**Anosmia/ and or ageusia in COVID19 patients: role of early corticosteroids and timeline; Randomized Controlled Trial**

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**Abstract**

**Background**: Since the emergence of the COVID-19 pandemic in China in December 2019, the disease first reported, the number of cases has been exploded. Olfactory and gustatory dysfunctions, unusual symptoms, started to be reported in an increasing number of COVID-19 cases.

**Aim of the work**: The study aimed to compare the effects of early corticosteroids administration versus no administration in the time-to-recovery from olfactory dysfunction in cases with COVID-19.

**Patients and methods:**This comparative, non-randomized study was conducted at Benha University hospital and another primary health center in Cairo, Egypt, from Jan-2021 to June-2021. Eighty-three patients who met the inclusion criteria were assigned into two groups: The early corticosteroids (CS) group (41 cases) and the No-CS group (42 cases).

**Results**: There was no significant difference between the two study groups as regards age, BMI, and gender (p-values > 0.05). Females constituted 65.9% & 59.5% of cases in the early-CS group & the No-CS group, respectively. Also, both groups are comparable with regard to smoking, alcohol abuse, DM, hypertension, and morbid obesity (p-values > 0.05). At presentation, as regards the severity of anosmia, both groups are comparable (p-value = 0.302). Complete anosmia was reported in 80.5% and 78.6% of the early-CS group & the No-CS group, respectively. The mean duration for anosmia onset was 3.7±1 & 4.1±1.8 days in the early-CS group & the No-CS group, respectively (p-value = 0.204). Cacosmia was reported in 14.6% and 4.8% of the early-CS group & the No-CS group, respectively (p-value = 0.156). Also, dysgeusia was seen in 87.8% and 83.3% of the early-CS group & the No-CS group, respectively (p-value = 0.562). Other reported symptoms at presentation were comparable between the two groups; the most frequent symptoms were cough and fatigue/malaise: reported in 80.5% & 75.6% and 71.4% & 73.8% of the early-CS group & the No-CS group, respectively (p-values = 0.335 & 0.85).

Time-to-recovery from anosmia was significantly less in the early-CS group median (IQR) = 7 (9) days than in the No-CS group 14 (10) days, (p-value < 0.001). About 95.1% of cases in the early-CS group recovered in the first two weeks versus only 66.7% in the No-CS group.

**Conclusion**: In conclusion, unless contraindicated, early administration of systemic corticosteroids reduces the time needed to recover from COVID-19 olfactory dysfunction.

**Keywords:** anosmia, olfactory dysfunction, corticosteroids, COVID-19

**Introduction**

Since the appearance of the COVID-19 pandemic in December 2019, the disease first reported, the number of cases has been exploded. 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 reported to the World Health Organization (WHO). There have been 246,909 confirmed cases of COVID-19 with 14,388 deaths in Egypt, reported to the WHO. [[1](#_1._World_Health)]

People of all age groups are at risk for infection and severe disease. However, older people ≥60 years and those with chronic comorbid medical conditions are at 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](#_2._Stokes_EK,)]

The symptoms of COVID-19 are many, with fever, cough, or shortness of breath (SOB) in 70% of cases, myalgia in 36%, and headaches in 34%. Other reported symptoms were rhinorrhea, anosmia, dysgeusia, sore throat, diarrhea, dizziness, abdominal pain, anorexia, and vomiting. [[2](#_2._Stokes_EK,)]

Primarily, COVID-19 is a respiratory disease; however, it also leads to cardiovascular, hematological, dermatologic, hepatic, renal, neurological, and other complications. [[3-11](#_3._Liu_PP,)]

Olfactory and gustatory dysfunctions, unusual symptoms, started to be reported in an increasing number of COVID-19 cases [[12](#_12._Jotz_GP,), [13](#_13._Vargas-Gandica_J,)]. That was reported in several research studies all over the world. In Italy, changes in smell and taste have been reported in more than the third of COVID-19 cases [[14](#_14._Kosugi_EM,)]. Also, in South Korea, anosmia has been reported in 30% of mild COVID-19 cases as the main sign of infection [[12](#_12._Jotz_GP,)]. Also, anosmia has been reported in other studies in Germany (>60% of cases with COVID-19) and Brazil (> 80% of COVID-19 cases) [[12](#_12._Jotz_GP,), [14](#_14._Kosugi_EM,)]. 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](#_15._Kang_YJ,)].

