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Effectiveness of platelet-rich plasma in long-lasting post-viral olfactory dysfunction: a case-series

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Abstract

Objective To investigate the platelet-rich plasma (PRP) effectiveness in patients with a long-lasting postviral olfactory dysfunction (LPOD).

Methods Forty-three consecutive patients with a long-lasting postviral OD were prospectively recruited. The injection of 1 mL of PRP was carried out in both olfactory clefts. The pre- to 6-month post-PRP injection change in olfaction was assessed with the olfactory disorder questionnaire (ODQ) and the threshold, discrimination, and identification (TDI) tests.

Results Forty-three patients received bilateral PRP injections (24 females). The mean age of patients was 58.9 ± 16.8 years. The mean duration of LPOD was 8.7 years. The pre to 6-month post-injection mean TDI significantly improved from 10.3 ± 10.2 to 20.12 ± 12.07 ($p = 0.001$). The mean ODQ significantly decreased from 29.8 ± 13.0 to 23.4 ± 11.3 ($p = 0.013$). The average change of the TDI and the ODQ were 9.8 and 6.4, respectively. Age was inversely associated with the 6-month threshold score.

Conclusion PRP appears to be a promising therapeutic strategy for long-lasting postviral OD. Our findings support the conduction of controlled randomized trial in this population of patients.

Keywords Smell · Recovery · Anosmia · Olfactory · Olfaction · Platelet rich plasma · Postviral · Otolaryngology

Introduction

The platelet-rich plasma (PRP) is currently used in many disciplines, including dermatology, orthopedic, and otolaryngology for its anti-inflammatory and recovery properties. Recent studies suggested that PRP may be effective for postviral olfactory dysfunction lasting for 6 to 18 months [1–3]. Currently, there are no publications investigating its usefulness for long-lasting postviral olfactory dysfunction (LPOD), which can be defined as OD without change 2 years after the onset of OD. The use of PRP in patients with LPOD could be promising given the several basic science studies suggesting that LPOD in patients and animal models could be related to the long-term persistence of viral proteins in the olfactory tissues, and a potentially related immune response [4, 5]. In that way, we could hypothesize that the anti-inflammatory effect of PRP could inhibit the immune response responsible for the chronic inflammation, while the regenerative properties could accelerate the recovery process.

The objective of this study was to investigate the effectiveness of PRP in the management of LPOD.

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Methods

Patients with postviral OD lasting for more than 3 years were consecutively recruited from the Dour ENT Medical Center (Belgium) from September 2021 to July, 2023. LPOD consisted of anosmia or hyposmia at the threshold, discrimination, and identification (TDI) test, and was documented after nasal infection in the patient medical record. Anosmia consisted of a TDI score ≤ 16 points, while hyposmia was established as a TDI score of less than 30.75 [6]. Patients with the following conditions were excluded: post-traumatic, neurological, post-COVID-19 OD; chronic rhinosinusitis with/without nasal polyposis; chronic rhinitis; anatomical obstructive olfactory clefts; history of nasal chemo/radiation or functional endoscopic sinus surgery, severe neurological or psychiatric comorbidities. The study protocol was approved by ethics committee (CHU-Saint-Pierre, SP2102028).

Platelet-rich plasma injection

The PRP injection was performed by the first authors (J.R.L.) regarding a standardized procedure[3] (Fig. 1). In sum, the procedure started with the blood extraction (20 mL) by the nurse into a tube with sodium citrate anticoagulant (RegenLab®, Regenkit-A-PRP, Lille, France). The PRP was isolated through a 5-min centrifugation at 4,200 rpm. The supernatant was drawn up into a 10 mL syringes. The the PRP was transferred in a 1 mL syringe armed with a 27-G needle (10 cm length). The local anesthesia was performed with Xylocain 10% spray 2 min after the injection of xylometazoline chlorhydrate drops into the nasal fossae. The injection was performed through a 30° rigid optic to guide the needle direction to the nasal septum of the olfactory cleft. The needle was bent to have better access to the septum because many patients have nasal deviation, which can limit the view of the olfactory cleft. Several points of 0.2 mL are carried out in the nasal septum in regard of the head of the middle turbine, and in the anterior part of the olfactory cleft region (1 mL per side). According to the initial procedure description [1, 3], the otolaryngologist did

