ORIGINAL ARTICLE

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Effectiveness of platelet-rich plasma on post-COVID chronic olfactory dysfunction

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the efficacy of platelet-rich plasma injection on the olfactory cleft of patients with post-COVID olfactory dysfunction lasting over 1 year, who were unresponsive to common treatments.

METHODS: Patients over 18 years of age with post-COVID olfactory dysfunction over 1 year whose complaints did not improve with intranasal steroids and D-panthenol/vitamin A combination nasal sprays with olfactory rehabilitation training for 1 month were prospectively collected and randomized into two groups: intranasal platelet-rich plasma group and control group. At the end of 1 month, Connecticut Chemosensory Clinical Research Center olfaction test scores of smell detection threshold and smell identification test were compared accordingly.

RESULTS: A total of 25 patients were randomized into platelet-rich plasma (n=12) and control (n=13) groups. In the platelet-rich plasma group, the mean smell detection threshold score increased from 5.63 (SD 0.68) to 6.46 (SD 0.45), and the mean smell identification test score increased from 11.42 (SD 1.17) to 15.17 (SD 0.39). In the control group, the mean smell detection threshold score changed from 5.69 (SD 0.66) to 5.77 (SD 0.70), and the mean smell identification test score changed from 11.20 (SD 1.12) to 11.85 (SD 1.57). Post-hoc analysis revealed that similar mean smell detection threshold (mean difference 0.07; p=0.994) and smell identification test (mean difference -0.50; p=0.703) scores were transformed into a significant difference between groups (smell detection threshold mean difference 0.69; p=0.037; smell identification test mean difference 3.32; p<0.001).

CONCLUSION: At the end of the first month, there was a significant improvement in olfactory threshold values in the platelet-rich plasma group compared to the control group. No side effect or adverse event related to platelet-rich plasma injection was observed.

KEYWORDS: COVID-19. Smell dysfunction. Platelet-rich plasma.

INTRODUCTION

As the number of cases of coronavirus disease 2019 (COVID-19) increased worldwide, patients admitting clinics with olfactory dysfunction (OD) had also increased. Up to 85% of patients with COVID-19 present with OD, which makes it one of the major symptoms[1,2]. It has been reported that infection and inflammation caused by viral infections lead to chronic olfactory dysfunction (COD) by affecting the olfactory neuroepithelium. Similarly, it is postulated that persistence of the virus in the olfactory region causing an inflammation might be the reason of prolonged OD in COVID-19[3].

In this study, it is reported that even though during the course of COVID-19 infection, distorted olfactory or gustatory function improved in most cases, symptoms related to smell and taste are still the most common complaints of patients after 1 month of PCR positivity[4]. The prevalence of patient informed persistent OD 1 year after COVID-19 was found as high as 70%[5-8].

Recently, there is no efficient treatment for COD patients. Olfactory training (OT) and some supplements are recommended by some physicians but the effects are still unknown[9,10].

Platelet-rich plasma (PRP) has been used in many different areas of the body due to its regenerative effects. Vocal cord scar treatment, neck fistulas, and tympanic membrane perforation repair are some of the PRP usage areas in otolaryngology[10].

The Connecticut Chemosensory Clinical Research Center olfaction (CCCRC) test is a simple and cost-effective tool for olfactory testing. It consists of smell detection threshold (STC) and smell identification test (SIC)[11]. It is validated and can be easily applied in-office settings.

The aim of our study was to investigate the effectiveness and clinical application of intranasal PRP injection in patients with post-COVID COD, lasting more than 1 year.

METHODS

Patients above the age of 18 years with OD complaints for 1 year or more after a COVID-19 infection confirmed with PCR positivity in the otolaryngology outpatient clinic, from April 2022 to November 2022, were prospectively included in the

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study. All patients were treated with nasal steroids and nasal D-panthenol/vitamin A combination sprays for 1 month, after admission to our clinic. Additionally, all patients were given olfactory rehabilitation training and asked to continue rehabilitation during this 1-month period. Patients unresponsive to the aforementioned treatment were then randomized into two groups: PRP and control.

