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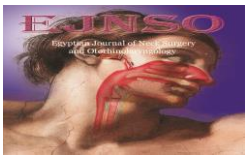

Platelet-rich plasma in the management of anosmia

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Abstract:

Background: Anosmia is a loss of sense of smell that means inability to perceive odors. Functional anosmia is loss of smell due to nasal obstruction. In contrast, organic anosmia is due to damage of the peripheral olfactory area causing permanent loss of smell as post-traumatic anosmia.

Objectives: A diagnostic approach to detect the effect of platelet-rich plasma (PRP) injection in the olfactory area as a treatment for anosmia.

Study design and methodology: A prospective study was done in otorhinolaryngology department, Aswan university hospital, from June 2018 to August 2019; 80 patients were fulfilling the inclusion criteria presented with anosmia were enrolled from otorhinolaryngology outpatient to share in this study. Approximately an amount of 1mL of PRP was injected in each nasal cavity in the olfactory area (located on superior turbinate and superior portion of lateral and medial walls of nasal cavity) guided by nasal endoscope. The procedure is done with follow-up of patients after one month.

Results: Results of our study revealed that 46 out of 80 patients (57.5%) said that "their smell came back" while 34 out of 80 patients (42.5%) showed no improvement. Thus these results show no statistical significance between proportion in the group showing improvement and proportion in the group showing no improvement. Five patients with idiopathic anosmia improved with 100% ratio.

Conclusion: Although there is no statistical significance difference between the two groups of patients, all patients with idiopathic anosmia were improved.

Keywords: Anosmia, Platelet-rich plasma, olfactory area.

Introduction

Anosmia is the inability to perceive the odor or a lack of functioning olfaction; it may be temporary or permanent. Functional anosmia is loss of smell due to nasal obstruction caused by sinonasal diseases (as nasal polypi, tumors, postoperative, allergic rhinitis, atrophic rhinitis, or nasal trauma) preventing odorant molecules from reaching olfactory mucosa by sniffing. Functional anosmia affects up to 5% of the general population and 10% of those older than 65. [1] Organic anosmia is due to damage of peripheral olfactory area causing permanent loss of smell as post-traumatic anosmia. [2] 20% of individuals aged 20 to 90 years have impaired olfactory Function. [3-4]

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This ratio means that quality of life, as well as eating habits and nutritional intake, may be severely altered in a large proportion of patients with olfactory disorders. [5-6]

Platelet-rich plasma (PRP) for topical use is prepared after various processing of a whole blood sample, mostly through centrifugation.[7] The blood components were separated in order to discard non-usable elements (mostly the red blood cells) and to collect and concentrate the elements that may be used for therapeutic applications (fibrinogen/fibrin, platelets, growth factors, leukocytes, and other forms of circulating cells, in solution in liquid plasma). [8]

The use of platelet concentrate was contrived to enhance wound healing, like the fibrin glues used for more than 40 years as surgical adjuvants to improve healing. PRP has become the promoted glorious instrument of new regenerative medicine strategies. [9]

The PRP seems to be beneficial in cleft palate repair surgery, myringoplasty, and in endoscopic sinus surgery.[10-11] There is broad variability in the production of PRP by various concentrating equipment and techniques. [12]

Previous studies discussed the effectiveness of platelet-rich plasma in an anosmia-induced mice model. Other studies discussed the effectiveness of platelet-rich plasma in patients with post-traumatic anosmia and applied this technique on low number of patients. [13-14]

Patients and Methods:

A prospective study was done in otorhinolaryngology department, Aswan university hospital, from June 2018 to August 2019. The study was approved by the institutional ethics committee of Aswan University and after obtaining consent from patients sharing in this study.

Eighty patients presented with anosmia, whose olfactory function was assessed using the university of pennsylvania smell identification test (UPSIT), were enrolled from otorhinolaryngology outpatients, Aswan university hospital, to share in this study.

Inclusion criteria:

- UPSIT score up to 10 of 40
- Adult patients who suffer from anosmia.
- Normal airway passage after management of primary cause.
- CT scan of nose and paranasal sinuses does not show any nasal obstructing lesions.

