corticosteroid.

4. Discussion

The higher rate of cases experiencing COVID-19-related OD and the psychological burden induced by anosmia is creating an unprecedented need for a definitive management strategy for it. COVID-19-OD patients are being seen earlier in the course of the disease at the ear, nose, and throat clinics. This presents a good chance for early intervention and raises the question of whether such a treatment strategy is needed to increase the chance for smell recovery [21].

Systemic CSs are a part of ear, nose, and throat tools in several inflammatory and sensorineural conditions. Because COVID-19-OD is likely due to an inflammatory and neurosensory process, systemic CSs can be considered an option for treatment [21].

The current study showed that females are more affected than males. Complete anosmia was reported in the majority of cases in both the early-CS

Table 3. Associated symptoms at presentation.

	Early-CS group		No-CS group		
	$N = 41$		$N = 42$		P value
Dysgeusia	36	87.8%	35	83.3%	0.562
Vertigo	19	46.3%	15	35.7%	0.325
Cacosmia	6	14.6%	2	4.8%	0.156
Hoarseness	4	9.8%	0	0.0%	0.055
Fever	20	48.8%	19	45.2%	0.746
Headache	25	61.0%	20	47.6%	0.222
Rhinorrhea	26	63.4%	26	61.9%	0.887
Sore throat	24	58.5%	21	50.0%	0.435
Shortness of breath	22	53.7%	23	54.8%	0.92
Chest pain	24	58.5%	18	42.9%	0.153
Palpitation	10	24.4%	9	21.4%	0.748
Cough	33	80.5%	30	71.4%	0.335
Nausea/vomiting	10	24.4%	10	23.8%	0.951
Abdominal pain	15	36.6%	12	28.6%	0.436
Diarrhea	18	43.9%	17	40.5%	0.752
Anorexia	7	17.1%	7	16.7%	0.961
Dry mouth	12	29.3%	18	42.9%	0.198
Fatigue/malaise	31	75.6%	31	73.8%	0.85
Myalgia/bone pain	21	51.2%	18	42.9%	0.445
Arthralgia	8	19.5%	8	19.0%	0.957

CS, corticosteroid.

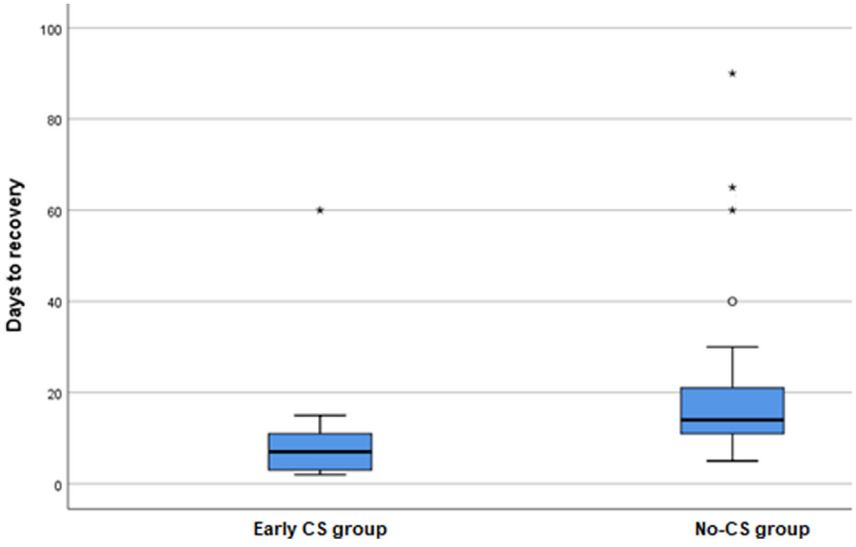

Fig. 1. Time-to-recovery from anosmia.

group and the no-CS group. Moreover, dysgeusia was seen in the majority of the early-CS group and the no-CS group. In our study, the mean duration for anosmia onset was 3.7 ± 1 and 4.1 ± 1.8 days in the early-CS group and the no-CS group, respectively. The results of the current work showed that early administration of CS had a beneficial effect with less time-to-recovery from anosmia than without administration. Time-to-recovery from anosmia was significantly less in the early-CS group, with median (IQR) of 7 (9) days than in the no-CS group, with median of 14 (10) days ($P < 0.001$). Approximately 95.1% of cases in the early-CS group recovered in the first 2 weeks versus only 66.7% in the no-CS group.

The risks and benefits of systemic CS should be balanced. In the absence of data supporting the lack of significant adverse effects of systemic CS in COVID-19-infected patients, several calls for caution were made and in addition to a recommendation against the use of systemic CS in CRS during COVID-19 [22]. Therefore, when we considered whether such treatment could be used in COVID-19-OD, the potential added benefit versus risk was carefully considered.

Table 4. Time-to-recovery from anosmia: frequency distribution.

	Early-CS group		No-CS group		
	$N = 41$		$N = 42$		P value
Week 1	21	51.2%	1	2.4%	<0.001
Week 2	18	43.9%	27	64.3%	
Week 3	1	2.4%	6	14.3%	
Week 4	0	0.0%	3	7.1%	
Month 2	0	0.0%	2	4.8%	
Month 3	1	2.4%	2	4.8%	
Month 4	0	0.0%	1	2.4%	

CS, corticosteroid.

In a recent review, an expert group in clinical olfaction aimed to briefly review the evidence for and against CS treatment in COVID-19-OD based on the available literature. They used a Delphi process to collect individual opinions. They reported that, in general, there appears to be a high rate of recovery from COVID-19-OD. In the first month, authors found recovery rates of COVID-19-OD in 33–96% of cases. In the second month, a normal olfactory function was seen in 54% of cases. Further studies found 86% in the third month and 95% in the sixth month [21].

It appears from the literature at hand that COVID-19-OD is reversible mainly for the majority of cases in the short term (1 week) to medium term (1 month). In contrast, a minority progress to a persistent OD (hyposmia, parosmia, or cacosmia), typical of the postinfectious OD reported elsewhere [23].

Owing to their immunosuppressive effects in COVID-19, the WHO recommended using CSs only in cases with severe and critical COVID-19 as they can lower the mortality rates [24]. Contrariwise, their use was not recommended in mild cases of COVID-19 as it may increase the risk of death; however, such conditional recommendation was based only on low-certainty evidence, which is still debated [24–26].

The favorable effect of CS in postinfectious OD may be attributed to their anti-inflammatory effect [21]. It appears that systemic CS has a potential role in the management of COVID-19-OD. Indeed, CS could constitute a treatment option if signs of inflammation are present at the examination time.

A recent case report found that a case of COVID-19-OD that received an oral CS (prednisolone) improved within 6 days [27]. Nevertheless, such effect can be attributed to the spontaneous recovery of COVID-19-OD owing to the natural evolution of the disease. Recently, a prospective study that compared systemic CS plus olfactory training to olfactory training alone showed that only cases of the first group significantly improved from OD at the 10th week [28]. Therefore, there was no robust evidence supporting the potential effect of systemic CS in COVID-19-OD patients.

Finally, we believe that our study with enough sample size can be helpful to support the beneficial effects of CS in COVID-19-OD. However, one limitation of our study is that it was a nonrandomized study and could be subject to selection bias. Nevertheless, the two groups in our study are comparable regarding their demographics and clinical characteristics.

Therefore, we recommend conducting randomized placebo-controlled trials and investigating the dose and duration of the treatment. Long-term follow-up studies are needed to evaluate whether CS treatment can reduce the risk of developing post-COVID-19 qualitative ODs.

Conflicts of interest

There are no conflicts of interest.

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