Turkish validated version of the CCCRC olfaction test was administered to all patients as given in detail in the study by Veyseller et al.[12]. A baseline STC and SIC scores were obtained.

Patients with severe nasal septal deviation, allergic rhinitis, nasal polyposis, a known history of sinonasal surgery, or neurological pathology were excluded from the study.

PRP was prepared with the blood sample taken from patients and centrifuged and a single dose of 1 mL was injected into the olfactory cleft region. Patients in the control group were followed without any additional treatment. At the end of 1 month, the tests were applied again.

Continuous variables were summarized with either their means and standard deviations (SD) or medians and interquartile ranges (IQR) according to their distribution patterns tested with the Shapiro-Wilk test. Categorical variables were reported with counts and percentages. To compare the effect of time and treatment on STC and SIC by controlling for age and sex, a mixed-repeated-measures ANOVA modeling was used. Friedman test revealed similar results, which assured that the mixed-repeated-measures ANOVA was robust to violation of normality for this dataset. We checked the homogeneity of variances using Levene's test, detected outliers using a box plot, and checked sphericity using Mauchly's test. All p-value in the model were corrected as described by Greenhouse-Geisser. The effect of treatment options on STC and SIC values in time was tested with the mixed-ANOVA model, and interaction was quantified using partial eta-squared. Post-hoc comparisons were reported with p-values corrected as defined by Tukey.

The accepted maximum type I error in this study was 5%. The study protocol was approved by the ethics committee of our institution (prot. No: 2021/514/205/15). The written informed consent was obtained from all patients. Data analysis was conducted using the Jamovi Project Version 2.3.21 (2023) software (retrieved from https://www.jamovi.org).

RESULTS

A total of 32 patients were assessed for eligibility. After exclusions, 25 patients were included in the study. CCCRC test revealed a median STC score of 6 (IQR 5–6) and SIC score of 11 (IQR 10–12) at admission. After 1-month routine treatment, 5 patients were lost at follow-up, 2 patients were excluded, and the remaining 25 patients with persistent OD were randomized into the PRP (n=12) and control (n=13) groups (Figure 1).

In the PRP group 6/12 (50%) patients and in the control group 7/13 (53.8%) patients were females (p=0.848; chi-square test). The mean ages were 31.8 (SD 6.9) years and 33.5 (SD 11.1) years, respectively (p=0.653; t-test).

The change of STC and SIC scores in time was tested by the repeated-measures ANOVA, and the interaction effect of the treatment options was tested with the mixed-ANOVA model. In the PRP group, the mean STC score increased from 5.63 (SD 0.68) to 6.46 (SD 0.45), and the mean SIC score increased from 11.42 (SD 1.17) to 15.17 (SD 0.39). The simple main effect of time on STC and SIC scores in the PRP group was statistically significant (both Greenhouse-Geisser corrected p<0.001; partial eta-squared: STC 0.73 and SIC 0.94). In the control group, the mean STC score also changed from 5.69 (SD 0.66) to 5.77 (SD 0.70), and the mean SIC score changed from 11.20 (SD 1.12) to 11.85 (SD 1.57). The simple main effect of time on STC score in the control group was not statistically significant (Greenhouse-Geisser corrected p= 0.165 and partial eta-squared=0.15). The simple main effect

