

Assessment of Olfactory Dysfunction after Treatment with Platelet-Rich Plasma

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ABSTRACT

Background: The number of olfactory dysfunction cases resistant to the therapy increased after the pandemic of COVID-19, so platelet rich plasma (PRP) maybe effective.

Objective: Assessment of role of platelet-rich plasma in managing olfactory dysfunction.

Patients and methods: In a prospective study, twelve patient were recruited from the ENT Outpatient Clinic, Zagazig University Hospital. Each patient had been enrolled in two groups control side and injection side of platelet rich plasma. Anterior rhinoscopy, nasal endoscopy and CT scanning were done to all cases.

Results: Both groups differed significantly regarding smell after intervention. Six patients of sides received PRP had normal smell and two patients had hyposmia, while four patients still had anosmia. No change was reported in control side in PRP group, there was significant improvement in smell, both groups differed significantly regarding smell improvement after intervention, no change was reported in control sides while 66.7% of PRP sides showed improvement in smell intensity, there was statistically significant relation between improvement in smell and etiology and disease duration. Genetic causes were associated with no improvement while post-viral was more liable for improvement after PRP. Longer disease duration is associated with no improvement.

Conclusion: Platelet-rich plasma injection use in the olfactory cleft is easy and safe to be used to improve olfactory dysfunction especially in post viral cases.

Keyword: Olfactory dysfunction, Platelet-rich plasma.

INTRODUCTION

Inability to detect unpleasant odors, such as those produced by spoiled foods, gas, and smoke, is a serious issue brought on by the widespread disorder known as olfactory dysfunction⁽¹⁾. Loss of smell can be caused by a number of factors, including viruses, injuries, and neurological disorders that have yet to be diagnosed. There are two types of olfactory dysfunction, conductive (caused by a literal restriction of airflow to the olfactory mucosa) and sensorineural (disturbance of olfactory neural pathway)⁽²⁾. The most prevalent reason for impaired smell is an upper respiratory infection. The most prevalent cause of olfactory dysfunction is postviral olfactory dysfunction (PVOD), which is thought to stem from sensorineural failure due to degeneration of the olfactory epithelium and conductive malfunction due to mucosal edema. With the advent of the coronavirus disease 2019 (COVID-19) pandemic, PVOD has taken on new significance due to the extraordinary global spread of olfactory neuroepithelium damage caused by the virus⁽³⁾.

Overall, no pharmacological treatment for post viral anosmia has been shown to be effective. Similarly, we could deal with OD during the COVID-19 era as though it were postviral anosmia, taking into account that there is no specific treatment and the sensorineural type prognosis is poor and sometimes irreversible⁽⁴⁾. However, research in animal models have revealed that growth factors applied topically cause neural regeneration, and stem cell applications have been observed⁽⁵⁾. Centrifuging a blood sample from a patient or experimental animal yields platelet-rich plasma (PRP), a platelet concentration. Platelets, which are formed by megakaryocytes in the bone marrow, are tiny, non-nucleated cells with a diameter of around 2 µm

and a primary physiological function of hemostasis. The cellular level is where the mending is sped up. A number of growth factors that hasten mitosis, vasculogenesis, and differentiation can be found in the alpha granules of platelets. These include transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), platelet derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1) and hepatocyte growth factor (HGF) as well as vascular endothelial growth factor (VEGF). Upon platelet activation, they are released⁽⁶⁾. Platelets' ability to release growth factors and active metabolites has positive implications for their application in therapeutic settings requiring quick tissue repair⁽⁷⁾. Therefore, this study aimed to assess the role of platelet-rich plasma in managing olfactory dysfunction.

SUBJECTS AND METHODS

This prospective study was conducted on twelve patient recruited from the ENT Outpatient Clinic, Zagazig University Hospital during the period from December 2021 to December 2022. All of them were complaining of olfactory dysfunction.

All patients had persistent symptoms not temporarily relieved by medical therapy (topical and systemic steroids, decongestants and vitamins supplementary) not olfactory training. CT scan was done to exclude any nasal and paranasal pathologies.

Inclusion criteria: All patients were over the age of > 18 years old and with good general health condition. Patients with resistant olfactory dysfunction not responding to other therapy for 3 months at least as steroids, decongestive nasal drops, zinc supplementary, vitamin B and olfactory training were included.

