



Efficacy and safety of oral corticosteroids and olfactory training in the management of COVID-19-related loss of smell

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Abstract

Purpose As the COVID-19 pandemic continues, an increasing number of patients are afflicted by olfactory loss, a now well-recognized symptom of the disease. Though many patients seem to recover their sense of smell after a few weeks, a certain proportion of them seem to develop long-lasting olfactory disorder. Yet, as of October 2020, there is no recommended standardized treatment to reduce the risk of developing long-term olfactory disorder. In this pilot study, we investigated the efficacy and the safety of oral corticosteroids and olfactory training as a treatment for patients with persistent olfactory dysfunction as a result of COVID-19.

Methods Non-hospitalized patients with a sudden loss of smell and a confirmed COVID-19 diagnosis were recruited by hospital call from February to April 2020. These participants were submitted to an extensive psychophysical testing in order to identify those with persistent dysosmia. Dysosmic patients were then treated either by a 10-day course of oral corticosteroids combined with olfactory training, or by olfactory training alone. All participants were subject to a second olfactory test after a mean of 10 weeks.

Results 72 subjects with documented COVID-19 infection performed the initial olfactory test, on average 5 weeks after losing their sense of smell. Amongst them, 27 (37.5%) patients showed persistent dysosmia and were all included in this study. Nine participants received oral corticosteroids and performed olfactory training (OCS + OT), while 18 performed olfactory training (OT) only. Only participants in the OCS + OT group had significantly improved their olfactory score and did so above the minimal clinically important difference for subjective improvement of smell ($p=0.007$). Three of the participants who received oral corticosteroids reported minimal and transient side effects.

Conclusion This pilot study may suggest the combination of a short course of oral corticosteroids and olfactory training is safe and may be beneficial in helping patients with enduring dysosmia recover from olfactory loss due to COVID-19. There is a crucial need for further investigation with larger cohorts to corroborate these findings.

Keywords Oral corticosteroids · Olfactory training · Loss of smell · Anosmia · COVID-19

Introduction

The clinical evolution of loss of smell due to COVID-19 is still unclear as reports of recovery vary significantly, ranging from 4 to 89% a month after the onset of anosmia [1, 2].

Studies relying on more reliable data, such as psychophysical testing, showed persistent abnormal olfactory scores in 37% to 52% of patients 5 weeks after onset [2, 3]. Loss of smell due to COVID-19 may be more prevalent and severe than in other viral upper respiratory infections. Huart et al. found that olfactory function was more affected in patients with COVID-19 than those with common cold [4]. As they pointed out, though most patients should make a full recovery, it is likely that a certain proportion of them will develop permanent post-viral olfactory dysfunction (PVOD). This is already known to be the case for patients with an upper respiratory infection caused by viruses such as parainfluenza, rhinovirus, or other coronaviruses [5]. Even a small

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proportion of affected patients may number in the tens of thousands in the case of COVID-19. Permanent olfactory loss may lead many to suffer from known comorbidities, such as depression and impaired cognition, and even maybe from earlier death [6, 7].

To date there is no evidence-based medical intervention to help patients with persistent dysosmia due to COVID-19, although olfactory training (OT) has been recommended [8]. Initially, oral corticosteroids (OCS) were strongly contraindicated by the World Health Organization; however, mounting evidence shows significant benefit on mortality in patients with severe forms of COVID-19 [9–11]. Moreover, some studies have shown that systemic corticosteroids actually improve olfaction in some patients with PVOD [12, 13]. However, it has been argued that this benefit may only be observed if the patient is treated at an early stage of the acute phase [14]. Currently, no studies have investigated the use of OCS and OT in a prospective cohort. In this short communication, we report a short-term evaluation of efficacy and safety of OCS and OT in patients with persisting dysosmia due to COVID-19.

Material and methods

This pilot prospective study is the continuation of our study on 72 non-hospitalized patients with loss of smell due to COVID-19 [2]. The study protocol was approved by the Review Board of our institution (CHUSP 200422). Written informed consent was obtained from all participants.

Orthonasal olfactory function was evaluated by the “Sniffin’ Sticks” battery test (Burghart GmbH, Wedel, Germany) which comprises three olfactory tasks: threshold, discrimination, and identification. The sum of the scores from the three subtests makes up the “threshold discrimination identification score” (or TDI score) which was used clinically to assess olfactory performance. Participants were considered normosmic or dysosmic when $TDI \geq 30.75$ and < 30.75 , respectively [15].

The first olfactory testing session (TDI-1) was performed in April 2020, 5 weeks after the onset of loss of smell on average. Patients who scored in dysosmic levels were separated into two groups: one receiving a 10-day course of 32 mg of methylprednisolone once daily combined with OT, and the other performing OT alone. All patients showed no persistent symptoms of COVID infection, except for olfactory loss. They were all checked for potential contraindications to OCS, such as immunosuppressive conditions (e.g., AIDS, chemotherapy), active infection, peptic ulcer, diabetes, glaucoma, psychotic disorder, or recent attenuated vaccine. Given the safety concerns about oral steroid use held by the medical community and by the general population, participants were informed about potential side effects of a

short course of OCS (such as sleeplessness, sugar craving, stomach upset, blood pressure increase) and were asked to opt for treatment group on a voluntary basis. All patients performed a second olfactory testing session (TDI-2) after 10 weeks to assess the evolution of olfactory function. The change in TDI scores between both sessions is referred here as $\Delta TDI = TDI-2 - TDI-1$.

