Efficacy of corticosteroid therapy in the treatment of long-lasting olfactory disorders in COVID-19 patients*

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Abstract

Background: The growing number of COVID-19 patients with long-lasting olfactory disorders makes it necessary to identify effective treatments that enhance the spontaneous recovery of olfactory function.

Methods: Multicentre randomised case-control study that involved 18 patients with COVID-19 related anosmia or severe hyposmia for more than 30 days. Nine patients were prescribed systemic prednisone and nasal irrigation with betamethasone, ambroxol and rinazine for 15 days. The other 9, untreated, patients were used as controls. The olfactory function was evaluated with CCCRC test at 20 and 40 days from the first evaluation.

Results: In the control group, a median olfactory score of 20 (IQR 30) was detected at baseline. At the 20-day control there was no significant improvement in olfactory function. The improvement in olfactory performance became significant at the 40-day follow-up compared to baseline scores [60 (IQR 60) versus 20 (IQR 30)]. In the treatment group, patients had a mean olfactory score of 10 (IQR 15) at initial control. At the 20-day control, a significant im-provement in the olfactory scores, compared to the baseline, was detected [70 (IQR 40) versus 10 (IQR 15)]. Olfactory function further improved at 40 days [median score 90 (IQR 50)]. Patients in the treatment group reported significantly higher improvements of the olfactory scores than the controls at both the 20-day [40 (IQR 45) versus 10 (IQR 15)] and 40-day [60 (IQR 40) versus 30 (IQR 25)] evaluations.

Conclusions: Based on the results of this study, the mix of drugs including steroids could represent a useful specific therapy to reduce the prevalence of this long-term morbidity.

Key words: COVID-19, anosmia, hyposmia, olfactory, corticosteroid

Introduction

Olfactory disorders (OD) represent one of the most frequent and earliest symptoms of coronavirus disease 2019 (COVID-19) [1-10]. Although most patients recover normal olfactory function

within 15 days, severe anosmia or hyposmia persist in 7-8% of patients two months after clinical onset[11-13]. This frequency of severe OD, given the high prevalence of COVID-19, means that there will be a significant number of patients with long-term morbidity. For this reason there is a need to identify effective treatment that enhance the spontaneous recovery of olfactory function. Although trials of treatment for post-viral loss due to other viruses have been reported[14], to date there is only one case report in which a COVID-19 patient with anosmia was treated with oral corticosteroids obtaining regression of the dysfunction[15]. Guidelines suggest that systemic steroids and steroid rinses may be considered in the management of COVID-19 related OD[16].

In addition to the paucity of prospective studies investigating the prevalence of long term OD, a further challenge is that the pathogenesis of OD in COVID-19 has not yet been fully elucidated[17]. Only recently, researchers have shifted their attention from the olfactory bulb to the olfactory epithelium (OE) as a possible site of viral damage[18]. This paradigm shift was driven by the tendency to rapid and complete regression of the OD in most cases[11-13], by radiological evidence of olfactory cleft obstruction in anosmic patients[19], by the high concentration of ACE2 receptors in the supporting cells of the OE[20,21] and from the detection of high concentrations of proinflammatory cytokines in the OE in COVID-19 patients with OD[22]. More recently, the first histopathological studies reported inflammatory neuropathy with prominent leukocytic infiltrates in the lamina propria, focal atrophy of the olfactory mucosa and digestion chambers in the neuronal fibers in the acute phase of the infection[23] and the massive disruption of the olfactory epithelium and mild chronic inflammatory infiltrate in a COVID-19 patient with long term anosmia[24].

All of these evidences support the possible role of corticosteroid therapy in the prevention and treatment of long-lasting OD in COVID-19 patients and the purpose of this case-control study was to evaluate its efficacy.

Materials and Methods

Ethics

This multicentre prospective randomised case-control study was conducted at the University Hospital of Sassari and the Bellaria-Maggiore Hospital in Bologna (Italy). The evaluation protocol was approved by an independent ethics committee (n° 378-2020-OSS-AUSLBO) and informed consent for participation in the study was obtained. Patients were not concurrently participating in any other studies and their outcomes were not included in any other cohorts.

