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Research Article

Role of Platelet-Rich Plasma in the Treatment of Post COVID-19 Olfactory Dysfunction

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Abstract

Background: COVID-19-related olfactory dysfunction is a serious problem that affects quality of life. With Limited effective therapies, we discuss the role of Platelet-Rich Plasma as a therapeutic agent for this problem. **Aim of the study:** Evaluation of the effect of platelet-rich plasma in the treatment of Post COVID-19 Olfactory Dysfunction. **Patients and methods:** The study recruited 28 patients with post-COVID-19 olfactory Dysfunction (Anosmia / hyposmia / Cacosmia) From the E.N.T outpatient clinic of Minya University Hospital. Patients received platelet-rich plasma only in the form of injection in the olfactory cleft. **Results:** The median of the Butanol Threshold test before for patients was 3 (1.5 – 4), and the median of the Butanol Threshold test after for patients was 3(1.5 – 5). There was a highly statistically significant increase in the butanol threshold test after treatment than the butanol threshold test before treatment. **Conclusions:** In conclusion, our findings indicated that using PRP significantly reduced the duration of anosmia in patients. Notably, A highly statistically significant increase in Butanol Threshold tests after treatment compared to before, underscoring the potential benefit of PRP in addressing olfactory dysfunction in post-COVID-19 patients.

Key words: COVID-19, olfactory dysfunction, platelet-rich plasma.

Introduction

The impairment of the sense of smell, known as olfactory dysfunction, is a common condition that impacts around 20% of the overall population. The condition has significant consequences for an individual's well-being, leading to a lower standard of life and heightened rates of illness and death. [1-3]

Sinonasal disorders, post-viral neurological disorders that produce olfactory dysfunction, and post-traumatic olfactory nerve injuries are the most common causes of olfactory dysfunction.[1]

The incidence of Olfactory Dysfunction has significantly risen, ranging from 30% to 86% among patients, after the emergence of the COVID-19 pandemic in 2019.[4-6]

The Olfactory Dysfunction can manifest as anosmia, hyposmia, phantosmia, or parosmia, depending on the stage of the disease.[7]

The angiotensin-converting enzyme 2 receptor, which is essential for the entry of SARS-CoV-2, is present in high quantities in nasal epithelial cells. This characteristic

makes coronaviruses, among other Dangerous microorganisms, capable of inducing post-infectious olfactory dysfunction. [8]

Disruption of cells within the olfactory neuroepithelium can lead to inflammatory alterations within the same neuroepithelium, which in turn can have an impact on the function of olfactory receptor neurons. In addition, such inflammatory changes may exacerbate damage to olfactory receptor neurons and limit subsequent neurogenesis. [9]

The olfactory neuroepithelium and olfactory file, which are peripheral nerve fibers that pass through the cribriform plate into the nasal cavity, exhibit regenerative capabilities. This character-ristic makes them potentially suitable for therapeutic interventions in individuals experiencing olfactory dysfunction. [10]

The popular features of platelet-rich plasma (PRP) include its anti-inflamm-atory and pro-regenerative effects, which are mediated through the activation of growth factors such as transforming growth factor, vascular endothelial growth factor, epidermal growth factor, and insulin-like growth factor. [10]

It has been applied in various medical situations as a secure therapy that is effective in treating peripheral neuropathies, wound healing, and inflammation. [11-13]

Specifically, PRP has the capacity to speed up the process of neuroregeneration and axon regeneration, according to earlier studies. [14-17]

Patients and methods

Study design:

the research that was performed at the Department of Otorhinolaryngology, Minia University Hospital from December 2022 to July 2023 to demonstrate the impact of platelet-rich plasma in the treatment of Post COVID-19 Olfactory Dysfunction

Sampling Criteria:

In this study 28 patients having Post COVID-19 Olfactory Dysfunction in outpatient clinic in the Department of Otorhinolaryngology Minia University Hospital. These patients were analyzed and examined.

Participants

The research participants were recruited from patients who have post COVID-19 olfactory Dysfunction in the Minia university hospital outpatient clinic.

- Patients will receive platelet-rich plasma in the form of injection in the olfactory area

- **Inclusion criteria**

Age: 18 years or older Patients

Sex: both sexes equally

History of COVID-19 infection either a confirmed case with a positive PCR test, or a recovered case suffering from sudden recent olfactory dysfunction by clinical evaluation.

The patients were selected randomly

- **Exclusion criteria**

1- Children up to 17 years
2- Previous nasal surgery
3- Apparent Nasal Diseases as;
   - Allergy, Sinonasal polyposis
4- Immunocompromised patients
5- General Debilitating Diseases

Methods:

A- Evaluation of the patients

1: history taking

A previous history of patients was collected before entering the study

Complete Medical history was recorded involving; gender, age, duration of COVID-19 illness.