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 and vitamin B complex on the recovery in patients diagnosed with COVID-19.

**Patients and methods**

This pilot non-randomized controlled, interventional study was conducted at Benha University hospital and another primary health center in Cairo, Egypt, upon 81 individuals diagnosed as COVID-19 cases and confirmed by PCR during the period from Jan-2021 to June-2021. The ethical review committee approved the study. The purpose of this study was clearly explained to all patients before their enrollment.

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 in the study. For inclusion in the current study, all of the following criteria were to be fulfilled: age 18 years or more, patients with PCR-confirmed COVID-19 were included in the present study. Exclusion criteria included: pregnancy or lactation, uncontrolled DM, 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, laboratory investigations in the form of erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) & complete blood count (CBC), and ferritin. At presentation, each patient was asked to rate the severity of their olfactory dysfunction on a Likert scale 0 to 5; 0 means no anosmia, 5 means complete loss of smell. They all were asked about the onset of their symptoms in general and the onset of olfactory dysfunction. The patients were categorized into two groups; the early-corticosteroid group, where corticosteroids were used early within 72 hours from their presentation, and the No-corticosteroid (No-CS) group. The dosage of corticosteroids was guided by their condition and inflammatory markers. Hydrocortisone, methylprednisolone, or dexamethasone was used according to their availability. All patients of the two groups were followed until improvement. Participants were informed about potential side effects of corticosteroids (such as sugar craving, sleeplessness, stomach upset, 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 was. The primary outcome measure was the time-to-recovery from anosmia. A p-value of < 0.05 is considered statistically significant. SPSS software (Statistical Package for the Social Sciences, version 24.0, SSPS Inc., Chicago, IL, USA) was used. Quantitative parametric data were presented as mean and standard deviation (mean ± SD). Quantitative non-parametric data were presented as the median and interquartile range (IQR). Qualitative data were presented as numbers and proportions. Comparisons between groups were made using the Chi-square test or Fisher exact test for categorical variables and the independent t-test or Mann-Whitney test for the continuous variables.

**Results**

Eighty-three patients who met the inclusion criteria were assigned into two groups: The early corticosteroids (CS) group (41 cases) and the No-CS group (42 cases).

There was no significant difference between the two study groups as regards age (p-value = 0.691) and BMI (p-value = 0.459). The mean age was 40.7±14.5 and 39.5±12.4 years for the early-CS group & the no-CS group, respectively. The mean BMI was 30.6±7.1 and 29.4±7.2 kg/m2 for the early-CS group & the no-CS group, respectively.

Also, there was no significant difference between the two study groups as regard gender (p-value = 0.551. Females constituted 65.9% & 59.5% of cases in the early-CS group & the no-CS group, respectively. Also, both groups are comparable with regard to smoking, alcohol abuse, DM, hypertension, and morbid obesity (p-values > 0.05), as shown in Table 1.

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

Cacosmia was reported in 14.6% and 4.8% of the early-CS group & the no-CS group, respectively (p-value = 0.156). Also, dysgeusia was seen in 87.8% and 83.3% of the early-CS group & the no-CS group, respectively (p-value = 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: reported in 80.5% & 75.6% and 71.4% & 73.8% of the early-CS group & the no-CS group, respectively (p-values = 0.335 & 0.85).

