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Efficacy of Platelet-Rich Plasma as an Adjuvant Therapy to Endoscopic Sinus Surgery in Anosmia Patients with Sinonasal Polyposis: A Randomized Controlled Clinical Trial

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Abstract

Background: Treatment of patients with anosmia is a major therapeutic challenge. The present study evaluated the efficacy of platelet-rich plasma (PRP) in the treatment of anosmia in patients with sinonasal polyposis.

Methods: In the present clinical trial, atotal of 48 patients with sinonasal polyposis with theIran Smell Identification Test (I-SIT) score of <6 who completed the medical treatment and were observed 3 months after the sinus surgery were included and randomly divided in to 2groups. After endoscopic sinus surgery, the intranasal injection of 1 mL PRP and normal saline was performed in the olfactory region in the intervention and control groups, respectively. Odor function was assessed using the I-SIT at the baseline and at the end of the studyby an independent samples ttest.

Results: Based on the findings of the present study, the I-SIT improved in both groups during the follow-up, as it reached from 2.63 ± 2.63 to 5.85 ± 2.46 after oral steroid administration and 18.93 ± 1.14 after surgery in the intervention group and from the baseline of 2.10 ± 2.83 to 5.62 ± 2.99 after receiving standard medical treatment and 18.43 ± 1.36in the control groupafter surgery. Although this improvement was significant in both groups in either time interval (all with p<0.001), there was no significant difference between the 2groups in terms of changes in the I-SIT score (p=0.802).

Conclusion: According to the current study, PRP injection showed no short-term effect on the recovery of olfactory function in patients with sinonasal polyposis.

Keywords: Anosmia, Platelet-Rich Plasma, Olfactory Epithelium, Sinonasal Polyposis

Conflicts of Interest: *None declared*
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Introduction

Olfactory dysfunction (OD) affects 3% to 20% of the population (1). The disorder is becoming more prevalent in elder patients as more than 20% of adults over the age of 60 years are suffering from olfactory dysfunction (2).

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↑What is "already known" in this topic:
Olfactory dysfunction in patients with sinonasal polyposis is a major therapeutic challenge. However, intranasal glucocorticoids are widely accepted for the management of patients with anosmia, antihistamines, systemic glucocorticoids, and antibiotics are indicated in special cases. Besides, surgical intervention is an effective choice in patients in whom conservative treatments have failed.

→What this article adds:
Oral corticosteroids and functional endoscopic sinus surgery provided a significant improvement in the olfactory functions of patients with sinonasal polyposis. However, PRP injection as an adjuvant therapy showed no short-term effect on the recovery of olfactory function.

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Although the inflammatory and obstructive disorders of the sinonasal region (eg, rhinitis, rhino sinusitis, and nasal polyps) accounted for 50% to 70% of cases of OD, Other underlying causes of anosmia include head trauma, neurodegenerative processes, congenital anosmia, endocrine disorders (eg, hypothyroidism, diabetes mellitus, renal and liver dysfunction, and Kallmann syndrome), and any disorder that interferes with the olfactory pathway (3-10).

Treatment of anosmia depends on its etiology. Due to the high prevalence of inflammatory and obstructive disorders, intranasal glucocorticoids are widely accepted for the management of patients with anosmia, with the addition of other pharmacological agents, including antihistamines, systemic glucocorticoids, and antibiotics, if necessary. Surgical intervention can also be effective in patients with chronic sinus disorders and nasal polyps in whom conservative treatments have failed (11).Given the importance of diagnosing the underlying cause of anosmia for its treatment and as the pathophysiological mechanism of anosmia and hypoxemia is not clear, the treatment of patients with anosmia is still challenging and there is still no standard treatment (12-15). Although patients with conductive OD, such as chronic rhinosinusitis, have a more established course of treatment, it is often difficult to distinguish between conductive and nonconductive anosmia in practice as in some cases, such as chronic rhinosinusitis, both are present at the same time. Due to this shortcoming, patients with OD are often neglected by the medical community and have a lower quality of life (2).

Platelet-rich plasma (PRP) contains a high number of platelets, growth factors (GF), and bioactive and neurotropic agents, crucial for wound healing and tissue repair. PRP has been used in various medical realms, such as orthopedic surgery, maxillofacial interventions, wound healing, and post-burn care (16, 17).PRP has been studied in recent years as an alternative treatment for anosmia (12, 18).

According to animal studies, in the presence of neurodegeneration processes, the application of GFs and stem cells can lead to the regeneration of olfactory nerves, and the improvement of anosmia (19, 20). Due to the high concentration of GFs and neurotropic factors in PRP, some authors have evaluated the effect of PRP in the treatment of anosmia through its role in enhancing thehealing process in animal models (12).In this study, we aimed to evaluate the efficacy of PRP in the treatment of anosmia in patients with sinonasal polyposis.