2: General Examination

A general examination was done to exclude any medical disease that can affect the smell as (conditions affect nervous sys as Parkinson's disease)

3: local (E.N.T) Examination

E.N.T examination was done by sinuscope to exclude any abnormalities in the Nose as; Deviated septum, sinonasal polyposis

4: Butanol Threshold test

The patients were investigated for olfactory disorders using (Butanol Threshold test) for assessing smell disorders before the

injection and after the Injection twice once after 1 month and once after 3 months of injection.

Butanol Threshold test

The olfactory threshold, the minimum odor concentration below which a person may reliably detect an odor, was calculated using this method.

Bottles with varying amounts of butanol, labeled 0 through 9, were used to determine the olfactory threshold .

The remaining butanol concentrations were generated by diluting the highest concentration (4%) bottle (0) with deionized water at various ratios, beginning with 1:1 and progressing through 1:2, 1:3, and 1:4. Because of this, bottle 9 contained the least concentration of Butanol.

The higher the concentration at which the patient could smell, the worse the olfactory function.

Procedure:

1/ Preparation of platelet-rich plasma

Twenty milliliters of whole blood were collected from the case, the anticoagulant sodium citrate was placed in it, and the PRP was separated by centrifugation at 4200 revolutions per minute for ten minutes.

The supernatant (2 mL of PRP).

The PRP was transferred to two distinct syringes of 1 milliliter each, and then a 27-gauge needle was used to inject it intranasally into each of the patient's nasal cavity.

2/ Injection of PRP

A spray containing 10% xylocaine was used to administer local anesthetic two minutes following xylometazoline chlorhydrate drops were placed in the nasal fossae of the patient .

The injection was carried out through a rigid optic set at 0 degrees to guide the needle direction in the middle turbinate & the nasal septum in relation to the head of the middle turbine.

The technique is carried out in a same manner on the contralateral side. After the procedure, the patient was monitored for 15 minutes for potential adverse effects and was discharged.

Figure (1): Centrifugation of whole blood with the supernatant (PRP)

Figure (2): collection of (PRP) by 1 milliliter syringe

Figure (3): Bottles containing different concentrations of Butanol

Results:

* Table (1) The Butanol Threshold test before ranged from 0 to 5 with median 3, while The Butanol Threshold test after ranged from 0 to 7 with median 3.5.

Table (1): Distribution of the studied cases according to Butanol Threshold test

Butanol Threshold test		**No. = 28**
Before	**Mean ± SD**	2.62 ± 1.69
	Median (IQR)	3 (1 – 4)
	Range	0 – 5
After	**Mean ± SD**	3.22 ± 2.16
	Median (IQR)	3.5 (2 – 5)
	Range	0 – 7

* Table (2) show that the number of males to females in Prp group was 17:118

Table (2): Comparison between studied groups regarding Sex

Sex	Prp		Test value	P-value	Sig.
	No.	%			
Female	11	39.3%	0.014*	0.907	NS
Male	17	60.7%			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S);
P-value< 0.01: highly significant (HS)
***: Chi-square test, •: Independent t-test**

* Table (3) show that the mean of Age for patients of Prp group was 31.96 ± 8.32.

Table (3): Comparison between studied groups regarding Age

Age	Prp	Test value	P-value	Sig.
	No. = 28			
Mean ± SD	31.96 ± 8.32	0.984•	0.326	NS
Range	19 – 50			

P-value >0.05: Non significant (NS); P-value <0.05: Significant(S);
P-value< 0.01: highly significant (HS)
***: Chi-square test, •: Independent t-test**

Table (4): Comparison regarding Butanol Threshold test before and after PRP Usage

Butanol Threshold test		Prp	Test value	P-value	Sig.
		No. = 28			
Before	**Median (IQR)**	3 (1.5 – 4)	-0.497 ***ȧ***	0.619	NS
	Range	0 – 5			
After	**Median (IQR)**	3 (1.5 – 5)	-0.218 ***ȧ***	0.827	NS
	Range	0 – 6			
Test value µ		-3.464	–	–	–
P-value		0.001	–	–	–
Sig.		HS	–	–	–

P-value >0.05: Non significant (NS); P-value <0.05: Significant(S);
P-value< 0.01: highly significant (HS)
***ȧ*: Mann-Whitney test, µ: Willcoxon Test**

* Table (4) shows, the median value of the Butanol Threshold test before PRP injection for patients in the Prp group was determined to be 3 (with a range of 1.5 – 4).
- the median value of the Butanol Threshold test after PRP injection for patients in the Prp group was determined to be 3 (with a range of 1.5 – 5).
we observed a substantial and statistically significant rise in the butanol threshold test following treatment compared to the butanol threshold test prior to treatment.