Exclusion criteria:

- UPSIT score more than 10 of 40
- Severe nasal septum deviation.
- Chronic sinusitis, nasal polyps, tumors or any lesion obstructing airway.
- Medical history of blood disease.
- Any medication known to affect platelet or bone marrow function for 2 weeks prior to testing.

Method:

1- A proper evaluation of the patient, including a detailed history and physical examination:

A) Detailed history was taken from the patients regarding nasal symptoms (history of nasal obstruction, nasal discharge, sneezing, snoring, post-nasal discharge, facial pain, or previous nasal operations), associated aural, pharyngeal, or laryngeal symptoms, and history of chronic diseases as hypertension, diabetes mellitus or blood diseases.

B) Careful physical examination, including General examination and Local nasal examination.

C) Investigations included CT nose and paranasal sinuses and diagnostic nasal endoscopy.

D) Assessment of patients using the university of pennsylvania smell identification test (UPSIT), a widely used odor identification test based on the four alternatives in forced choice technique. Odors are microencapsulated on paper and released by scratching its surface ("scratch and sniff" method). For each odor, the subject had to choose one of four possible answers. Perfect smell sensation on this test gives a score of 40 (normal range: 34–40); complete anosmia a score up to 10 out of 40.

- Patients enrolled in the study include as regarding the history and physical examination:
  - Ten patients had idiopathic anosmia.
  - Eighteen patients had a history of anosmia with chronic sinusitis. Functional endoscopic sinus surgery was done, but anosmia didn't improve even after three months of post-surgical medical treatment (local nasal and systemic steroids, local alkaline nasal wash, antihistamine tablet, and nasal decongestant).
  - Four patients had a history of anosmia with atrophic rhinitis that did not show any improvement after three months of medical treatment.
  - Eighty patients had history of anosmia with allergic rhinitis, and these patients did not show improvement regarding anosmia after 3 months of treatment with antihistamine tablets in addition to local and systemic steroids (allergy was controlled after treatment for 3 months and patients had patent airway with anosmia and were only on antihistamine tablets).
  - Ten patients had a history of anosmia with diabetes mellitus (controlled random blood sugar with their anti-diabetic tablets).
  - Six patients had a history of anosmia, DM, chronic sinusitis and did FESS, these patients had controlled random blood sugar with their anti-diabetic tablets, but anosmia didn't improve even after 3 months of post-surgical medical treatment (local nasal steroids, local alkaline nasal wash, and nasal decongestant).
  - Fourteen patients had history of anosmia with DM and allergic rhinitis, these patients had controlled random blood sugar with their anti-diabetic tablets, but anosmia didn't improve even after 3 months of treatment with antihistamine tablets in addition to local steroids (allergy was controlled after treatment for 3 month and patients had patent airway with anosmia and were only on antihistamine tablets).

2- PRP preparation:

A 5-mL syringe prefilled with 1 mL of acid citrate dextrose (ACD-A) was used for the standardized blood draw. ACD-A binds calcium and prevents blood clotting with no known interference to platelet function.

The 5 milliliters of blood were divided into two sterile glass tubes to produce 1 mL of PRP (Platelet-rich plasma). Tubes were centrifuged at 1500 rpm for three minutes. This separated the erythrocytes from the remaining plasma components. The top portion of plasma was drawn up with the use of the inner syringe without disruption of the erythrocyte layer.

3- Administration of PRP in the patient nose:

Firstly, a solution of decongestion nasal drops with Emla® 5% and 10% Xylocaine spray in cotton, which was placed in the nose for 30 minutes.

The 2nd step was the submucosal injection of PRP in the olfactory area of the nose via 1 ml syringe.

With the help of nasal endoscope (Storz tele pack X [20045020], Storz 0 degree lens, and Storz telecam), approximately an amount of 1mL of PRP was injected in each nasal cavity in the olfactory area (located on superior turbinate and superior portion of lateral and medial wall of nasal cavity).

PRP is injected 3 times locally in the olfactory area in the nose with 4 weeks interval with follow up of the patient for one month after PRP injection using UPSIT, and results were obtained after one month of last PRP injection.

