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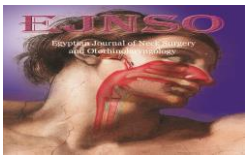

Outcomes of Platelet-Rich Plasma Versus olfactory training in Post Covid-19 Smell Disorders: A comparative study

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Abstract:

Background: Olfactory dysfunction often arises from viral infections (such as upper respiratory infections and COVID-19), head trauma, neurodegenerative diseases, or sinonasal issues. Traditional treatment, such as olfactory training, corticosteroids, and surgery, frequently show limited and inconsistent results. This has led to growing interest in alternative therapies like Platelet-Rich Plasma (PRP) injection as a potential treatment option.
Patients and Methods: This randomized prospective clinical trial was carried out on 42 patients aged >18 years old including both sexes, who had suffered from post-COVID-19 persistent smell dysfunction for more than six months. Patients were divided into two groups; group 1 was treated with PRP injection into the olfactory area and group 2 was treated with olfactory training (OT), and olfactory function was assessed by threshold, discrimination, and identification tests (TDIT).
Results: Our result showed that 19 out of 42 patients (45,2%) had improved while the remaining 23 patients (54.8%) showed no improvement. Each of PRP injection and OT showed a statistically significant improvement with p values (<0,001 - 0,002) respectively after one-month follow-up.
Conclusions: PRP has a promising outcome for the treatment of post-COVID-19 smell disorders. Although OT was beneficial, it could be used as a supplementary therapy rather than a primary treatment modality for post-COVID-19 olfactory dysfunctions.
Keywords: Platelet-Rich Plasma, PRP, COVID-19, Smell Disorders, olfactory training, OT

Introduction

Olfactory dysfunction (OD) was one of hallmarks of COVID 19 infection. Most of post covid 19 smell disorders patients recovered spontaneously as olfactory neuroepithelium has a regenerative power [1] while a small proportion seemed to display persistent olfactory dysfunction. [2]

Smell dysfunction is thought to be due to covid 19 ability for neuro-invasion and its neurotrophic activities. [3] OD affects the quality of patients' life badly specially the ability to identify hazardous smells. [4] Several modalities like lifestyle modification, smoking cessation and OT have been suggested for treatment post COVID-19 olfactory dysfunction. [5]

Recent attention has been drawn to the potential of platelet-rich plasma

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(PRP) therapy. [6] PRP is an autologous biological product derived from fresh whole blood characterized by its regenerative and anti-inflammatory properties, that can stimulate neuroregeneration through the upregulation of growth factors such as transforming growth factor, vascular endothelial growth factor, epidermal growth factor, and insulin-like growth factor. [7]

We aimed to evaluate the efficacy of Platelet Rich plasma as a new treatment modality.

Patients and methods:

This randomized prospective clinical trial was conducted between July 2021 to July 2023 after approval by the local ethical Committee (IRB.17101728). It was carried out on 42 patients who suffered from persistent post covid -19 smell disorders for more than six months. Patients were randomly allocated into two groups (21 in each group). Group 1 Patient was treated with PRP injection into the olfactory area while group 2 Patients was treated with olfactory training.

We had excluded patients with lesions obstructing nasal airway (nasal polyps, tumors, chronic sinusitis, and structural abnormalities that my hinder local injection of PRP), previous sinonasal surgery, atrophic rhinitis, nasal granulomas, and history of bleeding disorders or receiving any medication affecting platelets or bone marrow function. An informed consent was taken from all participants. After medical history and clinical examination (general, neurological, endoscopic nasal and nasopharyngeal examination using 0 degree/ 4mm, Storz endoscope, Germany), all patients were subjected to laboratory and radiological investigations. Olfactory testing was performed before the start of treatment using odor threshold, discrimination and identification tests (TDIT). [8]

PRP preparations :8 ml whole blood sample was obtained by venipuncture in Glass Blood Collection Tubes containing Acid Citrate Dextrose (ACD) (PRP tubes). The blood was centrifuged for 10 minutes using a soft spin 2000 revolutions per minute (RPM) (Hettchi bench top centrifuge, Rotoix 32 A, Tokyo, Japan). The supernatant plasma containing platelets was transferred to another sterile tube without anticoagulant (Kemico Z serum plain tube). The second tube was centrifuged at a higher speed 3000 RPM for 10 minutes (Hettchi bench top centrifuge, Rotoix 32 A, Germeny) to obtain a platelet concentrate. The platelets pellet is seen at lower 1\3 of the tube with an overlaying 2\3Platelet poor plasma. Platelet poor plasma (PPP) was removed and the PRP was suspended in 1 ml by heavy mixing.