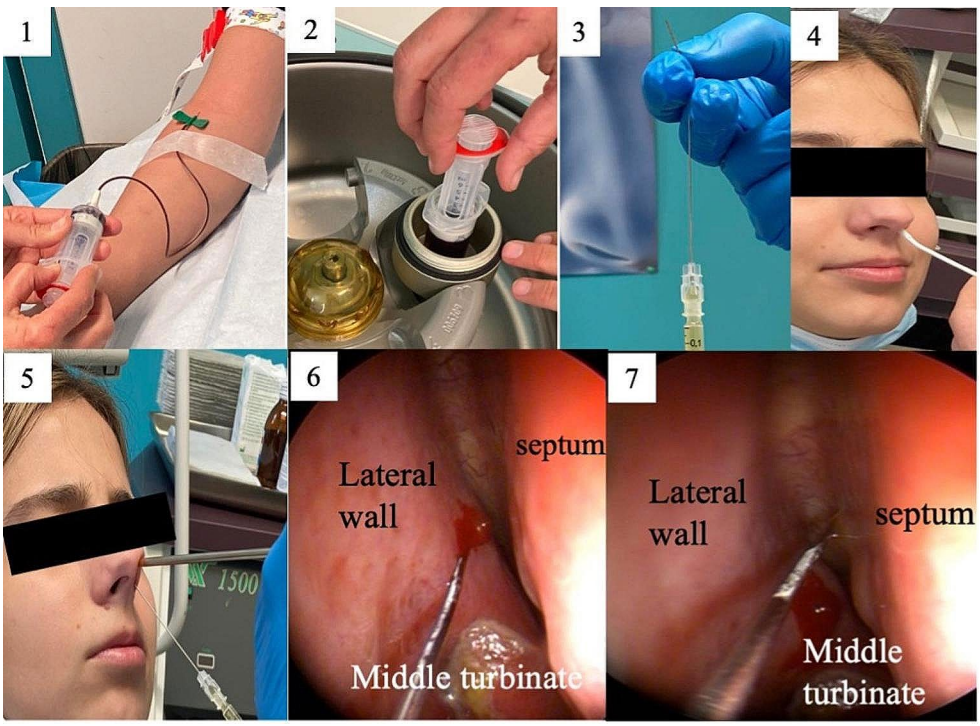

Fig. 1 Injection procedure and outcomes. The blood extraction was performed into a 20 mL tube with sodium citrate anticoagulant (1). The isolation of PRP was performed with a 10-min centrifugation at 4,200 rpm (2). The supernatant was drawn up into a 10 mL syringe and the PRP was consecutively transferred into a 1 mL syringe (3). The injection was performed with a 27-G needle (10 cm). The nasal anesthesia was performed with Xylocain 10% spray (4). The injection was performed through a 0° or 30° rigid endoscope to guide the needle direction (5). Septal deviations limiting the access to olfactory cleft require bent needle (3). The presence of nasal deviation can limit the injection, which explain why the practitioner can inject 1 mL in one side and more (2 mL) in the other side. Otolaryngologist performed bilateral four to six injections of 0.1–0.2 mL in the nasal septum of the olfactory cleft, 1 to 2 cm below the papyracea bone (nasal roof; 6, 7). The number of injections was determined by the access and the length of the olfactory cleft. Patients were observed for 15 min after the procedure for potential adverse events, bleeding and were then discharged

Table 1 Patient olfactory features

Outcomes	Patients ($N=43$)
Age (mean, SD)	58.9 ± 16.8
Sex (N, %)	
Male	19 (44)
Female	24 (56)
Duration of OD (month; mean, SD)	104.7 ± 67.2
Intervention at the OD onset (N, %)	
Olfactory training (12 weeks)	15 (35)
Nasal corticosteroids	14 (33)
Oral corticosteroids	7 (16)
Zinc	6 (14)
Vitamin B	4 (9)
Alpha lipoic acid	1 (2)
Vitamin A	1 (2)
Omega 3	0 (0)
ODQ outcomes (mean, SD)	
Parosmia statement	3.4 ± 2.6
Life quality statement	21.5 ± 10.6
Sincerity statement	4.8 ± 2.7
ODQ total score	29.8 ± 13.0
Psychophysical evaluations (mean, SD)	
Threshold	1.3 ± 2.2
Discrimination	4.5 ± 4.4
Identification	4.5 ± 4.2
TDI total score	10.3 ± 10.3
OD types (TDI; N, %)	
Anosmia	32 (74)
Hyposmia	11 (26)