Follow up:

Patients follow up continued for one month after the last PRP injection for assessing the degree of regaining olfactory function using UPSIT.

Evaluation:

Data were analyzed for subjective assessment of regaining of olfactory function in patients with anosmia after the use of this new technique.

Statistical analysis :

Data obtained were analyzed statistically using SPSS program, and the results of this analysis were evaluated and discussed.

Results:

All the obtained data were recorded in a special observation sheet then statistically analyzed and presented in tables as follows:

- Out of the studied patients, 66 (82.6%) were males, while 14 (17.4%) were females. Age mean was 53.32 years old (these data are regarding the number and gender of patients who were accepted to be enrolled in this study). **Table 1**

- Age of the studied patients ranged from 28 to 65 years old. **Table 1**

- Duration of anosmia in studied patients ranged from 2 to 8 years; Spearman correlation shows non-significant positive weak correlation between age of the patients and duration of anosmia. **Table 2**

- The highest number of patients as those who had chronic sinusitis and did endoscopic sinus surgery and those who had allergic rhinitis. Improvement happened in 46 cases (57.5 %), and the Mean duration of anosmia was 5.22 years. **Table 3**

- Out of the studied patients, 46 (57.5%) showed improvement while 34 (42.5%) did not show improvement, and this shows no statistical significance between proportion in the group showing improvement and proportion in the group showing no improvement and that prove toward acceptance of the alternative hypothesis that indicates that there is a difference and to reject the null hypothesis. **Table 4**

- As regard the history of the studied patients:

  - Ten patients had idiopathic anosmia and showed 100% improvement after PRP local nasal injection.
  - Eighteen patients had a history of anosmia with chronic sinusitis and did functional endoscopic sinus surgery, 14 of these patients showed improvement, while 4 patients didn't show improvement after PRP local nasal injection.
  - Four patients had a history of anosmia with atrophic rhinitis and they didn't show improvement after PRP local nasal injection.

- Eighty patients had a history of anosmia with allergic rhinitis, 14 of these patients showed improvement while 4 patients didn't show improvement after PRP local nasal injection.
- Ten patients had a history of anosmia with diabetes mellitus and didn't show improvement after PRP local nasal injection.
- Six patients had a history of anosmia, DM, chronic sinusitis and did FESS, 2 of these patients showed improvement, while 4 patients didn't show improvement after PRP local nasal injection.
- Fourteen patients had a history of anosmia with DM and allergic rhinitis, 6 of these patients showed improvement while eight patients didn't show improvement after PRP local nasal injection.

So, there is highly statistical significance between the medical histories of the patients and improvement status as P value was < 0.005. The frequency of illness was highest in patients with a history of chronic sinusitis and allergic rhinitis that shows improvement, while in group that shows no improvement, the highest presentations were DM and allergic rhinitis associated with DM that indicate a great effect of DM. **Table 5**

- As regarding relation between duration of anosmia and improvement status of patients, there was no statistical significance (P-value 0.587) between duration of anosmia in the group showing improvement and duration of anosmia in group showing no improvement, which indicate that the improvement status was not affected by the duration of anosmia. **Table 6**

-As regarding the relation between gender of patients and improvement status, there was no statistical significance (P-value 0.432) between gender and improvement status (regarding the number of patients and their gender who accepted to be enrolled in this study) that indicate that the improvement status is not affected by gender. **Table 7**

-UPSIT score: Patients who showed improvement in their olfactory function, their UPSIT score range was 22 to 34.

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Table 1: Demographic data characteristics:

Variable		Number (N=80)	Percentage %
Gender	Male	66	82.6 %
	Female	14	17.4 %
Age (years)	53.32 ± 12.06 (range: 28 years old - 65 years old)		

Data were expressed in the form of mean and SD.

Table 2: Spearman correlation between patients` age and duration of anosmia:

	Age	*P*-value	Total patients (N = 80)
Duration of anosmia (by years)	r value = 0.139	0.392	

P value <0.05 is significant.
Spearman correlation shows a non-significant positive weak correlation between age of the patients and duration of anosmia.