Exclusion criteria: Patients with one or more of the following criteria were excluded from the study:

- Sever posterior deviated septum.
- Nasal polyposis.
- Marked nasal adhesions.
- Sinonasal tumors.
- Allergic fungal rhino sinusitis.
- Pregnancy.
- Uncontrolled diabetes.
- Uncontrolled hypertension.
- Patient with sinonasal surgery < 6 months of smell loss.

All patients were subjected to assessment protocol that included:

History taking:

Detailed history taking. Analysis of the chief symptoms of the patient was obtained. The main symptom was loss of smell. Every patient had to answer several questions as the following:

- Onset, course and duration of smell loss.
- Site of smell loss whether unilateral, bilateral or alternating.
- Whether smell loss is accompanied by any symptoms.
- History of applying any topical decongestants or corticosteroids.
- History of taking any systemic steroids or any other drug intake.
- History of previous nasal or sinus surgery.

Examination:

Every patient had a standard ear, nose, and throat exam, with a focus on the nose:

- **Anterior rhinoscopy and nasal endoscopy:** Noting any visible congestion, discharge, polyps, adhesions, nasal masses or synechia.
- **Olfactory testing:** Using NeilMed Smell Restore - All Natural Smell Training Kits.
- **CT scanning:** CT scanning of the nose and paranasal sinuses was done for each patient.
- **Every CT was examined carefully aiming at addressing the following point:**
- To exclude any nasal and paranasal pathologies.

Procedure:

First, 5 mL of blood were drawn into a tube containing sodium citrate as an anticoagulant, and then PRP was separated after being centrifuged for 10 minutes at 4200 rpm. The otolaryngologist drew the supernatant into 3 mL syringes and aliquoted the PRP into 1 mL syringes. After injecting otrivin drops into the nasal fossae for 10 minutes, local anaesthesia was achieved by spraying lidocaine on cotton for 2 minutes before injecting 1 ml of PRP with a 1 ml syringe. This was done on the right side of the nose, near the olfactory area. After 15 minutes of post-procedure observation for possible complications, the patient was released. Patients returned to clinic for olfactory testing at 1 month post treatment, and performing nasal endoscopy for evaluation of nasal mucosa.

Ethical approval: This experiment was ethically approved by the Faculty of Medicine Zagazig University Ethical Board. After being fully informed, all participants provided written consents. The study was conducted out in line with the Helsinki Declaration.

Statistical analysis

For this study, we used IBM SPSS Version 27.0. Numerical data were summarized using minimum and maximum values, as well as means, standard deviations, medians, and interquartile ranges. The results were considered significant if they fell within a 95% confidence interval. There was a Chi-square test performed. Mann-Whitney for comparing data that did not follow a normal distribution and also the U test was used. For this purpose, we employed either the Chi-square or Fisher's exact test to compare categorical variables. P value ≤ 0.05 was considered significant.

RESULTS

This study included 12 patients with partial and total loss of smell. Female represented 58.3% of them. Age ranged from 18 to 60 with a mean of 36.58 ± 15.37 years for evaluation of platelet-rich plasma effects in treating olfactory dysfunction. Each patient had been enrolled in two groups control side and injection side. Three patients (25%) were smokers. Regarding cause of smell loss, eight patients (66.7%) had post-viral smell loss, two (16.7%) had genetic causes, one had idiopathic cause and one had traumatic etiology. Concerning degree of loss of smell, nine patients (75%) had complete loss of smell and three had partial loss of smell (25%). Duration of smell ranged from 3 months to 60 years with median 11 months (Table 1).

Table (1): Patients different characters and data

	N=12	%
Gender:		
Female	7	58.3%
Male	5	41.7%
	Mean ± SD	Range
Age (year)	36.58 ± 15.37	18 – 60
Smoking:		
No	9	75%
Yes	3	25%
Etiology:		
Genetic	2	16.7%
Idiopathic	1	8.3%
Post-viral	8	66.7%
Traumatic	1	8.3%
Anosmia:		
Partial	3	25%
Complete	9	75%
Duration of smell loss (year)	11 months (0.52 – 10.75)	
Median (IQR)	3 months – 60	
Range	years	

Both groups did not differ significantly regarding smell before intervention while smell differed significantly between both groups after intervention.

Six patients of sides received PRP had normal smell and two patients had hyposmia, while four patients still had anosmia. No change was reported in control side in PRP group, there is significant improvement in smell (Table 2).