Abbreviations N = number; *ODQ* = olfactory disorder questionnaire; *TDI* = threshold, discrimination, identification; *SD* = standard deviation

not inject the lateral wall (middle turbinate). The procedure is similarly performed in both nasal cavities. The otolaryngologist (J.R.L.) injected 2 mL in the right side and 1.0 mL in the left side. Patients were commonly observed for 15 min post-procedure in the waiting room for potential adverse events. Only one injection was carried out in patients. Patients were encouraged to adhere to a standardized olfactory training for 12 weeks [7].

Demographic, clinical and olfactory outcomes

The following data were collected through a standardized online questionnaire at the first evaluation: age; gender; comorbidities; allergy; tobacco consumption; previous adherence to an olfactory training protocol or medication/dietary supplements. From pre- to 6-month post-PRP injection, patients completed the French version of the olfactory disorder questionnaire (ODQ) [8], which is a validated and standardized patient-reported outcome questionnaire including parosmia (/12), quality of life (/57), and sincerity (/18) scores. The psychophysical tests (TDI; Medisense, Groningen, Netherlands) were performed at baseline and 6-month post-injection [6].

Table 2 Comorbidities

Comorbidities	Patients ($N=43$)
Reflux	11 (26)
Hypertension	9 (21)
Cholesterol disorder	9 (21)
Thyroid disorder	6 (14)
Arthrosis	6 (14)
Diabetes	4 (9)
Asthma	2 (5)
Cardiologic affections	2 (5)
Depression	1 (2)
Cancer history	1 (2)
Respiratory insufficiency	1 (2)
Renal insufficiency	1 (2)
Psoriasis	1 (2)
Autoimmune disease (arthritis rheumatoid)	1 (2)
Hepatic insufficiency	0 (0)
Allergy	6 (14)
Tobacco consumption	3 (7)

Outcomes consist of number and percentage

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (v.29.0; IBM Corp, Armonk, USA). The pre- to post-injection ODQ and TDI changes were assessed with Wilcoxon Rank test and the average differences in ODQ and TDI. According to the literature, the minimal clinically important difference (MCID) consist of 5.5 and 5.2 for the TDI and the ODQ, respectively [3, 9]. The correlation analysis between demographics, clinical, and olfactory outcomes was performed with Spearman rho. The association was considered as low, moderate and strong for $r_s<0.30$, 0.30–0.60, and $r_s>0.60$, respectively. A p-value < 0.05 was considered as significant.

Results

Setting and patients

Forty-three patients received bilateral PRP injections (24 females). Eight patients were lost of follow-up. The mean age of patients was 58.9 ± 16.8 years old. The demographics and olfactory features are described in Table 1. The patient comorbidities are available in Table 2. Most patients were anosmic. The mean duration of OD was 104.7 ± 67.2 months (8.7 years). The interventions at the onset of the OD were reported in Table 1. At the time of the PRP protocol, no medication was prescribed to patients.

Fourteen patients (32.6%) had never adhered to an olfactory training protocol since the onset of OD. Fifteen patients (34.9%) recognized having adhered to a 12-week olfactory training protocol in the past, prior to the inclusion in the present study without subjective olfactory change. Among them, 5 patients reported subjective substantial improvements in their sense of smell after the first olfactory training protocols a few years ago. The remaining patients ($N=14$, 32.6%) had adhered to several olfactory training protocols in the past few years. Among patients who underwent olfactory trainings, 19 (44.2%) reported sniffing daily odors or essential oils every day since the smell loss and prior to the inclusion in the present study.

Post-injection outcomes

Twenty patients (46.5%) had transient nasal bleeding in the 10 min following the injection and two patients (4.7%) reported transient postnasal drip in the 3 days following the procedure.

The 6-month endoscopic examination did not report olfactory cleft abnormalities or inflammation. A personalized olfactory training was completed by 41 patients (95%). The first smell improvements were perceived by patients after a mean of 3 weeks. The mean ODQ and TDI sub- and total scores significantly improved from baseline to 6-month post-injection. The average difference of the TDI and the ODQ were 9.8 and 6.4, respectively (Table 3), reaching the MCID. The TDI significantly increased in 87.5%, respectively. According to ODQ, 71.4% of patients self-reported a significant improvement of smell sense. The response to PRP (changes of TDI and ODQ) was similar in patients adhering to an olfactory training prior to the inclusion in the study versus those without history of olfactory training.

