Post-COVID-19 olfactory training: How to improve results?

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Objective: To evaluate the response to olfactory training (OT) in patients with persistent olfactory dysfunction (OD) post-COVID-19, in addition to clarifying whether periodic change or increase in the number of essences in OT is capable of increasing therapeutic success in these patients.

Method: Multicenter randomized randomized trial, including individuals with post-COVID-19 OD who remained with olfactory complaints after 4 weeks of infection. The patients were randomized into 3 groups for OT: the first group received 1 kit with classical olfactory training (OCD) with 4 essences, the second received modified TO (TOM) (3 different kits with 4 essences in each, with monthly toggle of the kits) and the third received advanced TO (TOA) (3 kits with 8 essences each, with monthly alternation of the kits). All patients underwent a complete ENT physical examination, followed by subjective measurement of smell and taste through the Visual Analog Scale (VAS), in addition to psychophysical evaluation through the Smell Identification Test of the University of Pennsylvania (UPSIT). The evaluation was repeated after 12 weeks of follow-up.

Results: Of the 340 patients initially selected, 77 patients between 18 and 60 years of age were followed, with the following distribution: 25 patients in the OCD group, 23 in TOM and 29 in TOA. The groups had homogeneous distribution regarding age, gender, history of smoking, magnitude of the complaint in the infection and interval between infection and initiation of treatment. In all groups, there was a statistically significant improvement after 12 weeks in both UPSIT ($p < 0.0001$) and VAS (p 0.001). The mean increase in UPSIT was 2.8 points and subjective improvement occurred in 74% of patients. In the comparison between the groups, there was no statistically significant difference between OCD, TOM and TOA both in the psychophysical test and in the subjective evaluation of smell and taste. Among the factors related to the therapeutic response, a negative correlation was found between the COVID-19 interval and the beginning of treatment and the increase in the UPSIT score with treatment (p 0.032), but with a weak correlation (Spearman's correlation coefficient 0.24). In patients who reported olfactory fluctuation (periods of improvement and worsening) at the first visit, the UPSIT score was significantly higher both in the first evaluation ($p < 0.001$) and after 12 weeks (p 0.001).

Discussion: Several studies continue to reinforce the central role of OD in the treatment of persistent OD1, but little is known about post-COVID-19 OD and it is very interesting to know how to optimize its results. In the present study, in 12 weeks of OT there was an improvement in both the UPSIT score ($p < 0.0001$) and the VAS (p 0.001). This was the first study to compare the response to OCD and the variations performed, however, we did not obtain statistically significant differences between the OT groups. Rezaeyan et al. compared periodic alternation of odors with OCD and also found no difference. However, when studying post-infectious OD, Altundag et al., OT with alternating essences was higher than OCD at 36 weeks, but this difference was more significant only after 12 weeks. In the evaluation of the general group, patients who started OT early obtained significantly higher scores in the UPSIT, reinforcing the importance of not delayed the beginning of treatment. Olfactory fluctuation at the onset of OT was associated with better prognosis which may suggest that this symptom is related to neuroepithelium regeneration.

Conclusion: The data indicate that the early precocity of OT in patients with persistent OD post-COVID-19 is associated with better response, whereas periodic change or increase in the number of essences for 12 weeks is not superior to the classical method. In addition, a fluctuating olfactory ability at the beginning of treatment seems to be related to a better UPSIT score.

Keywords: Olfaction; COVID-19; Rehabilitation.

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Correlation between acute inflammatory markers and late evaluation of post-COVID olfactory function

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Objectives: To evaluate the relationship between late olfactory function in post-COVID-19 patients and serological inflammatory markers in the acute phase.

Methods: Cross-sectional, analytical and observational study. A number of 123 patients with a history of hospitalization by COVID-19 were recruited. Olfactory dysfunction (OC) was evaluated using the Connecticut Chemosensory Clinical Research Center (CCCRC) test, and data from the medical records were reviewed regarding serological markers of acute systemic inflammation – lymphocytes, lactate dehydrogenase (LDH), ferritin, C-reactive protein (PCR) and D-dimmer.

Results: The mean interval between onset of COVID symptoms and the CCCRC test was 172 days. There was a significant association between age over 60 years and CCCRC ($p = 0.03$). It was verified the presence of a relationship with statistical significance between increased LDH values and worse score in the CCCRC ($p = 0.049$). However, the correlation found was weak ($r = 0.19$). The other markers evaluated did not present statistical significance when crossed with CRF. The result was similar in the cross between serum inflammatory markers and degree of severity of OD.