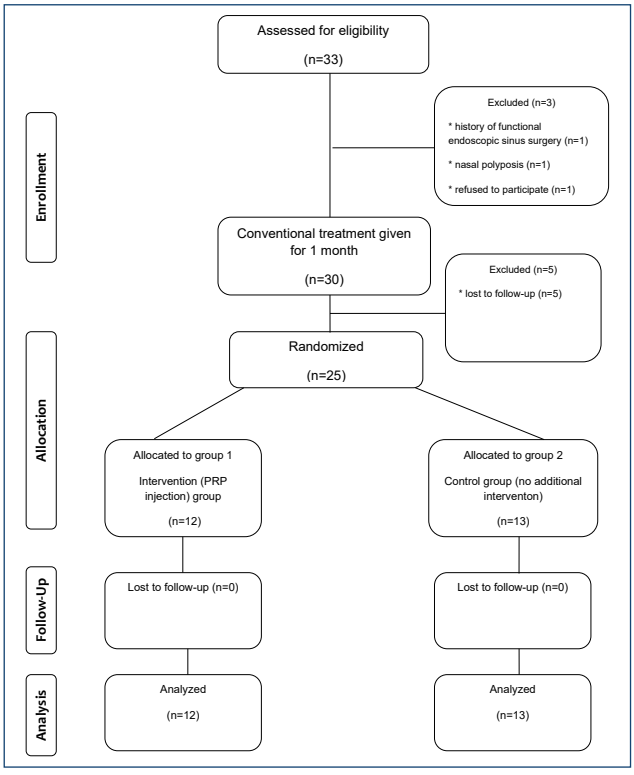

Figure 1. CONSORT flow diagram.

of time on SIC score in the control group was not significant (Greenhouse-Geisser corrected p=0.089 and partial eta-squared=0.69) (Table 1). The interaction effect of treatment options (groups) on the change of both STC and SIC scores in time were statistically significant, i.e., a significant difference was found between treatment groups (STC: Greenhouse-Geisser corrected p<0.001; partial eta-squared=0.50; and SIC: Greenhouse-Geisser corrected p<0.001; partial eta-squared=0.77). Post-hoc analysis revealed that similar mean STC (mean difference 0.07; p=0.994) and SIC (mean difference -0.50; p=0.703) scores were transformed into a significant difference between groups (STC: mean difference 0.69; p=0.037; and SIC: mean difference 3.32; p<0.001; Figure 2).

No adverse effects were reported throughout the study.

DISCUSSION

OD is reported to be the most common clinical symptom of COVID-19 and observed in 30–86% of the infected population. Its pathological mechanism is related to a potential viral invasion of the olfactory bulb and central nervous system through the nasal neuroepithelium[13-15]. Recent studies have shown the efficiency of oral or topical corticosteroids on OD induced by factors other than sinonasal diseases[16,17]. In our clinical practice, we commonly use nasal corticosteroids as the primary treatment for patients admitted to our clinic with OD. Additionally, OT is shown to have positive effects on OD caused by viral infections and is recommended in the treatment of post-COVID OD[9,18,19]. We recommend OT in OD cases, but in our common practice, we have observed that it does not seem practical for our patients since it has to be applied for weeks[20]. Therefore, we believe that there is a need for an alternative treatment method that is more feasible and easily applied.

In our study, all COD patients were given nasal steroids and nasal D-panthenol/vitamin A combination sprays for 1 month, concomitant with OT. The OD did not resolve in any of them, showing the ineffectiveness of steroid treatment in post-COVID COD. When we performed the CCCRC olfaction test after 1 month of treatment, we observed no change in the mean values of SIC and STC.

PRP is an autologous blood product with anti-inflammatory and pro-regenerative features. It has been shown that PRP contains high levels of EGF and PDGF, providing neural and epithelial regeneration. Since it is autologous, risk of rejection or any adverse effects is extremely rare[10].

According to its possible pathophysiology, we aimed to inject PRP directly into the olfactory cleft of the randomized

Table 1. Smell detection threshold measurements and comparison.

	PRP group, n=12 Mean (SD)			Control group, n=13 Mean (SD)		
	Baseline	1st month	Mean difference, p	Baseline	1st month	Mean difference, p
STC	5.63 (0.68)	6.46 (0.45)	0.83 <0.001	5.69 (0.66)	5.77 (0.70)	0.08 0.165
SIC	11.42 (1.17)	15.17 (0.39)	3.75 <0.001	11.20 (1.12)	11.85 (1.57)	0.65 0.089

SD: standard deviation; STC: smell threshold score; SIC: smell identification score. p-value and mean differences were calculated using the mixed-repeated-measures ANOVA.