Table (2): Comparing studied groups regarding change of smell:

Smell	Intervention side	Control side	χ^2	P
	N=12 (%)	N=12 (%)		
Before				
Total anosmia	3 (25%)	3 (25%)	0	>0.99
Hyposmia	9 (75%)	9 (75%)		9
After				
Normosmia	6 (50%)	0 (0%)	6.8	0.008
Hyposmia	2 (16.7%)	3 (25%)	38	*
Anosmia	4 (33.3%)	9 (75%)		
P (Wx)	0.014*	>0.999		

Wx Wilcoxon signed rank test

Both groups differed significantly regarding smell improvement after intervention, no change was reported in control sides while 66.7% of PRP sides showed improvement in smell intensity (Table 3).

Table (3): Comparing studied groups regarding improvement in smell

Smell	Intervention side	Control side	χ^2	P
	N=12 (%)	N=12 (%)		
Improvement:				
No change	4 (33.3%)	12 (100%)	Fisher	0.001*
Improvement	8 (66.7%)	0 (0%)		*

There was statistically significant relation between improvement in smell and etiology and disease duration. Genetic causes was associated with no improvement while post-viral was more liable for improvement after PRP. Longer disease duration is

associated with no improvement. There is non-significant relation between improvement and either age, gender, or smoking (Table 4).

Table (4): Relation between improvement in smell after PRP and studied parameter

Smell	No change	Improvement	χ^2	P
	N=4 (%)	N=8 (%)		
Gender:				
Female	2 (50%)	5 (62.5%)	Fisher	>0.999
Male	2 (50%)	3 (37.5%)		
Smoking:				
No	2 (50%)	7 (87.5%)	Fisher	0.236
Yes	2 (50%)	1 (12.5%)		
Etiology:				
Genetic	2 (50%)	0 (0%)	MC	<0.001*
Idiopathic	0 (0%)	1 (12.5%)		
Post-viral	1 (25%)	7 (87.5%)		
Traumatic	1 (25%)	0 (0%)		
	Mean \pm SD	Mean \pm SD	t	P
Age	48.5 \pm 13.0	30.63 \pm 13.3	2.21	0.052
	Median (IQR)	Median (IQR)	Z	P
Disease duration	32 (5 – 57)	0.67 (0.42 – 0.92)	- 2.297	0.022*

Z Mann Whitney test t independent sample t test

Non-significant improvement was found in smell and follow-up times (Table 5 & figure 1).

Table (5): Relation between improvement and follow up time among PRP group

	No change (n=4)	Improvement (n=8)	t	P
	Mean \pm SD	Mean \pm SD		
Follow up time (weeks)	4 \pm 0	3.75 \pm 0.46	1.528	0.17