There was a moderate correlation between the duration of OD and both severities of parosmia score (r_s=-0.427; $p=0.007$) and ODQ (r_s=-0.438; $p=0.005$). Age was inversely associated with the 6-month threshold score (r_s=-0.420; $p=0.046$).

Table 3 Olfactory outcome changes

Outcomes (mean, SD)	Baseline	6 mo	*p*-value
Parosmia score	3.4 ± 2.6	2.2 ± 2.4	0.049
Life Quality Statement score	21.5 ± 10.6	16.1 ± 8.8	0.006
Sincerity Statement score	4.8 ± 2.7	5.1 ± 2.7	NS
Fr-ODQ total score	29.8 ± 13.0	23.4 ± 11.3	0.013
Threshold	1.3 ± 2.2	4.8 ± 4.8	0.001
Discrimination	4.5 ± 4.4	8.1 ± 4.7	0.001
Identification	4.5 ± 4.2	7.3 ± 4.7	0.014
TDI total score	10.3 ± 10.2	20.1 ± 12.1	0.001

Abbreviation: *mo* = month; *NS* = non-sgnificant; *ODQ* = olfactory disorder questionnaire; *TDI* = threshold, discrimination, identification; *SD* = standard deviation

Discussion

To date, there is a few solutions for patients with LPOD, while the injection of PRP into the olfactory cleft recently reported promising findings in patients with short-lasting POD [1–3].

The results of the present study supported that PRP may be proposed in patients with a LPOD. Indeed, mean average of the TDI and the ODQ reached the MCID reported in the literature [3, 9], while TDI and ODQ significantly improved from pre- to post-injection. The pathophysiology of LPOD is still poorly understood. In a recent study, de Melo et al. reported that humans with persistent OD related to COVID-19 have chronic inflammatory reaction in the olfactory neuroepithelium, and related prolonged or relapsing loss of smell [10]. Interestingly, authors observed that COVID-19 hamsters had long time anosmia lasting as long as the virus remained in the olfactory epithelium and the olfactory bulb. Thus, the long-term persistence of anosmia was associated with persistence of virus transcripts in infected cells, and protracted inflammation [10]. The study of de Melo et al. corroborates the findings of basic science and animal research conducted before the pandemic. Indeed, the olfactory neuroepithelium has been recognized for a long time as an important route for many viruses to invade the central nervous system. In LPOD, some experimental animal studies have reported that certain viruses, such as the Sendai virus or the para-influenza viruses, may persist in the olfactory neuroepithelium and/or bulb cells over time [4]. The persistence of the Sendai virus is associated with the impairment of the ability of olfactory sensory neurons to take up calcium ions after stimulation, by suppressing apoptosis of olfactory sensory neurons, which alters the normal regenerative ability of the olfactory epithelium over the long-term [4]. In the same vein, Mori et al. detected para-influenza virus nucleoprotein gene in the cells of the olfactory bulb of infected mice more than 168 days post-infection [5]. In a murine model of viral rhinosinusitis, Klemens et al. observed that despite the resolution of infection, the T suppressor and T regulatory cell immune responses persisted over the long-term in the olfactory region [11]. All these studies suggest that patients with LPOD might maintain long-term persistence of viral proteins within the olfactory tissues, and a potentially related immune response. The PRP was initially suggested as a promising treatment for LPOD in 2018 by Yasak et al. who investigated the effectiveness of PRP on anosmia in a mouse model of anosmia [12]. In this study, the authors injected PRP or a saline solution into the mice and observed that food-finding test, epithelial thickness, and epithelial damage scores were significantly better in the PRP group compared to the control at 21 days post-injection [12]. Accordingly, we could hypothesize that PRP

