



Association between Administration of Systemic Corticosteroids and the Recovery of Olfactory and/or Gustatory Functions in Patients with COVID-19: A Prospective Cohort Study

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Abstract

AIM: This study is a prospective cohort study aimed to assess the effect of systemic corticosteroids administration time in the recovery of gustatory and olfactory sensations dysfunction (ageusia and anosmia) in COVID-19 patients.

MATERIALS AND METHODS: Sixty-seven COVID-19 patients with symptoms of ageusia and anosmia were recruited (that their COVID infection was confirmed using polymerase chain reaction). Daily 10 mg of systemic corticosteroids were prescribed in the 1st week and then reduced to 5 mg in the 2nd week to all the patients to observe taste and smell sensation recovery. All data were recorded and then analyzed. Patients were then grouped into two groups (early and late groups) according to the duration of their taste and smell dysfunction.

RESULTS: Regression analysis showed that early corticosteroid administration resulted in a significant decrease in recovery time of ageusia and anosmia (0.27 [0.2–0.35], $p < 0.001$). Patients in the early administration group (<1 week) showed faster improvement in regaining taste and smell functions than in the late administration group (>1 week) with significant difference ($p < 0.001$).

CONCLUSIONS: The use of systemic corticosteroids in early phases of covid-19 infection help in faster recovery of ageusia and anosmia.

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Introduction

Coronavirus is a global pandemic with a high mortality rate; it is started in China in 2019 and rapidly spread worldwide, reaching its epidemic peak in March 2020 [1]. Coronavirus is a family of viruses that usually affect animals. They also can affect the respiratory system of humans, causing different manifestations such as difficulty in breathing, coughing, fever, invasive lung lesions, and viral pneumonia [2].

Literature reported that Coronavirus 2019 (COVID-19) affects multiple systems other than lungs, such as cardiovascular, hematological, renal, hepatobiliary gastrointestinal, neurological, endocrinologic, ophthalmologic, and dermatologic. Those different affected systems may be due to extrapulmonary dissemination of the virus or widespread immunopathological sequelae of the disease [3].

The recorded hematological manifestations of COVID-19 are lymphopenia, thrombocytopenia, elevated erythrocyte sedimentation rate, C-reactive protein, ferritin, while cardiac reported manifestation as myocardial ischemia, cardiomyopathy, and arrhythmia. Renal manifestations as hematuria, proteinuria, and metabolic acidosis [3].

Neurological and ophthalmologic recorded manifestations as headaches, dizziness, anosmia, ageusia, and anorexia. Ageusia and anosmia were recorded in many COVID-19 cases in various degrees [4], [5], [6]. Smell and taste dysfunction is more frequent in the initial stages of COVID-19 infection that occur within the first 5 days and may be used as pivotal symptoms in the early diagnosis of the disease [6]. Complete recovery of ageusia and anosmia occurs in most COVID-19 patients with 21 days of infection except few cases that show the persistence of those manifestations for an extended period [7].

To date, no evidence-based medical interventions are recommended to help in improving the persistent ageusia and anosmia that may occur in some COVID-19 patients. The use of systemic corticosteroids may improve those manifestations, especially if they are taken in the early phase of the infection. However, their efficacy is still under investigation [8].

This study aimed to assess the effect of systemic corticosteroids administration time in the recovery of gustatory and olfactory sensations dysfunction in COVID-19 patients.

Materials and Methods

Study design

Prospective cohort study.

Sample size estimation

A pilot study of 55 COVID-19 patients was examined and treated based on the suggested protocol. A significant positive correlation resulted between corticosteroid administration and onsite recovery ($p < 0.001$). A large effect size of 0.5 was considered based on Cohen's 1988 [9]. By adopting an alpha level of (0.05) and a beta of (0.2), the expected sample size (n) was found to be (55) cases. The proposed sample size will be enough to detect a difference of (-0.04) between the null hypothesis correlation of 0.1 and alternative hypothesis correlation of 0.5 using a 2-sided hypothesis. The sample size was increased by 20% to account for possible dropouts during follow-up intervals to be (74) cases. Sample size calculation was performed using G*Power version 3.1.9.7 [10].

Subjects

After ethical approval, a total of 80 participants of both genders, 46 females and 34 males above 18, participated in this study. They were selected and recruited from the out-patient ENT and dental clinic of Al Rayan hospital Maadi, Cairo, Egypt, from May 2021 to August 2021. All the selected patients were tested positive to COVID-19 using polymerase chain reaction and complained of loss of taste and smell sensation. All demographic data were recorded, patients with absolute contraindications for systemic corticosteroids administration, pregnant women, smokers, and patients with any systemic disease or taking any medications that cause loss of taste or smell were excluded from this study.