t independent sample t test

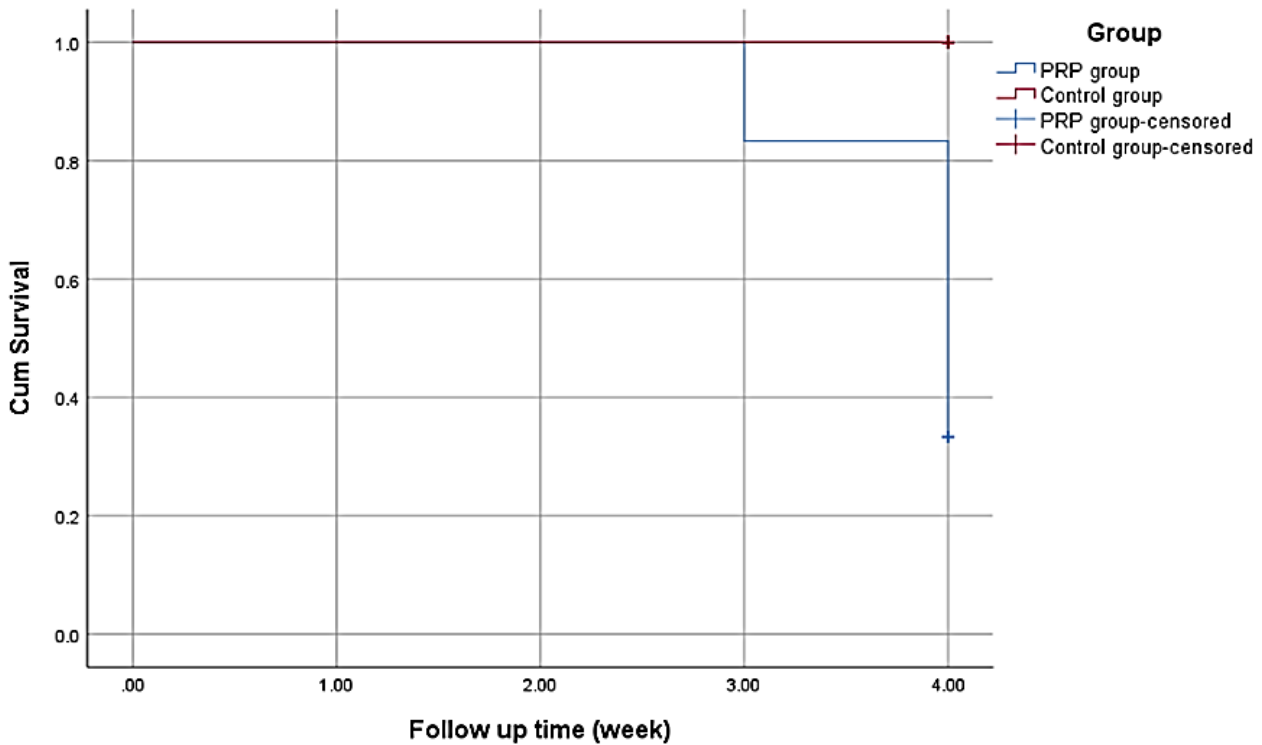


Figure (1): Kaplan Miere showing comparison between groups regarding till change in smell.

DISCUSSION

Preparing platelet-rich plasma (PRP) for topical use entails several steps, the most significant of which is spinning of a blood sample. The red blood cells and other non-essential components of the blood were removed so that the therapeutically useful components could be collected and concentrated⁽⁸⁾. Similar to the fibrin glues that have been used for over 40 years as surgical adjuvants to aid healing, platelet concentrate appeared to expedite wound closure. Platelet-rich plasma (PRP) has been heralded as a miraculous tool for cutting-edge regenerative medicine techniques⁽⁹⁾.

Our result demonstrated that female represented 58.3%. Age ranged from 18 to 60 years with a mean of 36.58 ± 15.37 years. **Tabrizi et al.**⁽¹⁰⁾ showed that the 48 patients included 34 men and 14 women, with ages ranging from 20 to 50 (mean = 35.96 ± 7.39).

We showed that three patients (25%) were smokers. Regarding cause of smell loss, eight patients (66.7%) had post-viral smell loss, two (16.7%) had smell loss since birth, one had idiopathic cause and one had traumatic etiology. **Yan et al.**⁽¹¹⁾ showed that nonsmoking patients were enrolled in this study. Post-exposure to a virus, trauma, or anaesthesia can all lead to a loss of smell. **Kütük et al.**⁽¹²⁾ showed that about a third (9) of the patients in the control group are smokers, and 10% (3 patients) have a history of surgery. Additionally, 86.6% (or 26 patients) of those in the experimental group had a history of environmental

allergies, 36.6% (or 11 patients) suffered from allergic rhinitis, 23.4% (or 7 patients) were affected by asthma, and 76.6% (or 23 patients) experienced chronic nasal congestion. Eighty percent (24 patients) have nasal obstruction, 53.4% (11 patients) have septum deviation, 43.4% (13 patients) have concha hypertrophy, and 53.4% (16 patients) had congestion.

Concerning degree of loss of smell, nine patients (75%) had complete loss of smell and three had partial loss of smell (25%). Duration of smell loss ranged from 3 months to 60 years with median 11 months. **Yan et al.**⁽¹¹⁾ showed that non-sinonasal illness' etiologies accounted for patients' olfactory dysfunction lasting between 6 and 11 months. **Aboelmagd et al.**⁽⁹⁾ showed that Patients evaluated had anosmia for a range of 2 years to 8 years, with a weak positive association between patient age and anosmia duration (P.05 on the Spearman test). Mean anosmia duration was 5.22 years and improvement occurred in 46 cases (57.5%).

We demonstrated that both groups did not differ significantly regarding smell before intervention while smell differed significantly between both groups after intervention. Six patients of sides received PRP had normal smell and two patients had hyposmia while four patients still had anosmia. No change was reported in control side in PRP group, there is significant improvement in smell. We showed that in terms of post-intervention smell improvement, there was a statistically significant difference between the two

groups. No change was reported in control sides while 66.7% of PRP sides showed improvement in smell intensity. In agreement with our study, **Yan et al.** ⁽¹¹⁾ showed that at the one-month follow-up appointment after receiving PRP injection, all patients reported a subjective improvement in their sense of smell. Patients reported being able to identify previously undetectable aromas, such as rosemary, varnish, and soaps. Three months after therapy, no patients reported any further improvement in their sense of smell compared to the base line at 1 month.