Patients

To be enrolled in the study the patients had to meet the following inclusion criteria: adult over 18 years of age, previous SARS-CoV-2 infection confirmed after nasopharyngeal swab, recovery from infection confirmed by at least two negative nasopharyngeal swabs, Connecticut chemosensory clinical research center (CCCRC) test score ≤ 40 (e.g. anosmia or severe hyposmia) at 30 days after clinical onset. Patients with a history of previous olfactory dysfunction, trauma, surgery or radiotherapy in the oral and nasal cavities, self-reported allergic rhinitis or rhinosinusitis, psychiatric or neurological diseases and contraindications to corticosteroid therapy were excluded from the study.

The patients included in the study were randomly divided into two groups using a computer-generated random number table: the treatment group that was prescribed corticosteroid treatment and the control group that did not receive any therapy.

The therapy group was treated with the therapeutic scheme routinely used in our centers for the treatment of anosmia of inflammatory aetiology. The use of systemic and local corticosteroids for the treatment of olfactory disorders has al-ready been described in the literature and its effectiveness is well recognized[25,26]. All the patient of the treatment group were prescribed systemic cortisone therapy with prednisone, starting with 1 mg/kg/day and tapering the dose for 15 days and nasal irrigation with betamethasone, ambroxol, a mucolytic, and rinazine, a decongestant, for 15 days.

Olfactory function

Olfactory function of all the patients in both groups was re-evaluated by means of the CCCRC test 20 (5 days after the end of therapy in the treatment group) and 40 days after the first evaluation. The CCCRC is a simple, validated and widely used test, that includes a butanol threshold assessment and an odor identification test using common odors[27-29].

Threshold testing was performed presenting solutions of N-butanol in deionized waters, decreasing concentration in 8 steps. The strongest butanol concentration was 4% in 60 mL of deionized water (bottle 0). Each other bottle (from 1 to 8) contained a subsequent 1:3 N-butanol dilution. Two identical squeezable bottles were presented to the patient: one containing the N-butanol solution, starting from the major dilution, and the other filled with deionized water. The patient was then asked to close one nostril and squeeze the bottle immediately below the other, reporting which of the two bottles smelled most. The threshold was identified when the subject gave the correct answer 4 times. In case of error, the next most concentrated solution was given to the patient. The threshold was quantified for each of the two nostrils with a score from 0 to 8 corresponding to less concentrated bottle that the patient was able to correctly detect. The average between values of the two nostrils expressed the overall score.

For the identification test, ten well-known Italian odorants were used: chocolate (Nutella, Ferrero, Italy), coffee, baby powder (Manetti & Roberts, Florence, Italy), Vicks-VapoRub (Proctor &

Table 1. Connecticut chemosensory clinical research center test results.

Patient ID / Sex / Age	CCCRC score		
	Baseline	20 Days	40 Days
Treatment group median (IQR)	10 (15)	70 (40)	90 (50)
1/M/38	0	40	60
2/F/55	10	20	40
3/F/42	30	70	90
4/F/27	10	70	100
5/M/51	20	40	80
6/F/34	10	70	100
7/M/50	10	70	90
8/F/47	0	0	20
9/M/39	20	80	100
Control group median (IQR)	20 (30)	30 (30)	60 (60)
1/F/44	20	30	50
2/F/51	0	0	10
3/F/28	10	30	80
4/F/31	30	30	70
5/M/45	0	0	10
6/M/37	20	20	60
7/F/39	0	10	20
8/F/42	30	40	60
9/M/57	40	60	80

Table 2. Statistical analysis results.