For each session of OT, patients were asked to mindfully sniff four odors for approximately 10 s each (rose, eucalyptus, lemon, cloves). These were provided in a ‘Smell Training Kit’ (Dos Medical-BV, Heteren, Netherlands). Patients were asked to perform sniffing sessions twice daily, for 10 weeks. They had to report their compliance to OT which was evaluated with the following formula: number of OT sessions per day/2 × number of days per week/7 × number of weeks/10.

Continuous variables were compared using Wilcoxon signed-rank test and Mann–Whitney test for two related and independent groups, respectively. Fisher’s exact test was used to compare categorical data, and Spearman correlation to analyze the relationship between age, sex, compliance to OT, and ΔTDI score. Statistical significance was fixed at $\alpha = 0.05$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS version 25; IBM Corp, Armonk, NY, USA).

Results

Based on extensive olfactory psychophysical testing, 27 (37.5%) out of 72 patients were still dysosmic 5 weeks after having lost their sense of smell (6 had anosmia, 21 had hyposmia). Only 9 participants volunteered for the OCS + OT group, whereas 18 opted for performing OT alone. As aforementioned, this mismatch in group size was mainly due to safety concerns about steroid use among study participants. Although both groups were not randomized, age, sex and initial olfactory score (TDI-1) showed no statistically significant difference (Table 1). After 10 weeks, patients in the OCS + OT group had significantly improved their olfactory score by 7.7 points on average ($p = 0.007$), compared with a 2.1-point increase in the OT group ($p = 0.126$) (Fig. 1). Additionally, a Mann–Whitney U Test confirmed the significant difference in ΔTDI scores between the OCS + OT group and the OT group ($p = 0.046$).

Average compliance to OT was 43% (CI 23–63%) for the OCS + OT group, and 31% (CI 16–47%) for the OT alone group, but this difference was not statistically significant. Neither age, sex, or compliance to OT was correlated to TDI score in any group. Of the nine participants who received OCS, three reported minimal and transient side effects such as abdominal pain and insomnia. No patient reported side effects related to olfactory training.

Table 1 Patient characteristics, olfactory scores, and compliance to olfactory training according to treatment group in 27 patients with persistent dysosmia due to COVID-19

	OCS + OT (N=9)	OT (N=18)	p value	Test
Patient characteristics				
Age (mean ± SD), years old	42 ± 14	44 ± 14	NS	MW
Sex (F/M)	7/2	14/4	NS	F
Olfactory testing				
TDI-1 score (mean ± SD), /48	19.7 ± 9.9	24.9 ± 6.1	NS	MW
ΔTDI score (mean ± SD), /48	7.7 ± 5.1	2.1 ± 5.5	0.046	MW
Olfactory training				
Compliance (mean ± SD), %	43 ± 26	31 ± 31	NS	MW

F/M female/male, F Fisher's exact test, MW Mann–Whitney U test, NS not significant, OCS oral corticosteroids, OT olfactory training, SD standard deviation, TDI score threshold–discrimination–identification score

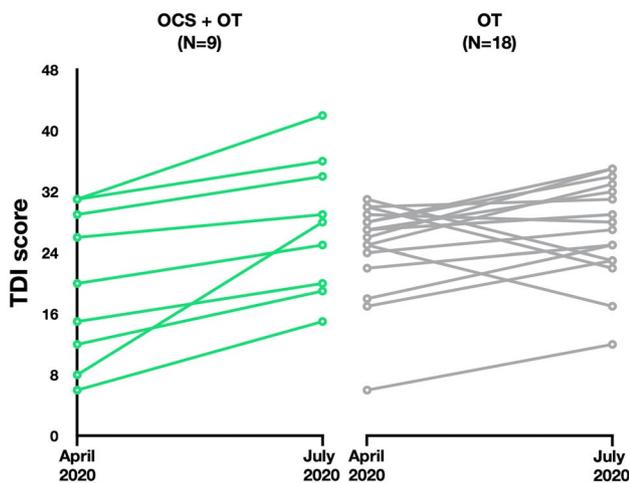


Fig. 1 Evolution of olfactory loss due to COVID-19 for two treatment protocols. Comparison of the evolution of olfactory function (TDI score) between April and July 2020 in dysosmic patients depending on their treatment group: oral corticosteroids and olfactory training (OCS + OT; $n=9$; left) versus olfactory training alone (OT; $n=18$; right). TDI score = threshold–discrimination–identification score

Discussion

The SARS-CoV-2 pandemic is still ongoing and many patients keep on presenting to medical centers with sudden onset olfactory dysfunction. Although, the majority seems to recover completely after a few weeks, a small proportion seems to display persistent olfactory dysfunction with disturbing symptoms such as parosmia and phantosmia [2]. A small proportion in a global pandemic still represents a colossal number of patients, especially as the number of infected patients continues to grow worldwide. Although typically a very rare complaint in daily ENT practice, permanent olfactory dysfunction may thus become a frequent reason for consultation and solicitation for medical treatment. For this reason, a potential medical

treatment may prevent future patients from experiencing a permanent decline in quality of life.