Administration of PRP: Nasal pack soaked with a mixture of xylometazoline chlorhydrate 0.1% and 10% Xylocaine was placed in spheno-ethmoidal recess and the area between nasal septum and inferior turbinate using (0 degree/ 4mm, Storz, Germany endoscope for 10 minutes). Patients were placed in semi sitting position where the head of the bed was elevated 20 degrees. PRP was mixed with 0.1ml of calcium gluconate to activate secretion of growth factors and was injected submucosally using a syringe and 22-G needle into the olfactory area especially in the posterior part of the middle turbinate and adjacent part of nasal septum. Fig 1

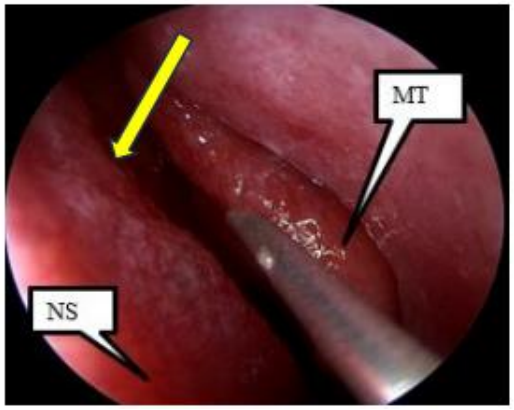

Fig 1: left side nasal cavity showing site of injection (yellow arrow), MT (middle turbinate), IT (inferior turbinate) NS (nasal septum).

Patients were asked to report pain intensity as none, mild, moderate, or severe using a visual analogue scale of pain (VAS). [9] Patients were observed for 15 min after the procedure for potential adverse events. The procedure was repeated 3 times with one month interval and patients were examined before each injection to rule out any mucosal changes. Patients were evaluated 1 month after the last PRP injection for recovery of olfaction. While Olfactory training was done as described by **Hummel et al.**[10]**.** Evaluation the degree of regaining of olfaction was done one month after cessation of treatment by using TDIT

Results

The study was carried out on 42 patients allocated into two groups according to modality of treatment; 21 patients (group 1) were treated with PRP injection into the olfactory area while the other 21 patients (group 2) were treated with olfactory training. Their age ranged between 18 to 60 years with a mean age of 29.98± 7.47 years. It was noticed that both groups were matching in gender with no statistically significant differences between both groups regarding sex, smoking or medical history.

Out of the studied patients each of anosmia and hyposmia was observed in 15 patients (35.7%), Meanwhile 12 patients (28.6%) reported parosmia with no statistically significant difference among smell disorders between both groups. Also, recovery of olfactory function one month after treatment was observed in 45.2% of patients including both groups as shown in **Table 1**

During PRP injection, we noticed the mean time of PRP procedure was 14.76 ±1.41minutes including anesthesia time (10 minutes), with no major complications apart from mild epistaxis encountered in three patients (14.28 %) and it was controlled by temporary nasal packing. According to VAS score for pain, 15 patients (71.4%) described pain as very mild, pain was tolerable in five patients (23.8%), and only one male patient had distressing pain (4.8%) as shown in **table 2**

We also found all smokers within the PRP group didn't improve, while 12 out 17 non-smokers were improved with a statistically significant difference between smokers and non-smokers (p-value 0.021). We noticed that patients who received systemic steroid treatment for any indication showed better outcomes with a statistically significant difference (p-value 0.021). There was no statistically significant difference between age or gender of patients and improvement status (P value =0.490, 0.670) respectively. While in OT group none of the socio-demographic variables like age, sex, residence, smoking or history of steroid use- affected the outcome as shown in **Table 3**

We found that six patients out of eight patients complaining from parosmia were improved representing 50% of improved cases and four patients out of seven patients complaining from hyposmia were improved representing 33.3 % of improved cases. While, most

of anosmic patients (4 cases) didn't show any improvement with no statistically significant difference between improvement status after PRP injection and type of smell disorders. Meanwhile olfactory training was highly effective for treatment of hyposmia, with a strong response seen in the majority of patients (85.7%). However, olfactory training seems to be ineffective for parosmia, as none of the patients had improved. Also, in anosmia only one patient had improved. There was statistically significant difference between improvement status with olfactory training and type of smell disorders suggesting that olfactory training may be better for hyposmia but with limited outcome for both anosmia and parosmia as shown in **Table 4**