Discussion

The outbreak of the coronavirus illness 2019 (COVID-19) resulted in a rise in the occurrence of olfactory dysfunction (OD) within the general population. (OD) is a prevalent symptom observed in patients affected by the illness, with a reported incidence ranging from 30% to 86% depending on the specific variations.[18]

The majority of patients see a gradual restoration of their olfactory function throughout the weeks following the infection. However, there are certain

individuals who continue to experience olfactory dysfunction for an extended period of time. This dysfunction can manifest as many conditions such as anosmia, hyposmia, phantosmia, or parosmia. According to a study conducted by Boscolo-Rizzo et al., it was found that the 12-month persistence rate of olfactory dysfunction (OD) based on psycho-physical olfactory evaluations can reach up to 46% of cases. [19]

According to other sources, the incidence of patient-reported olfactory dysfunction varied between 15% and 70% within one year following the infection. Currently, there is a lack of alternatives to treatment for the chronic overdose condition. It is advisable for patients to comply with a prescribed olfactory training regimen, and in certain cases, healthcare professionals may suggest the use of dietary supplements such as omega 3, zinc, and vitamin B12 .[20]

In the year 2019, A preliminary publication released wherein they detailed the administration of platelet-rich plasma (PRP) into the olfactory cleft of seven patients suffering from post-viral olfactory dysfunction (OD). This novel intervention was proposed as a prospective method to enhance the recovery of olfactory function. [21]

In the management of persistent anosmia associated with long-term COVID-19 infection. Platelet-rich plasma (PRP) has been extensively utilized in various therapeutic disciplines and has shown considerable potential in promoting the regeneration of peripheral nerves. This is achieved by stimulating the formation of blood vessels and nerve fibers through the action of growth factors, as well as by modulating the inflammatory response within the microenvironment .[22]

Several more studies have provided evidence supporting the safety of platelet-rich plasma (PRP) in its application for osteoarthritis (OD). In an experimental study using mice to simulate anosmia, the application of platelet-rich plasma (PRP) by intranasal administration led to enhanced olfactory function and the regeneration of a fully functional olfactory epithelium. Prior single-arm clinical trials of PRP for OD indicated no adverse consequences and a potential increase in olfactory function .[23]

This aligns with the study conducted by Lechien et al.,[24] which sought to examine the safety, feasibility, and efficacy of administering platelet-rich plasma (PRP) injections into the olfactory clefts of patients suffering from persistent olfactory dysfunction (OD) caused by COVID-19. A subset of participants (n= 37) performed a further evaluation two months after undergoing a platelet-rich plasma (PRP) injection. These people experienced notable enhancements in their ODQ (Olfactory disorder questionnaire) and TDI (threshold, Discrimination and Identification) scores.

The present dataset corroborates the findings of a preliminary investigation conducted by Yan et al.,[21] that explored the efficacy of platelet-rich plasma in managing olfactory dysfunction in a sample of seven individuals. These participants had experienced a prolonged loss of olfactory function exceeding six months, exhibited no indications of sinonasal inflammatory disease, and failed to observe any improvement through olfactory training or the application of topical budesonide rinses. It was found that all patients initially exhibited a subjective enhancement in olfactory perce-ption subsequent to the administration of the injection, although this improvement promptly reached a state of stability. The study observed that two individuals diagnosed with functional anosmia did not exhibit statistically significantly improve-ment in their condition after a period of three months following therapy. At the three-month post-intervention assessment, it was observed that a total of five patients diagnosed with hyposmia had notable improvement, with 60% of them success-fully attaining normosmia.

The efficacy of injecting platelet-rich plasma (PRP) into the olfactory cleft has

been substantiated in a recent study conducted by Steffens et al., The researchers found that patients who received PRP injections for persistent olfactory dysfunction (OD) lasting more than one year reported significantly greater improvements in TDI scores one month after the injection, in comparison to patients who did not receive the treatment. The findings of the research conducted by Steffens et al. may provide empirical support for the observations made in our investigation. [23]

It was demonstrated in a new single-blinded, randomized controlled research that administering platelet-rich plasma (PRP) treatment resulted in a more substantial improvement in overall olfaction ratings when compared to the placebo. The study revealed that the probability of achieving a therapeutic response after three months was 12.5 times greater in the group receiving platelet-rich plasma (PRP) treatment. The submucosal delivery of platelet-rich plasma (PRP) into the olfactorily cleft was found to be well-tolerated, and no significant adverse effects were seen. The submitted results suggest that platelet-rich plasma (PRP) has the potential to be a safe therapy option for individuals with olfactory impairment caused by COVID-19. However, no statistically significant difference was seen in the overall subjective improvement between the group treated with platelet-rich plasma (PRP) and the group receiving a placebo. Significant improvements were observed in both arms of the study at the 1-month and 3-month follow-up periods. The lack of noticeable variance may be attributed to a study sample that was not well powered, neglecting to account for the degree of spontaneous recovery or the placebo effect. Furthermore, the most notable improvement demonstrated by the utilization of platelet-rich plasma (PRP) therapy was observed in the domain of olfactory discrimination. The variety of olfactory perception enhancement is contingent upon individual differences, since each person may attribute different levels of importance to characteristics such as the intensity, differentiation, and recognition of odors. Based on the findings of Yan et al., it was observed that the control group demonstrated a much greater enhancement in olfactory function in comparison to the experimental group. The control group exhibited a mean rise of 3.0 points during the three-month follow-up period, while the experimental group displayed a mean gain of only 0.5 points at the one-month follow-up.[25]