Two recent articles by Miwa et al. and Hura et al. reviewed the literature on medical management for PVOD which included zinc, traditional Japanese medicine, alpha-lipoic acid, vitamin A, minocycline, theophylline, acupuncture, systemic and topical steroids, and OT [6, 14]. Although none of these treatment options reached grade A evidence of efficacy, both reviews concluded that OT is the recommended approach. OT was associated with minimal harm effect and was found to be of most benefit in improving olfactory function, all the more so if started early on and with high compliance. The only inconvenience was the need for a sustained daily training for months. By contrast, in our study, we did not observe a significant increase in olfactory function in patients performing OT alone after 10 weeks of training [16].

Whether COVID-19-related olfactory dysfunction is the result of excessive inflammation or a sensorineural disorder, or a combination of both is unknown. Similarly, the mechanism by which OT and steroid therapy could reduce the risk of PVOD and improve olfaction is yet to be determined. Studies on dysosmic mice suggest that the decision to treat with steroids or OT may ultimately depend on the cause of the olfactory loss [17]. Recently, MRI studies showed signs of inflammation of the olfactory clefts of COVID-19 patients with acute anosmia compared to healthy controls, suggesting a possible role for anti-inflammatory drugs such as steroids [18, 19]. The idea of treating PVOD with corticosteroids is not new, but high-evidence studies are lacking and the few available studies provide conflicting results. As Miwa et al. highlighted, steroid treatment may be effective for post-viral olfactory loss only in the early stages of the disease, when lesions are not yet irreversible. This could explain why patients suffering from PVOD for many years have not responded to steroid therapy. Taken together, both reviews conclude that steroids may be a treatment option if given early on in

the disease course and in selected patients without medical contra-indications.

In this pilot study, participants in the OCS + OT group showed a significant increase of 7.7 points on average in their TDI score, compared to an insignificant 2.1-increase in the OT group. Moreover, Gudziol et al. showed that the minimal clinically important difference for subjective improvement of smell was a 5.5-point increase in TDI score, suggesting a possible clinical benefit in the OCS + OT group [20]. Besides, as participants started OCS on average 5 weeks after the acute loss of smell, future studies may observe better TDI recovery scores from treating patients during the acute phase of COVID-19. As of today, the use of OCS to treat COVID-19 is still contentious, though significant benefit has been shown on mortality among severe COVID patients with no risk of serious adverse event [10]. With regard to the use of steroids for olfactory dysfunction due to COVID-19, only a case report has been published which endorses the use of oral prednisolone as soon as nasal swab becomes negative [21].

Our study's main limitation was its small sample size, particularly those in the OCS group. This was mainly due to safety concerns surrounding the use of steroids in treating COVID-19 in April 2020. Unfortunately, this prevented us from randomizing our treatment groups. In turn, it is difficult for our preliminary findings to be conclusive about the potential benefits of OCS and OT, and caution is warranted. Ideally, larger cohorts and a control group of dysosmic patients would help separate the effect of treatment from spontaneous recovery. A final limitation was the low level of compliance for olfactory training, which did not exceed 50% on average in either groups. The fact that only 6 out of 27 patients were anosmic may have limited participants' motivation to perform OT correctly in some hyposmic patients [22]. Moreover, low compliance may partly explain the absence of noticeable improvement in the OT group in our study. Although our statistical tests did not find a correlation between higher compliance to OT and higher TDI score, this is most likely due to the limited group size of our study. Future studies on OT may benefit from higher compliance, longer duration of training, and larger cohorts.

Conclusion

The findings of this pilot study support the safety and efficacy of combining oral corticosteroids and olfactory training in the management of olfactory dysfunction resulting from COVID-19 infection as well as give impetus for randomized clinical trials to corroborate these results. Future studies on olfactory loss due to COVID-19 may investigate the use of steroids in larger cohorts and earlier in the course of the disease now that safety concerns about corticosteroids may

be less founded than previously thought and patients more inclined to take them.

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Author contributions LB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization and Methodology: LB, H. Acquisition, analysis, or interpretation of data: LB, H, PI, PR. Original draft preparation: LB. Critical revision of the manuscript for important intellectual content: H, L, K. Statistical analysis: LB.

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Compliance with ethical standards

Conflict of interests The authors have no conflict of interests to declare.

Ethics approval The study was performed in accordance with the Declaration of Helsinki on Biomedical Studies Involving Human Subjects. The study protocol was approved by the Review Board of CHU Saint-Pierre, Brussels, Belgium (CHUSP 200422).

Consent to participate Informed written consent was obtained from all participants to participate in the study.

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