In addition, **Steffens et al.** ⁽¹³⁾ demonstrated that one month after receiving PRP injections, the PRP group showed a statistically significant improvement of 6.7 points on the TDI compared to the control group, which saw no change. **Tabrizi et al.** ⁽¹⁰⁾ showed that all individuals' I-SIT scores increased during the course of the research, with the oral therapy group reaching 5.75 ± 2.68 and the surgical group reaching 18.71 ± 1.25 . The evaluation of I-SIT showed a temporal interaction ($F(1,36) = 1392.8, p < 0.001$). This indicates that the increasing pattern of I-SIT seen throughout the trial was statistically significant. Improvement was seen in both therapy groups. After oral steroid medication, the I-SIT for the intervention group was 5.85 ± 2.46 and the control group was 5.62 ± 2.83 , and at three months after surgery, the I-SIT was 18.93 ± 1.14 and 18.43 ± 1.36 , respectively.

Because COVID-19 OD symptoms, such as a diminished sense of smell, may be caused by the virus's ability to remain dormant in the olfactory region and by inflammation of the neuroepithelium, the use of PRP in this condition is particularly attracting ⁽¹⁴⁾. Olfactory tissue regeneration may be aided by PRP's anti-inflammatory properties, which could lessen chronic inflammation and cell-related damage ⁽¹⁵⁾.

We demonstrated that there is statistically significant relation between improvement in smell and etiology and disease duration. Genetic causes were associated with no improvement while post-viral was more liable for improvement after PRP. Longer disease duration is associated with no improvement. There is non-significant relation between improvement and either age, gender, or smoking.

In agreement with our study, **Steffens et al.** ⁽¹³⁾ showed that controls had not changed noticeably. Differences in TDI scores were somewhat correlated with OD length in the PRP group ($r = .387, p = .035$) but not in controls. When compared to the score (0.3) of healthy persons, the PRP group's mean self-assessment of improvement in smell function (mild-to-moderate) was considerably greater ($p < 0.001$). The entire trial period passed with no known ill effects. Patients who had lost their sense of smell for less than 12 months and those who had lost it for more than 12 months did not differ significantly from one another ($p = 0.093$). In addition, **Aboelmagd et al.** ⁽⁹⁾ showed that after receiving a PRP local nasal injection, ten individuals with idiopathic anosmia reported a complete recovery.

Functional endoscopic sinus surgery was performed on 18 patients who had a history of anosmia due to chronic sinusitis; 14 of these patients improved following PRP local nasal injection, whereas 4 did not. The local nasal injection of platelet-rich plasma (PRP) did not relieve the symptoms of anosmia in four patients who had a history of atrophic rhinitis. Eighty individuals had a history of anosmia due to allergic rhinitis; 14 of them improved following PRP local nasal injection, whereas 4 did not. Anosmia was a chronic problem for 10 individuals who also had a history of diabetes mellitus, and they did not improve with PRP local nasal injection. FESS was performed on six individuals with a history of anosmia, diabetes, and chronic sinusitis, PRP local nasal injection resulted in improvement for 2 of these individuals but not for the other 4. There were fourteen patients who had a history of anosmia, diabetes, and allergic rhinitis; six of these patients improved following PRP local nasal injection, while eight did not. Since the P value was less than 0.005, there was strong statistical evidence linking the patients' medical histories to their degree of progress. Patients with a history of chronic sinusitis and allergic rhinitis who improved had the highest frequency of illness presentations, while those who did not recover had the highest presentations of DM and allergic rhinitis linked with DM, suggesting a significant effect of DM. There was no statistically significant difference ($P = 0.587$) between the duration of anosmia in the group that improved and the duration of anosmia in the group that did not, suggesting that the improvement status was not influenced by the duration of anosmia, contrary to the findings of our study. Statistical analysis of the number of patients of each gender who agreed to participate in this study found no association between gender and improvement status ($P = 0.432$), suggesting that the improvement status is unaffected by gender.

No patient reported any substantial loss of scent at any time after receiving PRP therapy. In disagreement with our study, **Steffens et al.** ⁽¹³⁾ demonstrated that in the group monitored for 6-12 months, the average monthly TDI gain was 9 points, whereas the corresponding figure for the 12-18 month group was 4. This difference may be due to different follow up times. Also, **Tabrizi et al.** ⁽¹⁰⁾ showed that there was no discernible variation in the cumulative effect of time and development.

CONCLUSION

Platelet-rich plasma injection use in the olfactory cleft is easy and safe to be used to improve olfactory dysfunction especially in post viral cases.

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