Wilcoxon signed-rank test		
	Z	P-value
Treatment group		
20 days versus baseline	-2.484	0.013
40 days versus baseline	-2.620	0.009
Control group		
20 days versus baseline	-1.932	0.053
40 days versus baseline	-2.620	0.009

Mann-Whitney U test			
	CCCRC Score at baseline Median (IQR)	CCCRC Score improvement at 20 days Median (IQR)	CCCRC Score improvement at 40 days Median (IQR)
Treatment group	10 (15)	40 (45)	60 (40)
Control group	20 (30)	10 (15)	30 (25)
P-value	0.586	0.011	0.024

Gamble, Cincinnati, OH, USA), ammonia, fruit-flavored chewing gum (Perfetti Van Melle Italia S.r.l, Lainate, Italy), ketchup (Heinz, Pittsburgh, PA, USA), orange, soap (Ivory, Proctor & Gamble, Cincinnati, OH, USA) and black pepper. The odorants were presented one at a time, in identical and opaque 180 mL containers covered by gauze. Therefore, the patient had to identify the odorant on a 20 items list containing the 10 test samples and 10 distractors.

The threshold and identification test scores were finally converted into the CCCRC composite score which allows to classify the olfactory function of patients in normal (score 90 and 100), mild hyposmia (score 70 and 80), moderate hyposmia (score 50 and 60), severe hyposmia (score between 20 and 40) and anosmia (score 0 and 10)(27-30).

Statistical analysis

Both the researcher who performed the pre- and post-treatment psychophysical assessment of smell and the statistician who analyzed the data were blinded to the patient allocation group. Statistical analysis was performed with SPSS 26.0 (IBM, Armonk, NY, USA). Categorical va-riables are expressed in numerals and percentages of the total. Descriptive statistics for quantitative variables are given as the mean ± standard deviation (SD). Wilcoxon signed-rank test for paired data was performed to evaluate the statistical significance of changes in olfactory scores between the first and the second evaluation times. The analysis of the differences in scores between the two groups was performed by means of Mann-Whitney U-test. The level of statistical significance was set at $p < 0.05$ with a 95% confidence interval.

Results

Eighteen patients (7 males, 11 females, mean age 42.1 years) with anosmia or severe hyposmia 30 days after the clinical onset of COVID-19 were enrolled for the study. All patients enrolled in this study had mild or moderate forms of COVID-19 and did not require hospitalization. None of the patients received corticosteroid therapy during the infection.The patients were randomly divided into the two study groups of 9 patients each. The two groups did not show significant differences in the gender ($p = 0.629$), age ($p = 0.894$) and baseline olfactory score ($p = 0.586$) of the patients.

Table 1 and Figure 1 report the evolution of the olfactory scores during the observation period for all patients of both groups. Table 2 provides a summary of the results of the statistical analysis. In the control group, a median olfactory score of 20 (IQR 30) was detected at baseline, 4 patients were anosmic while severe hyposmia was detected in 5 cases. At the 20-day control there was no significant improvement in olfactory function ($p = 0.053$). The improvement in olfactory perfor-mance became significant at the 40-day follow-up compared to baseline scores [60 (IQR 60) ver-sus 20 (IQR 30); $p = 0.009$]. At the end of the observation