Patients were illegible to differentiate dysgeusia with loss of appetite. Detailed case history, all signs

and symptoms were recorded included fever $>38^{\circ}\text{C}$, fatigue, myalgia, arthralgia, sore throat, headache, and its localization (diffuse, frontal, other localization), rhinorrhea, nasal obstruction, epistaxis, tinnitus, and hearing loss, sneezing, cough, sputum production, hemoptysis, dyspnea, respiratory rate >22 , crackling sounds during auscultation, nausea, vomiting, diarrhea, and abdominal pain.

After data collection and informing the patients with the nature of the study and signing the informed consent, 10 mg systemic corticosteroid administration was prescribed for all patients as a single dose in the early morning after a meal for the 1st week. It was then reduced to 5 mg in the 2nd week to withdraw it gradually. Weekly follow-up until the regain of taste and smell sensation was done (up to 3 months). Any changes or regain of taste and smell function were recorded in each visit by questioning the patients by investigators. Gustatory and olfactory questions were formulated to detect the reduced, distorted, or complete loss of taste and smell. Time of recovery from anosmia and ageusia after steroid administration were recorded and analyzed.

At the end of the study, patients were assigned into early and late groups according to the duration of their taste and smell dysfunction. Patients with a history of anosmia and ageusia for 2 days up to 1 week were considered in the early group, and more than that considered in the late group.

Statistical analyses

Statistical analysis of the data was performed using Stata (Version 16; StataCorp LLC, TX, USA). Regression analysis was performed to determine statistical significance and the association of time of corticosteroid administrations, Age, gender, and ENT manifestations on recovery duration. $p < 0.05$ was considered statistically significant ($\alpha = 0.05$).

Results

A total number of 80 COVID-19 (41 females and 39 males with non-significant differences between sex with $p = 0.355$ and ages ranged from 18 to 67) patients were examined over 3 months (descriptive characteristics of the study sample presented in the Appendix). Sixty-seven patients completed all the visits till the regain of taste and smell sensation, and 13 patients were excluded from the study as they did not complete their scheduled follow-up. All patients regained their taste and smell functions at the end of the study, and the patients or the investigators reported no side effects from corticosteroids.

Table 1: Regression analysis showing the effect of tested variables on the Duration of Recovery

Duration of Recovery	Coef. (95% Conf. Interval)	SE	t	p-value	Beta
Age	0.07 (-0.09 to 0.24)	0.09	0.83	0.410	0.07
ENT manifestations (Yes)	2.03 (-2.22 to 6.28)	2.13	0.95	0.343	0.09
Sex (M)	2.11 (-1.61 to 5.84)	1.86	1.14	0.260	0.11
Time of corticosteroids administrations	0.27 (0.19 to 0.35)	0.04	7.14	<0.001	0.66
Cons	-0.78 (-7.54 to 5.97)	3.38	-0.23	0.818	

Significance level was set at $p < 0.05$.

Table 1 and Figure 1 representing regression analysis demonstrating that early corticosteroid administration resulted in significant decrease in recovery time (0.27 [0.2–0.35], $p < 0.001$, Beta = 0.66).

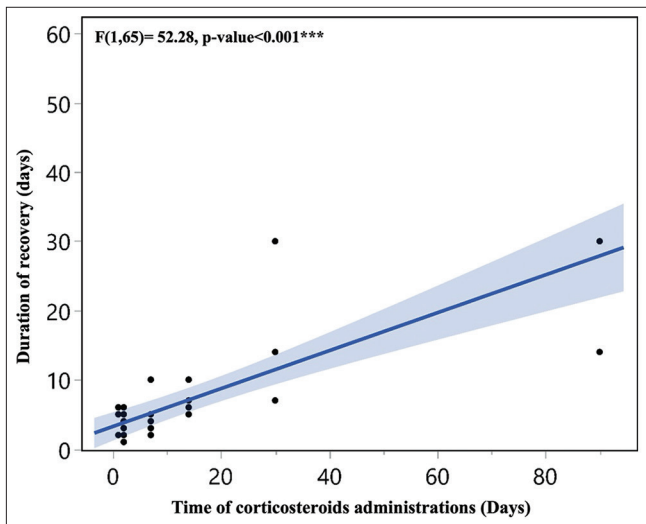


Figure 1: Scatter plot showing the correlation between time of corticosteroid administration and duration of recovery

At the end of the study, all 67 patients were assigned into two groups, early administration group (34 participants), 19 (55.9%) females, and 15 (44.1%) males, while for late administration group; a total of 33 participants 19 (57.6%) female and 14 (42.4%) males.