In their recent study, Abo El Naga et al.,[26] observed a substantial enhancement in post-COVID olfactory parosmia following the administration of three sets of platelet-rich plasma (PRP) injections in the olfactory cleft, with each set consisting of three injections given over a period of three weeks. The findings revealed a statistically significant disparity between the case group and the control group, with the former exhibiting more advantageous results.

Upon doing a literature review, several writers have examined the potential impact of platelet-rich plasma (PRP) in the treatment of anosmia, without specifically addressing post-COVID olfactoiry impairment. In a study conducted by Mavrogeni et al., platelet-rich plasma injections were administered to a cohort of five patients diagnosed with anosmia. Four patients experienced a restoration of their olfactory function following the completion of their third and, subsequently, fourth therapeutic interventions. On the contrary, the final patient expressed the ability to perceive a substantial range of odors, but not comprehensively. The authors believe that the administration of platelet-rich plasma to the olfactory region holds potential as a viable intervention for total anosmia, particularly as a final resort.[27]

A prospective experiment conducted by Aboelmagd et al.,[28] involved the participation of eighty patients who presented with different causes of anosmia. The intervention employed in this study was platelet-rich plasma. The researchers discovered that among the sample of 80 patients, 34 individuals (42.5%) did not experience any improve-ment, while 46

patients (57.5%) reported a restoration of their sense of smell. Notably, all patients with idiopathic anosmia demonstrated improvementt; however, there was noo statistically significantt distinction observed between the patient group and the control group.

From a physiological standpoint, the platelet-rich plasma (PRP) pockets located inside the mucosa gradually discharge anti-inflammatorry and pro-regeneratives substances that originate from platelets. The process mentioned earlier leads to the stimulation of specific factors by cellular components found in nasal and olfactory tissues. Several factors that might be cited as examples include growth and trans-forrming factors, vascular endotthelial growth molecules, epiidermal growth factor, and insuline-like growth factor. Furthermore, Soler et al. put up the notion that PRP possesses the capacity to augment the process of axon regenerration and neuroreigeneration. The significance of platelet-rich plasma (PRP) in persons with olfactory impairment (OD) caused by COVID-19 lies in its anti-inflammatory characteristics. [29]

The previously mentioned observation might be attributed to the results obtained from a recent multicenter investigation, which have demonstrated that individuals with olfactory dysfunction (OD) may manifest a sustained presence of viral particles in the olfactory region, concomitant with inflammation in the neuroepithelium. The presence of inflammation may potentially have a role in the extended or recurrent olfactory dysfunction observed in these people .[30]

According to the research conducted by Scangas et al., [32] it has been shown that the application of topical steroids has been associated with enhanced recovery in individuals suffering from post-infectious olfactory impairment. In a study conducted by Heilmann et al.,[31] it was observed that the use of mometasone nasal spray locally resulted in enhanced olfactory function in individuals with olfactory impairment due to upper respiratory tract infections. However, the viral infection that was the cause in the aforementioned investigations did not involve the novel coronavirus, for which our understanding of its pathophysiology in relation to anosmia is limited.[31, 32]

The findings of a study conducted by Yaylacı et al.,[33] indicate that a far larger percentage of patients in the COT group experienced improvement in their olfactory scores beyond the threshold considered clinically significant, compared to the control group (40% versus 6%) ($p = 0.014$). The influence of COT on subjective olfactory perception was seen to be unaffected by several variables, such as age, gender, length of olfactory impairment, presence of parrosmia, and baseline olfactory score (all $p > 0.05$).

Few studies are found regarding the role of PRP or role of Dexamethasone in patients complaining of olfactory dysfun-ction, so future studies with larger number of patients will help determine optimal frequency and duration of use of PRP.

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Conflict-of-interest statement: The authors hereby declare that they have no competing interest.

Ethical approval: Ethical permission was taken from a local faculty of medicine research ethics committee (FMREC) No:580/2022. In accordance with the protocol established by the committee, all of the patients gave their permission to retrieve their data for the purposes of research following the confidentiality of their information was guaranteed. As a result, the study does not compromise the patients' health or safety in any way.

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