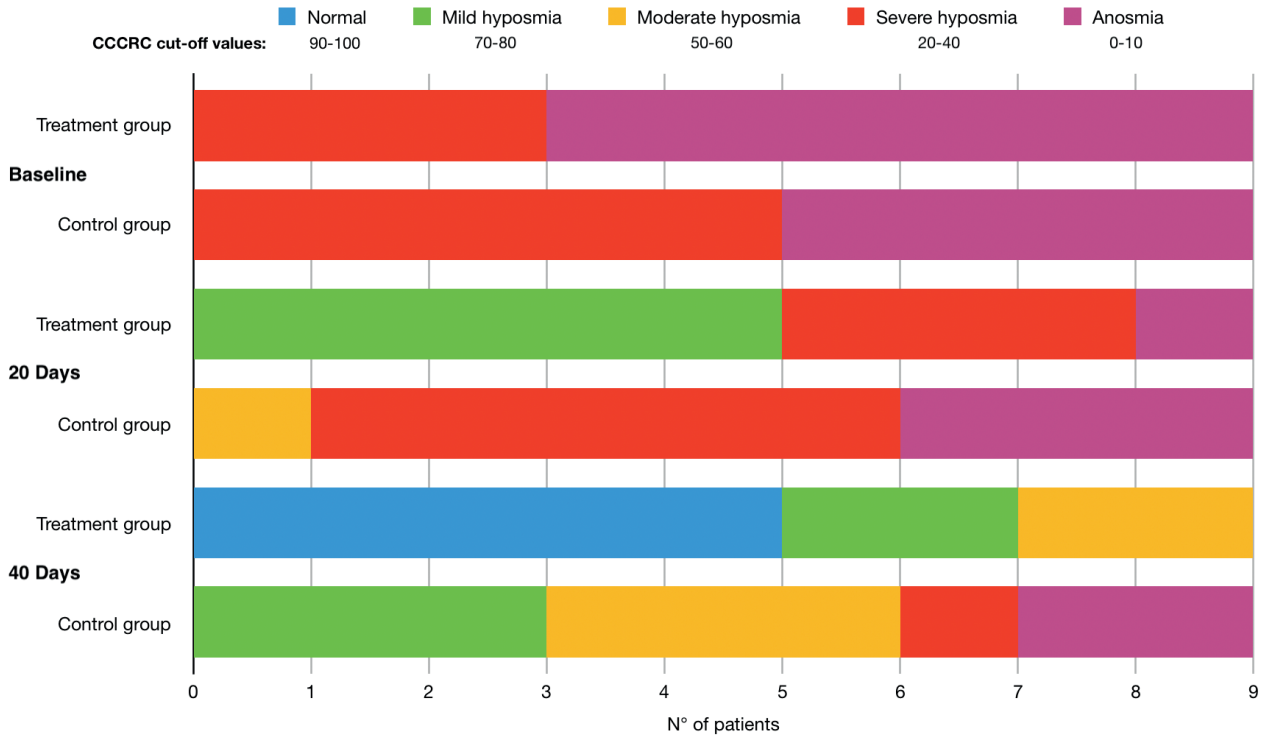

Figure 1. Clinical dysfunction at each observation time.

period, no patient presented with nor-mal olfactory function: mild and moderate hyposmia were each present in 3 patients, while a resid-ual anosmia and severe hyposmia were detected in 1 and 2 cases, respectively (Figure 1).

In the treatment group, patients had a median olfactory score of 10 (IQR 15) at initial control 6 patients were anosmic while severe hyposmia was detected in 3 cases. At the 20-day control, 5 days after the end of therapy, a significant improvement in the olfactory scores, compared to the baseline, was detected [70 (IQR 40) versus 10 (IQR 15); p = 0.013). Olfactory function further improved at 40 days [median score 90 (IQR 50); p = 0.009), 5 patients had completely recovered their sense of smell and no subjects had residual severe hyposmia or anosmia [Figure 1]. No pa-tient developed any side effects related to the therapy.

Patients in the treatment group reported significantly higher improvements of the olfactory scores than the controls at both the 20-day [40 (IQR 45) versus 10 (IQR 15); p = 0.011] and 40-day [60 (IQR 40) versus 30 (IQR 25); p = 0.024] evaluations [Table 2].

Discussion

The results of this study regarding the efficacy of corticosteroid therapy in the treatment of long-lasting severe olfactory disorders in COVID-19 patients are encouraging. Patients undergoing treatment demonstrated a faster and more effective recovery of olfactory function than controls.

The use of systemic corticosteroids in COVID-19 therapy is still under discussion and their indication is limited to the treatment of more severe cases[31,32]. There are concerns regarding the use of systemic steroids in cases with or at risk of severe acute respiratory COVID-19, as systematic review of usage in influenza suggests possible harm[33] and delayed viral clearance has been demonstrated in SARS-CoV-2 infection[34].