might locally favor the recovery processes, which are altered for a long-time by long-lasting chronic inflammation. Based on current PRP knowledge in other indications, our findings could suggest that the injected PRP pockets into the neuroepithelium may progressively release anti-inflammatory and pro-regenerative factors, which upregulate some factors in olfactory cells, including growth and transforming factors, epidermal growth factor, and insulin-like growth factor [3, 13, 14]. The content of PRP and the role of molecule are summarized in Table 4 [15]. Thus, the mechanism of induction of regenerative process of the neuroepithelium could be related to the activities of growth factors (e.g., EGF, VEGF, Transforming growth factor β, Platelet-derived growth factor, Fibroblast growth factor, Insulin-like growth factor) and cytokines (e.g., CCL and CXCL families), which will stimulate the angiogenesis, the cell proliferation, and tissue component synthesis. Naturally, this hypothesis needs to be investigated in future biological studies comparing the PRP content of patients who recovered *versus* those without smell improvement. According to the virus-related differences in the neuroepithelium pathophysiological and histological changes, the effectiveness of PRP could vary from one virus-induced LPOD to another. This hypothesis can explain the better response of anosmic patients to PRP in this study compared to COVID-19 studies [2, 3].

Table 4 Platelet-rich plasma content

Content	Roles
Growth factors	
Epidermal growth factor	Cell proliferation stimulation, epithelial cell differentiation, cytokine secretion promotion
Vascular endothelium growth factor	Angiogenesis stimulation, endothelial cell mitosis and migration, permeability vessel increase, immune cell chemotaxis
Transforming growth factor β	Collagen synthesis immune cell chemotaxis, angiogenesis stimulation
Platelet-derived growth factor	Fibroblast chemotaxis, cell proliferation, collagen synthesis, macrophage activation
Fibroblast growth factor	Stimulation of mesenchymal cell proliferation, growth, and differentiation
Insulin-like growth factor	Promotion of cell growth and differentiation, collagen synthesis stimulation
Cytokines/chemokines	
CCL-2 (MCP-1)	Monocyte and dendritic cell attraction in inflammatory sites
CCL-3 (MIP-1α)	Macrophage and dendritic cell attraction in inflammatory sites
CCL-5 (RANTES)	T cell and monocytes attraction in inflammatory sites
CCL-7 (MCP-3)	T cell, dendritic cell, monocytes recruitment in inflammatory sites for tissue healing
CXCL-1 (GRO-α)	Neutrophil recruitment in inflammatory site for tissue healing
CXCL-2 (MIP-2)	Neutrophil recruitment in inflammatory site for tissue healing
CXCL-4 (PF4)	Coagulation regulation and modulation of leucocyte activity in healing process
CXCL-5 (ENA-78)	Neutrophil recruitment in inflammatory site for tissue healing
CXCL-6 (LIX)	Neutrophil recruitment in inflammatory site for tissue healing and defense against infection
CXCL-8 (IL-8)	Migration and activation of neutrophils in tissue healing
CXCL-12 (SDF-1α)	Vascular stem cell activation for angiogenesis

The common content of platelet-rich plasma found in the literature is described in this table

This study is the first investigation of PRP effectiveness in LPOD patients, which is its primary strength. The use of both patient-reported outcome questionnaire and psychophysical tests is an additional strength. The small number of patients and the lack of control group are the primary limitations. The potential influence of olfactory re-training on the evolution of olfactory outcomes could be evaluated through a control group that included patients underwent olfactory re-training only. The lack of a control group is the primary limitation, even though 67.4% of patients had adhered to one, several, or continuous olfactory training protocols in the past few years without reporting substantial improvement. However, this case-series may be considered as a first step prior to conducting controlled study or a potential placebo-controlled randomized trial for this unexpected indication (LPOD). Another potential bias is the variability in the technique of injection across patients. It remains difficult to inject some patients with nasal deviation. With the experience, the practitioner can bend the needle and turn the 30° optic to see the olfactory cleft posteriorly to a minor nasal deviation. In case of major nasal deviation, some patients did receive one injection. These variation in the injection can influence the study outcomes and it is important to keep as standardized as possible in the injection procedure in future studies. Finally, we did not perform several injections in the present study, which should be a future way of investigation as re-injection protocols appear to be more effective in hair restoration or chronic muscle-tendon injuries compared to a single injecton [13, 14].

Conclusion

The injection of platelet-rich plasma into the olfactory clefts of patients with a long-term postviral OD history may be an effective procedure associated with significant improvements of ODQ and TDI. Future controlled randomized trials are needed to support the findings of the present study.

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ability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Sven Saussez: design, acquisition of data, data analysis & interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations

Ethical approval The Local IRB approved the study and patients consented to participate.

Informed consent Patients consented to participate.

Conflict of interest The author had no conflict of interest.

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