Figure 2 showing an insignificant difference between mean age for the early administration group

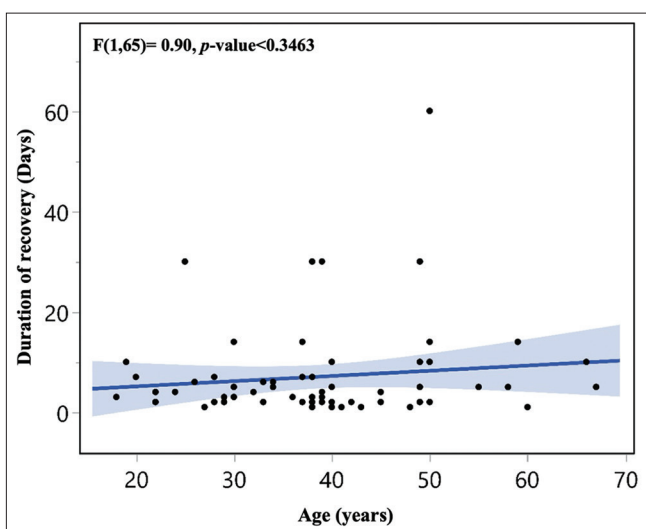


Figure 2: Scatter plot showing the correlation between Age and duration of recovery

(37.6 ± 8.6 years) compared to Late administration (39.3 ± 12.8 years) at $p = 0.520$.

Table 2: The mean and standard deviation of recovery duration in early and late groups

	Early	Late	p-value
Duration of recovery			
Mean	3.02	16.45	<0.001
SD	1.78	13.43	
Median	2.00	12.00	
Minimum	1.00	5.00	
Maximum	10.00	60.00	

Significant limit was set at $p < 0.05$.

Table 2, Figures 3 and 4 represent the difference in duration of recovery for early administration (<1 week) and late administration (>1 week) with a significant difference between them ($p \leq 0.001$).

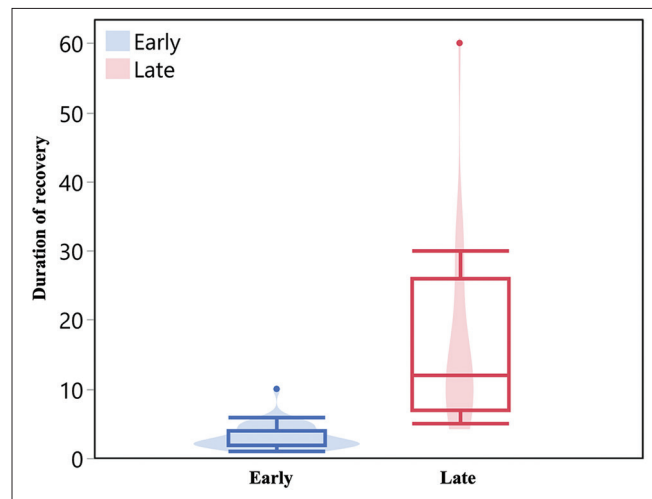


Figure 3: Box plot showing the distribution of duration of recovery for early administration (1 week) and late administration (>1 week)

Discussion

After the rapid spread of coronavirus all over the world with a high incidence of reported ageusia and anosmia in COVID-19 patients and the persistence of

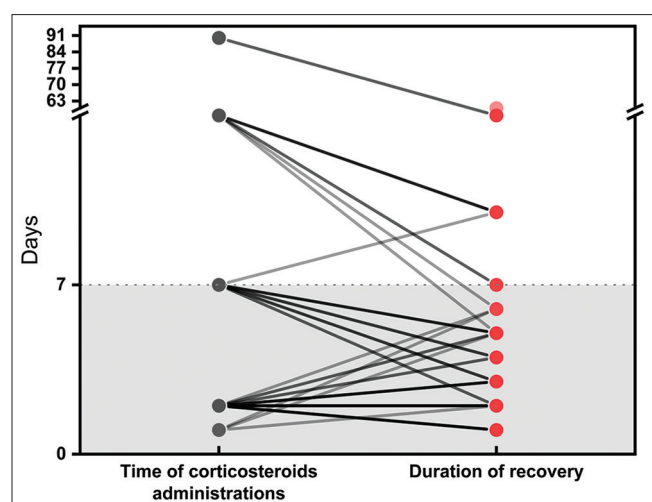


Figure 4: Before-and-after plot showing the time of corticosteroid administration and corresponding duration of recovery for each patient. Gray shaded area represents 1 week time frame