Table 3: Medical data of the 80 patients with anosmia:

Variable		**Number (N=80)**	**Percentage %**
History	Idiopathic	10	12.5 %
	Chronic sinusitis	18	22.5 %
	Atrophic Rhinitis	4	5 %
	Allergic Rhinitis	18	22.5%
	DM	10	12.5 %
	Chronic sinusitis + DM	6	7.5 %
	Allergic Rhinitis + DM	14	17.5 %
Improvement status	Yes	46	57.5 %
	No	34	42.5 %
Duration of anosmia by years (median ± IQ)	5.22 ± 1.97 (range: 2 years – 15 years)		

IQ: Interquartile range.

Table 4: Analysis between the two improvement statuses of the 80 patients enrolled in the study:

Improvement status	**Improvement (N= 46)**	**No improvement (N= 34)**	**P value**
	57.5%	42.5%	**0.343**

P value <0.05 is significant.

Table 5: Effect of medical histories of the patients on improvement status:

History	**Improvement** (N=46)		**No improvement** (N=34)		**Total** (N=80)	***P*-value**
Idiopathic	10	100%	0	0%	10	0.005*
Chronic sinusitis	14	77.78%	4	22.2%	18	
Atrophic Rhinitis	0	0%	4	100%	4	
Allergic Rhinitis	14	77.78%	4	22.2%	18	
DM	0	0%	10	100%	10	
Chronic sinusitis + DM	2	33.3%	4	66.67%	6	
Allergic Rhinitis + DM	6	42.8%	8	57.2%	14	

**P* value <0.05 is significant. *P* value <0.01 is highly significant.

Table 6: Univariate analysis of duration of anosmia associated with improvement status:

	Improvement (N= 46)	**No improvement (N= 34)**	***P*-value**
Duration of anosmia (years)	5.22 (4 -6.44)	5.22 (2.61-7.83)	0.587

Data were expressed in the form of the median (Interquartile range), *P*-value <0.05 is significant.

Table 7: Univariate analysis of gender associated with improvement status:

		Gender			*P*-value
		Male	Female	Total	
Improvement Status	Improvement	40	6	46	0.432
	No improvement	26	8	34	
Total		66	14	80	

P value <0.05 is significant.

Discussion :

The study was conducted to evaluate the efficacy of local PRP injection in olfactory area in the nose in patients complaining of anosmia due to the ability of PRP in tissue and nerve regeneration which has been discussed in different studies.

The use of PRP as a promising product in promoting peripheral nerve regeneration after nerve injury has revealed many beneficial effects on peripheral nerve regeneration by an autologous supply of growth factors.[15]

Another study about the sensory improvement of leprosy peripheral neuropathy in patients treated with perineural injection of platelet-rich plasma has revealed that perineural injection of PRP was significantly effective ($P < 0.05$), which shows that perineural PRP injection could promote the improvement of peripheral neuropathy sensibility in patients with leprosy due to its significant effect on nerve regeneration.[16]

The study population consisted of 80 patients complaining of anosmia due to different causes involving 66 males (82.6%) and 14 females (17.4%). The higher number of males did not seem to us a real more prevalence of the problem among males rather than hesitation of some patients to share in the study probably because of cultural issues.

This is in line with a recent study for the prevalence of anosmia and associated factors among U.S adults; results showed that the highest prevalence was found in black men (58.3%) and the lowest in white women years (2.4%). [17]

In another study on prevalence of anosmia and the effects of olfactory training in specific anosmia in more than 1600 participants, the results were that women showed a slightly reduced rate of anosmia compared to men (women 4.6% vs. men 6.5%; p¼ .017, Chi-Square¼5.8; phi¼ .041). [18]

Results of our study regarding number and gender of patients who had accepted to be enrolled in our study show that there is no statistical significance (p value 0.432) between gender and improvement status that indicate that the improvement status is not affected by gender of patients with anosmia.

Also, regression analysis for the relation between improvement status and history of patients at admission and their personal data showed that history of atrophic rhinitis and history of diabetes mellitus and male gender are high-risk factors for anosmia.

This is in line with a study of prevalence and risk factors of loss of smell, a population-based survey revealed that there was a significant age-related smell detection decline; however, smell recognition and identification increased up to the fourth decade and declined after the sixth decade of life, also showed that risk factors for anosmia were: male gender and older age. [19]

The age of our patients was at the range of 28 to 65 years old with mean

age 53.32. There were older age patients with anosmia but refused to share in this study.