Time-to-recovery from anosmia was significantly less in the early-CS group median (IQR) = 7 (9) days than in the no-CS group 14 (10) days, (p-value < 0.001), as shown in Figure 1 and in Table 4 & 5. 95.1% of cases in the early-CS group recovered in the first two 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 |
| Gender: 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 |

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% | |  | |

Table 3: Associated symptoms at presentation

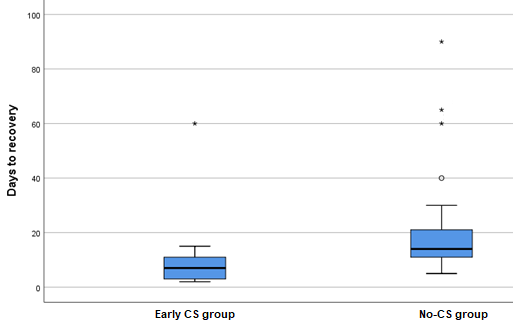
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Early CS group | | No-CS group | |  |
|  | N = 41 | | N = 42 | | P-value |
| Dysgeusia | 36 | 87.8% | 35 | 83.3% | 0.562 |
| Vertigo | 19 | 46.3% | 15 | 35.7% | 0.325 |
| Cacosmia | 6 | 14.6% | 2 | 4.8% | 0.156 |
| Hoarseness | 4 | 9.8% | 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 |

Table 4: Time-to-recovery from Anosmia

|  |  |  |  |
| --- | --- | --- | --- |
|  | Early CS group | No-CS group |  |
|  | N = 41 | N = 42 | P-value |
| Median | 7 | 14 | < 0.001 |
| Interquartile Range (IQR) | 9 | 10 |  |
| Minimum | 2 | 5 |  |
| Maximum | 60 | 90 |  |
| Mean | 8.9 | 18.8 |  |
| Standard deviation | 9.2 | 16.5 |  |

Table 5: 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% |  |



**Diagram 1: Time-to-recovery from Anosmia**

**Discussion**

The higher rate of cases experiencing coronavirus disease 2019 (COVID-19)-related olfactory dysfunction (COVID-19-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 (ENT) clinics. That 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](#_21._Huart,_C,)]

Systemic corticosteroids (CS) are part of ENT tools in several inflammatory and sensorineural conditions. Because COVID-19-OD is likely due to an inflammatory and neurosensory process, systemic CS can be considered an option for treatment. [[21](#_21._Huart,_C,)]

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 group & the No-CS group. Also, dysgeusia was seen in the majority of the early-CS group & the No-CS group. In our study, the mean duration for anosmia onset was 3.7±1 & 4.1±1.8 days in the early-CS group & the No-CS group, respectively. The results of the current work showed that early administration of corticosteroids had a beneficial effect with less time-to-recovery from anosmia than the No administration. Time-to-recovery from anosmia was significantly less in the early-CS group median (IQR) = 7 (9) days than in the No-CS group 14 (10) days, (p-value < 0.001). Around 95.1% of cases in the early-CS group recovered in the first two 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 side effects of systemic CS in COVID-19 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](#_22._Klimek_L,)]. Therefore, when we considered whether such treatment could be used in COVID-19-OD, the potential added benefit versus risk was carefully considered.

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](#_21._Huart,_C,)]

It appears from the literature at hand that COVID-19-OD is reversible mainly for the majority of cases in the short-term (one week) to medium-term (one month). In contrast, minority progress to a persistent OD (hyposmia, parosmia, or cacosmia) typical of the postinfectious OD reported elsewhere. [[23](#_23._Hong_S-C,)]

Owing to their immunosuppressive effect in COVID-19, the World Health Organization (WHO) recommended using CS only in cases with severe and critical COVID-19 as they can lower the mortality rates [[24](#_24._World_Health)]. Contrariwise, their use was not recommended in mild cases of COVID-19 as it may increase the risk of death; however, that conditional recommendation was based only on low-certainty evidence, which is still debated. [[24-26](#_24._World_Health)]

The favorable effect of corticosteroids in postinfectious OD may be attributed to their anti-inflammatory effect. [[21](#_21._Huart,_C,)] 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 received oral CS (prednisolone) improved within six days [[27](#_27._Touisserkani_SK,)]. Nevertheless, that can be attributed to the spontaneous recovery of COVID-19-OD due to the natural evolution of the disease. Recently, a prospective study that compared systemic CS plus olfactory training (OT) to OT alone showed that only cases of the first group significantly improved from OD at tenth week [[28](#_28._Le_Bon)]. 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 being non-randomized and could be subjected 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.

**References**