those manifestations for an extended period in 13.1% of affected patients [5], [7], [11] a primary concern was drawn to find a safe medical intervention to help in improving the persistent ageusia and anosmia in those patients to improve a person quality of life [8].

The pathophysiology mechanism of olfactory dysfunction that occurred in COVID-19 patients is still unclear. Still, it may be due to massive inflammation in the olfactory cleft or sensorineural disorder as the virus might cause damage to the olfactory epithelium changing the function and numbers of its receptors [8], [12].

A recent study by Le Bon *et al.* in 2021 [8] reported that MRI showed signs of inflammation in the olfactory clefts in patients with COVID-19 who suffer from anosmia compared to healthy patients. These results suggest that the use of anti-inflammatory drugs such as steroids may be helpful in the treatment of anosmia in COVID-19 patients.

The gustatory function is the ability to differentiate between flavors, mainly on the retronasal stimulation pathway. Its dysfunction is accompanied by retronasal olfactory dysfunction, occurring concurrently with smell dysfunction [1].

The efficacy of corticosteroids in the treatment of ageusia and anosmia in COVID-19 patients had been reported in previous studies [12], [13]. On the contrary, others reported the non-beneficial effect of corticosteroids in treating post-infectious ageusia and anosmia [14]. This may be due to the late administration of corticosteroids (within 3 weeks) in the treatment of patients with post-infectious olfactory dysfunction in those studies [14].

In the present study, patients with early administrations of systemic corticosteroids in the early phase (<1 week) showed an earlier significant improvement in taste and smell functions than those with late administration (>1 week) of systemic corticosteroids ($p < 0.001$). This may be due to the efficacy of corticosteroids to inhibit inflammation in the olfactory cleft [1]. In addition to its ability to improve the regeneration of olfactory sensory neurons and reduce scar tissue formation [15]. In the early phases of neuron treatment corticosteroids would decrease the inflammatory process and reduce injury-associated tissues, as it will be more effective in accelerating olfactory neuron recovery, and thus preventing the irreversible nerve degeneration and permanent olfactory loss [16].

Our results reported that only early corticosteroid administration significantly decreased recovery time (0.27 [0.2–0.35], $p < 0.001$) while other variables had a limited effect on recovery time. They were in accordance with other studies that reported the efficacy of administration of systemic corticosteroids in the early phase of COVID-19 infection than in the late phase in recovery of taste and smell dysfunction [17].

Various doses and duration of systemic

corticosteroids were prescribed in the treatment of post-infectious ageusia and anosmia in various studies that are ranged from 25 to 60 mg for 10 days up to 21 days [13], [14], [18]. In our study, we use low doses of systemic corticosteroids (10 mg) for 7 days and then reduced to 5 mg for other 7 days to investigate its efficacy in the treatment of ageusia and anosmia related to COVID-19 infection complications and to avoid systemic corticosteroids complications as adrenal suppression, recurrent viral, bacterial, and fungal infection and mucormycosis [19], [20]. However, other investigations are recommended to declare the effect of the early use and low doses of systemic corticosteroids in recovery of both taste and smell sensation.

Conclusions

The use of corticosteroids in early phases of COVID-19 infection help in faster improvement in loss of taste and smell dysfunction related to COVID-19 infection complications.

Limitations of the study

Subjective evaluation of regain of both taste and smell dysfunction and not objective.

Ethics

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional research committee (FU-SCSRE) and with the 1964 Helsinki Declaration. Ethical approval number (EC2130). Approval date 11 April 2021.

Clinical trials registration number:
NCT05148832

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Appendix

Appendix: Descriptive characteristics of the study sample

	Early	Late	p-value
Gender, n (%)			
F	19 (55.9%)	19 (57.6%)	0.889
M	15 (44.1%)	14 (42.4%)	
Age (Mean ± SD)	37.6 ± 8.6	39.3 ± 12.8	0.520

Significance level was set at $p < 0.05$.