On this basis, we think it is prudent to postpone the initiation of specific therapy for olfactory dysfunction in the first two weeks (where there remains a risk of respiratory deterioration, but also very high rates of spontaneous recovery of olfactory loss) or after nasopharyngeal swabs become negative. In our experience, therapy is more effective the earlier it is started. For this reason, in case of severe olfactory disturbances persisting after viral clearance has completed, we consider it ap-propriate to start treatment. Of course, there would still be a chance for a full and spontaneous recovery in the following weeks. But, as recently found in a prospective study conducted by our research group, the risk of having severe persistent olfactory dysfunction becomes significant al-ready in patients who present with a severe disorder 20 days after clinical onset[11]. We have observed that the effectiveness of this treatment regimen in patients with anosmia persisting for more than 3 months appears reduced compared with those receiving treatment at an earlier stage, and patients generally report only partial improvements in olfactory function. Extensive deepithelialization of OE with mild chronic inflammatory infiltrate was noted in a patient with persis-tent OD at 3 months[24]. This damage could be caused and maintained by inflammatory phenomena, particularly evident in

the earliest stages of infection[23]. Corticosteroids could reduce local in-flammation allowing OE to regenerate, while ongoing local inflammation may reduce the regenera-tive capacity of the OE causing loss of stem cells or other progenitor cells. However, optimum timing of treatment needs to be further evaluated as the reduced benefit of later treatment it may simply reflect selection bias of patients with a poorer prognosis presenting at a later stage.

This study has some limitations. Firstly, the findings should be replicated in a larger study, howev-er, significant differences were demonstrated between the two groups despite the relatively small patient number. There is a risk of type 1 error with the application of repeated tests, and we if cor-rection for multiple testing is applied, then the difference between groups at day 40 would not quite reach significance; given the small number in the study this itself could be a type 2 error, which itself is the drawback of the Bonferroni correction. Certainly a larger study would be helpful in this regard.

The treatment arm included a combination of intranasal and systemic steroids in addition to a mu-colytic and a decongestant. The latter two treatments were included on the assumption that a viral induced rhinitis would caused significant nasal congestion and nasal discharge and the aim of these two added treatments were to help ensure delivery of the intranasal steroid to the olfactory cleft. As our understanding of the pathophysiology has grown, we now know that patients do not report high rates of nasal discharge or blockage, and that oedema of the olfactory cleft is not frequently identified on imaging[19]. We therefore suspect that these two treatments have not made a significant contribution to the improvements reported in the treatment group, however it would be important to analyze the different components in the treatment regimen to understand if local and systemic corticosteroid therapies are more effective in combination or alone, and if the mucolytic or decongestant confer any added benefit. Ideally future studies should also be placebo controlled, although the use of psychophysical testing should reduce the risk of a placebo effect. Endoscopic assessment of patients was not included due to restrictions on aerosol-generating procedures, although it would be useful to include in future trials. Olfactory cleft oedema has been reported in patients undergoing MRI imaging within 15 days of onset of loss of smell, but had resolved on the majority at one month[35]. If still present in out cohort at the time of recruitment at day 20, it might be important in any effect of corticosteroids and decongestants and may be a predictor of response to therapy.

Finally, it will be important to extend the observation period up to over 60 days or more, as even at this distance from the clinical onset it is possible to detect significant improvements in olfactory function[11]. Longer follow-up will also help to determine if treatment reduces the development of parosmia, which is commonly reported in patients with COVID-19 related OD. We plan to follow these patients for 6-8 months after clinical onset.

The greatest strength of this study is that it one of the first reported randomised trials aimed to find an effective therapy to reduce the prevalence of long-lasting severe olfactory disorders in COVID-19 patients. In an untreated population, a prevalence of 7-8% is reported at 8 weeks[11, 36-38] and this means, given the high incidence of infection in the population, that there are significant and increasing numbers of patients with persistent smell disorders.

Conclusion

Based on the results of this study, the mix of drugs including steroids could represent a useful spe-cific therapy to reduce the prevalence of this long-term morbidity.

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Authorship contribution

LAV, MP, SC, GS, GdR, contributed to study design, data collection, interpretation of results, drafting and critical evaluation of the final manuscript. CH contributed to study design, interpretation of results, drafting and critical evaluation of the final manuscript. JL, CC-E, SS contributed to interpretation of results and critical evaluation of the final manuscript.

Conflict of interest

None declared.

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