A study by **Jing Dong** showed that prevalence of anosmia is higher with increasing age and highest at the age of 85 years old. [17]

In our study, patients complaining of anosmia gave positive history to variable causes like allergic rhinitis (22.5%), atrophic rhinitis (5%), diabetes mellitus (12.5%) and patients who had endoscopic sinus surgery (22.5%) while in the other patients anosmia was idiopathic (12.5%).

This is in line with a study of Robert C about the relation between chronic sinusitis and anosmia, which revealed that 7 patients of a total of 16 patients complaining of chronic sinusitis had abnormal UPSIT score (43.7%). [20]

Another study about the prevalence of olfactory dysfunction in chronic rhinosinusitis showed that a significant percentage of patients complaining of chronic rhinosinusitis experience olfactory dysfunction, and mean olfactory scores are within the dysosmic range. [21]

Also, in line with a study conducted in University of Pennsylvania in USA about the relation between patients complaining of allergic rhinitis and its effect on their olfactory function revealed that patients with allergic rhinitis have a decreased sense of smell relative to normal people that is independent of mucosal hypertrophy. [22]

Also, in line with this study which is about causes of olfactory dysfunction, which has revealed that the most commonly diagnosed etiologies of olfactory loss were head injury (18%), upper respiratory infection (18%), and nasal or sinus disease (14%). [23]

Also in line with this study that has discussed the rate of olfactory dysfunction in patients with type 2 diabetes mellitus in which results revealed that type 2 DM is associated with olfactory dysfunction with decreased odor threshold, odor discrimination, odor identification, and threshold discrimination identification (TDI) scores in patients with type 2 DM versus controls. [24]

Our study showed high statistical significance between the medical histories of the patients and improvement status as p-value was < 0.005. The frequency of illness was highest in patients with a history of FESS and allergic rhinitis that showed improvement, while in the group that showed no improvement, the highest presentations were DM and allergic rhinitis associated with DM that indicate a great effect of DM.

This study has discussed the effect of platelet-rich plasma on patients complaining of anosmia as a new line for management of persistent anosmia not responding to any local or systemic medication; the PRP is injected three times locally in the olfactory area in the nose with four weeks interval with follow up of the patient for one month after PRP injection.

The results in this study revealed that 46 (57.5%) patients of 80 patients were improved after one month of the last PRP injection, while 34 (42.5%) patients were not improved.

Another study by **Panayiota et al.** [25] had used PRP injection for management of anosmia, which was conducted on five patients complaining of anosmia with male to female ratio was two males to 3 females with a mean age of 49 years old, anosmia was secondary to viral rhinitis (80%) and secondary to nose and forehead trauma (20%).

Also, data gained by follow-up of patients based on subjective symptoms as there is no possibility for objective methods like measuring the odor-induced EEG changes or evoked potentials. The results of this study

showed that 80% (4 of 5) of patients regained their olfactory function while 20% (1 of 5) of patients showed mild improvement. [25]

Conclusion:

Anosmia is a very unpleasant sensation and life-threatening problem which had a negative impact on the patient life.

In our study, we used PRP for regaining olfactory function in patients with anosmia through submucosal local injection of PRP in the olfactory area after a proper evaluation of patients.

Results of our study revealed that 46 out of 80 patients (57.5%) said that "their smell came back" while 34 out of 80 patients (42.5%) showed no improvement; thus these results show no statistical significance between proportion in the group showing improvement and proportion in the group showing no improvement.

Recommendation:

Few studies are found regarding the role of PRP in patients complaining of anosmia, so we recommend further studies to discuss the impact of using PRP local injection as a new way for the management of anosmia.

Ethical consideration:

Informed consent was obtained from the patients enrolled in the study. The study was approved by the ethical committee in the faculty of medicine at Aswan University. The confidentiality of patient information was maintained during all steps of the study.

Financial support and sponsorship:

No financial support was obtained; PRP was prepared in the clinical pathology department in Aswan university hospital.

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