Regarding TDI score The PRP group demonstrated greater improvement in TDI score (p value <0,001) as Threshold Score was increased from 5.48 ± 3.076 to 8.67 ± 3.039 ($p < 0.001$), indicating a significant improvement in the ability to detect odors. Discrimination Score was improved from 4.29 ± 3.466 to 8.43 ± 3.655 ($p < 0.001$), demonstrating enhanced ability to distinguish between different odors. Also, identification Score was increased from 4.24 ± 3.223 to 8.57 ± 4.589 ($p < 0.001$), reflecting a notable enhancement in identifying specific odors. Total TDI Score was improved significantly from 14.00 ± 9.209 to 25.76 ± 10.977 ($p < 0.001$), indicating a substantial overall improvement in olfactory function. Also, there was statistically significant improvement in TDI scores after olfactory training therapy and the total TDI score had significantly increased with p-values 0.002 as shown in **table 5**

Table (1): Socio-demographics, smell disorders and outcome of treatment in both groups

		Total	PRP Injection group (n=21)	OT group (n=21)	P Value#
Mean age		29.98± 7.47	28.24± 6.715	31.71 ±7.944	0.134
Sex	Male	22(52.4%)	10	12	0.537
	Female	20(47.6%)	11	9	
No of smokers			4	4	1.000^
Medical history	No treatment	31(73.8%)	13	18	0.149
	Systemic Steroid	9(21.4%)	6	3	
	Anticoagulant	2(4.8%)	2	0	
Smell disorders	Anosmia	15(35.7%)	6	9	0.368
	Hyposmia	15(35.7%)	7	8	
	Parosmia	12(28.6%)	8	4	
Outcome	Improved	19(45.2%)	12	7	0.125
	Not-improved	23(54.8%)	9	14	

Table 2: Evaluation of PRP procedure

Duration in minutes		14.76±1.41
Epistaxis		3(14.28%)
VAS score for pain	Very mild tolerable Distressing	15 (71.4%) 5 (23.8%) 1(4.8%)

Table 3: Patients demographics in relation to outcome in both groups

Demographics	PRP injection group		P	OT group		P
	Improved (n= 12)	Not-improved (n=9)		Improved (n= 7)	Not-improved (n=14)	
Mean age	27.33± 6.34	29.44±7.38	0.490"	29.14 ± 10.54	33.0 ± 6.36	0.306 "
Male	5(41.7%)	5(55.6%)	0.670#	4 (33.3%)	8 (66.7%)	1.000
Female	7(58.3%)	4(44.4%)		3 (33.3%)	6 (66.7%)	
No of smokers	0(0.0%)	4(44.4%)	**0.021***	0 (0.0%)	4(28.6%)	0.255
No of non-smokers	12(100%)	5(55.6%)		7	10(71.4%)	
History of systemic Steroid	6(50%)	0(0.0%)	**0.019***	1(33.3%)	2(66.7%)	1.000

Table 4: Outcome of smell disorders in both groups

Smell disorders	PRP injection group		P value	OT		
	Improved (n= 12)	Not-improved (n=9)		Improved (n= 12)	Not-improved (n=9)	P value
Anosmia	2(16.7%)	4 (44.4%)	0.297	1 (14.3%)	8 (57.1%)	**0.006***
Hyposmia	4(33.3%)	3 (33.3%)		6 (85.7%)	2 (14.3%)	
Parosmia	6(50.0%)	2 (22.2%)		0 (0.0%)	4 (28.6%)	

Table 5: post treatment improvement in TDI scores after three months in both groups (total TDI score = 48)

(N= 21)		Pre – treatment score	Post – treatment score	
PRP	Threshold score	5.48 ± 3.076	8.67 ± 3.039	**<0.001***
	Discrimination score	4.29 ± 3.466	8.43 ± 3.655	**<0.001***
	Identification score	4.24 ± 3.223	8.57 ± 4.589	**<0.001***
	Total TDI score	14.00 ± 9.209	25.76 ± 10.977	**<0.001***
OT	Threshold score	5.05 ± 3.369	6.24 ± 3.576	**0.004***
	Discrimination score	4.81 ± 3.750	6.48 ± 4.389	**0.004***
	Identification score	3.90 ± 3.300	5.38 ± 4.500	**0.004***
	Total TDI score	13.76 ± 9.949	18.10 ± 12.128	**0.002***

Discussion:

In our study we compared the outcomes of the PRP injection technique and olfactory training on Post covid-19 olfactory dysfunction. The mean age of our patients was 29.98± 7.47 with a predominance of young age group. This was consistent with **Cheng et al [11] and Giacomelli et al [12]** who demonstrated that olfactory dysfunction was more frequent in younger patients infected by COVID-19, as younger patients have more contact and greater exposure to viral infection, which is an important risk factor. We thought that young patients were more concerned with olfactory dysfunction, which is an important part for their lifestyle.