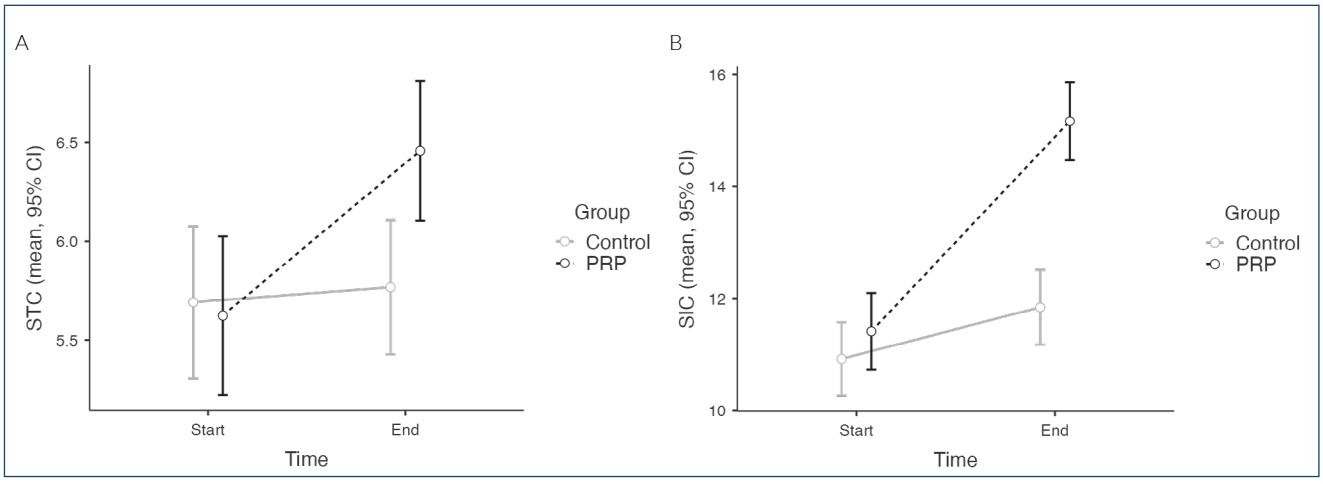

Figure 2. The change of (A) mean smell detection threshold and (B) smell identification test values with 95%CIs in both groups.

post-COVID COD patients to induce neuroepithelial regeneration. Significant improvement was detected on the smell threshold values and smell identification basal values in our PRP group 1 month after injection, whereas no significant improvement was found in the control group. We had similar findings about the efficacy of PRP in post-COVID COD patients with recent studies[10,13,21]. Steffens et al. and Lechien et al. proved the efficacy of PRP 2 months after injection[10,21]. Similarly, Yan et al. reported the continuous effects of PRP 3 months after injection[22]. When compared to aforementioned studies, the duration of the PRP effect could not be reported in our study because the patients did not have a longer follow-up time after PRP injection.

There was no procedure-induced morbidity or adverse event in our group, confirming the feasibility and safety of PRP injection in the treatment for post-COVID COD.

There are some limitations in our study. First, we had small number of patients, and second, the patients were followed up only for 1 month. However, it is thought that the duration of action of PRP and the need for repeated injections can only be understood with larger patient series and longer follow-ups.

CONCLUSION

Our study concludes that injection of PRP directly into the olfactory cleft of patients with post-COVID COD is an effective and easily applied procedure. We believe that the therapeutic effect of PRP injection may depend on timing of OD or effectiveness may change with repetitive doses. Future randomized controlled trials are needed to verify these results and investigate the long-standing effect of this novel approach.

INFORMED CONSENT

Informed written consents were taken from every patient included in the study. The ethical approval was taken from local ethical committee Kartal Dr. Lutfi Kirdar Training and Research Hospital (prot. No: 2021/514/205/15).

AUTHORS' CONTRIBUTIONS

MDE: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft. **ZEC:** Data curation, Formal Analysis, Methodology, Visualization, Writing – review & editing.

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