Discussion: In the presence of the pandemic by COVID-19, OD has become a complaint of high prevalence, leading to an important loss of quality of life for patients. According to Cazzola et al., the cells that express the angiotensin-

2-converter enzyme – including the nasal epithelial cells – are the target of attack for SARS-CoV-2. The attack on cells triggers the appearance of an inflammatory storm. The correlation between the severity of the infection and the degree and duration of OD is controversial. Although the relationship between worse olfactory score in the acute phase with exacerbated systemic inflammation and worse clinical outcomes has been reported, some studies have shown contradictory results. Mangia et al. demonstrated worse olfactory score in the acute phase in patients with worse clinical outcomes. However, Vaira et al. found no correlation between OD and poor prognosis. Similarly, Izquierdo-Dominguez et al. observed that the frequency of OD was more prominent in outpatient cases without pulmonary involvement. Regarding systemic inflammatory markers, studies have observed a relationship between elevated serum levels with the most severe forms of COVID-19, due to cytokine storm. The relationship of serum biomarkers with the highest severity of infection has also been constant in research. Chen et al. found higher CRP level in the severe group, but without statistical significance. Meta-analysis conducted by Zeng et al. demonstrated higher serum ferritin levels in patients with severe COVID-19. Izquierdo-Dominguez et al. observed in multivariate analysis that hospitalization and increase in serum CRP levels were associated with better olfactory. Analyzing the relationship between serological inflammatory markers in the serological phase and OD, Vaira et al. described that the correlations between olfactory and Serum levels of inflammatory markers were weak and not significant. In the present study, despite the statistically significant association between LDH levels and the CCCRC, the estimated correlation coefficient is low, corresponding to a weak correlation. In crossing the LDH with the degrees of severity of the CCCRC, no statistical significance was found. On the other than the other serum markers evaluated, the other serum markers did not present a significant correlation with the psychophysical test and were not associated with the degrees of severity of the CCCRC. The results found in this study are compatible with vaira et al. and Izquierdo-Dominguez et al., which may suggest little influence of systemic inflammation on the nasal mucosa.

Conclusion: The present study suggests that there is no relationship between high levels of serum markers – CRP, lymphocytes, D-dummy and ferritin – with worse late olfactory function in the post-COVID-19 patient. A low-grade correlation is observed between LDH and CCCRC; however, this association was not relevant when correlated with the degree of severity of OD.

Keywords: Coronavirus; Olfactory dysfunction; Inflammatory markers.

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Comparison among three brands of budesonide in the treatment of allergic rhinitis: An open label, randomized clinical trial

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Objective: To compare the efficacy of topical nasal budesonide brands available in Brazil in the treatment of allergic rhinitis (AR).

Methods: An open label, randomized clinical trial was conducted, involving patients with a confirmed diagnosis of AR. Fifty-seven individuals were randomized into three groups. Each group underwent a 30-day treatment cycle with one of the three brands of topical nasal budesonide currently available in Brazil: Budecort Acqua. (brand-name), Busonid. (brand-name) and Noex. (generic). Each patient was submitted to olfactory function tests (University of Pennsylvania Smell Identification Test, UPSIT), nasal obstruction questionnaire (Nose Obstruction Symptom Rating Scale, NOSE), Peak Nasal Inspiratory Flow (PNIF) and the Rhinitis Control Assessment Test (RCAT) before and after treatment. The results were analyzed using Analysis of Variance ANOVA (complemented by Tukey's test) and Kruskal–Wallis, for comparison purposes among the three groups.

Results: Nineteen patients received Budecort Acqua, 19 Busonid and 19 Noex. Of the 57 randomized patients, 50 returned for data collection after 30 days of treatment. The number of dropouts was not statistically significant among the groups ($p = 0.13$). All tests UPSIT, PNIF, NOSE and RCAT, significantly improved after 30 days of intervention in the three groups studied ($p < 0.01$). None of the tests showed a statistically significant difference when compared among the groups, both pre and post-treatment values, in both ITT and PP data analyses, UPSIT ($p = 0.24$ and $p = 0.26$), PNIF ($p = 0.83$ and $p = 0.79$), NOSE ($p = 0.74$ and $p = 0.58$) and RCAT ($p = 0.23$ and $p = 0.14$). No serious adverse effects were reported in any of the three groups analyzed by the present study.

Conclusions: This study showed that the generic form of nasal budesonide and two corresponding brand drugs have similar efficacy in the treatment of AR. Further trials are required to compare the efficacy and safety of generic and brand-name drugs on a long-term basis.

Keywords: Allergic rhinitis; Corticosteroid; Treatment.

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