Our study involved 22 males (52.4%) and 20 females (47.6%) with no gender predominance. Also Vaira et al, [13] found that there is no association between gender and the prevalence of olfactory loss after covid -19 infection. In contrast **Kosugi et al. [14]** and **Lechien et al.,[15]** reported that females were more predominant to have olfactory dysfunction, as females have a greater concern for their smell with a decreased capacity of men to perceive olfactory disorders. We found both anosmia and hyposmia accounted for 71.4%, parosmia (28.6%). Also, **Lechien et al.,**[16-17] and **da Costa et al.,[18]** reported that anosmia and hyposmia were the most prevalent olfactory dysfunctions after covid 19.

In our study the mean time of PRP procedure was 14.76±1.41 min including anesthesia time which was shorter than **Lechien et al.**[16] who reported that time of their procedure was 18.4±3.4 min. There were no significant complications following intranasal PRP injections in our study. The occurrence of transient epistaxis was experienced in 14.28% of patients and was controlled by transient nasal packing. Lechien et al[(16)] noticed that 36% of patients had post injection transient epistaxis, which was explained by several mucosal injection points. The injection-related pain was judged by VAS score for pain as mild pain by 71.4% of patients, tolerable to 23.8% and distressing to 4.8%. **Lechien et al.[17]** reported that 17 out of 90 patients (19%) had severe pain during the injection due to ineffective local anesthesia, while 41 (47%) and 22 (25%) evaluated the pain as moderate or low, respectively. This approved that local anesthesia in current study was more effective.

We found that after PRP injection, 57.1% of patients had improved. Also, Abo **El Naga et al.,[19,] Shawky and Hadeya [20] , and Evman and Cetin [21]** reported that improvement range was 50-60% and only **Lechien et al** [17] showed higher rate of success about 78%.

Regarding total TDI score there was significant improvement in post-covid-19 olfactory disorders after three months of PRP injection with p value <0.001. Also, **Steffens et al.,** [22] and **Lechien et al [16]** observed that patients treated by PRP injection reported a higher increase in total post treatment TDI score. This improvement highlighting the benefits of PRP which contains many bioactive factors that are associated with peripheral nerve regeneration. Moreover, PRP can fasten axon regeneration and neuroregeneration by promoting synthesis of proteins and lipids necessary for nerve regeneration.

After PRP injection we experienced improvement in all patients who had past history of systemic steroid intake. **Huart, et al.** [23]. Suggest that steroid treatment may substantially change the outcome of olfactory dysfunction. It is probably related to the effect of corticosteroids in resolving inflammation within the olfactory

mucosa, allowing faster regeneration of the epithelium. [24]

On the other hand, all smokers did not noticed any degree of recovery. So, smoking is considered a high-risk factor for olfactory dysfunction, while nonsmokers were statistically improved with p value =0.021. **Ajmani et al.,[25]** found that smokers are at a higher risk for olfactory dysfunction than non-smokers. This was explained as smoking is associated with irreversible sinonasal inflammation associated with olfactory dysfunction.

33.3% of patients who received olfactory training (OT group) showed marked improvement in total TDI score (p value 0.004). There are many studies supporting the effectiveness of olfactory training in patients with post-COVID olfactory dysfunction, explained as the repeated short-term exposure to odors may increase both the growth of olfactory receptor neurons and the expression of olfactory receptors in the olfactory cleft mucosa. [26-31]

Within OT group, hyposmia was the most responsive type of smell disorders (85.7%) followed by anosmia (14.3%) and none of the patients complained that parosmia was improved. Vandersteen et al.,[(30)] stated a significant change in the number of participants categorized as anosmic and hyposmic before and after the olfactory training. But a study by **Altundag et al.,** found olfactory training was an effective treatment modality for parosmia compared to the treatment of anosmia and hyposmia. [24]

The short follow up time after third injection (only one month) and disparity of treatment after recovery from COVID-19 -19 as some patients treated with INS, vitamins, and zinc were limitations in our study.

Conclusion

PRP could be considered a safe office-based procedure and has a promising initial outcome for the treatment of post-COVID-19 smell disorders. Nonsmokers and patients who have been previously treated with systemic steroids are considered better candidates for PRP injection. Also, PRP injection has a better outcome than olfactory training in the treatment of post-COVID-19 smell disorders.

Funding support: None.
Conflicts of interest: None.

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