Methods

Study Design and Subjects

This double-blinded randomized controlled trial performed with 60 consecutive patients with olfactory dysfunction who referred to the Otorhinolaryngology Clinic in Taleghani hospital, Tehran, Iran, during2017 and 2018. The study was approved by the ethics committee of the Shahid Beheshti University of Medical Sciences and Health Services (IR.SBMUMSP.REC.1398.011) and was registered in the Iranian registry of clinical trials (IRCT20200211046464N1).The present study was performed according to the Helsinki declaration and informed consent was obtained from all study participants.

Of 60 evaluated patients, 54entered the study, according to inclusion and exclusion criteria. The inclusion criteria were patients aged 15 to 50 years with chronic sinusitis with polyps, an Iran Smell Identification Test (I-SIT) score of <6, and anosmia duration of <2 years. The exclusion criteria were history of head trauma, previous sinonasa lsurgery, smoking, congenital anosmia, and the presence of systemic disorders causing OD (eg, Parkinson and Alzheimer).

Procedure

Enrolled patients were randomly assigned into the intervention(n= 27) or the control groups (n= 27) using randomly generated treatment allocations within sealed envelopes. History and demographic information were taken from all patients before the intervention. All patients underwent paranasal computed tomography scanning and the severity of nasal polyposis was assessed using the Lund-Mackay score (Table 1) (21).

The I-SIT (SIT kit, Saba Tajhiz Sabalan Medical Engineering Company) is the first standard method for assessing olfactory sensation in the Iranian population. It is the Iranian version of the University of Pennsylvania Smell Identification Test (UPSIT), modified based on using odors familiar to the Iranian people. The I-SIT is a kit containing 24 different types of odors in 8categories. The test results are reported as a number ranged from 0 to 24 with a normal range of 19 to 24 in patientsaged 15 to 50 years (22).

Patients initially received daily oral corticosteroids (25 mg prednisolone) for 5 days. After the end of the 5-day oral treatment course, the I-SIT was assessed by a single physician who was unaware of the study. Then, patients in either group underwent functional endoscopic sinus surgery(FESS) by the senior author. In the intervention group, the intranasal injection of 1 mL PRP was performed inside the operating room and during the anesthetic state. PRP was injected with a 1-cc syringe with 30 G needle in the olfactory region within an area of 1 cm^2 under endoscopic visualization and by the same surgeon. In the control group, 1-cc normal saline was injected in the same region.

Patients were unaware of their group allocation and the type of intervention performed. The surgeon was also blinded of the grouping and the injected substance. Fur-

Table 1. Lund-Mackay Scoring System Based on the Paranasal Computed TomographyScan

Sinus	Right Sinus	Left Sinus
Frontal	0-2	0-2
Maxillary	0-2	0-2
Anterior ethmoid	0-2	0-2
Posterior ethmoid	0-2	0-2
Sphenoid	0-2	0-2
Ostiomeatal complex	0 or 2	0 or 2

For the sinuses: 0= clear sinus; 1= partial opacification; 2= complete opacification.
For the ostiomeatal complex: 0= notobstructed; 2= obstructed.
Maximum total score: 24.
(*Reproduced from Okushi et al, AurisNasus Larynx. 2013 Dec 1; 40(6):548-53 (reference 21).

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thermore, the person in charge of data collection was not present during the surgical procedure. The I-SIT was assessed 3 months after the surgery by the same physician responsible for prior assessments.

PRP Preparation

The whole process of PRP preparation was done in the sports medicine department of Taleghani hospital using the PRP standard kit (ArjangianCo). The temperature was set at 21C°to 24 C° during PRP isolation to prevent clotting.

With this in mind, a wide spectrum of techniques mentioned for the production of PRP, our procedure followed these steps, under general anesthesia during functional sinus surgery, 25 cc of the patient's whole blood was collected and added to a PRP bag containing sodium citrate 3%. The blood was then centrifuged(ABALASE), first at 1300 speed /relative centrifugal force (RCF) for 15 minutes to separate the WBC and RBC from the plasma and platelets, then, recentrifuged at 2600 speed / RCF for 5 minutes. After discarding the subsequent platelet-poor plasma, 5 mL PRP remained. The platelet-rich plasma has then rested for about 30 minutes, during which time the platelet granules was released. At the time of injection, the PRP solution was combined with calcium carbonate, and thus was activated.

Statistical Analysis

Data analysis was performed using SPSS V22(SPSS Inc). The Kolmogorov-Smirnov test results showed a normal distribution of the data. Data were demonstrated using descriptive statistical measures (ie, frequency, percentage, mean, standard deviation). Independent samples ttest and chi-square tests were used to compare parametric and nonparametric data at baseline between groups. Mixed analysis of variance and post hoc tests were used to investigate the interaction effects of time and group. The significant threshold was considered to be less than 0.05.The person responsible for data analysis was blinded to the group allocation.

Results

The study was performedby 2 groups of 27 patients. During the course of the study, 6 patients dropped out of the control group, 5 were lost during the follow-up, and 1 was diagnosed with inverted papilloma. Finally, 27 patients in the intervention and 21 in the control group were analyzed (Fig. 1).

The baseline demographic and characteristics of all participants are presented in Table 2.

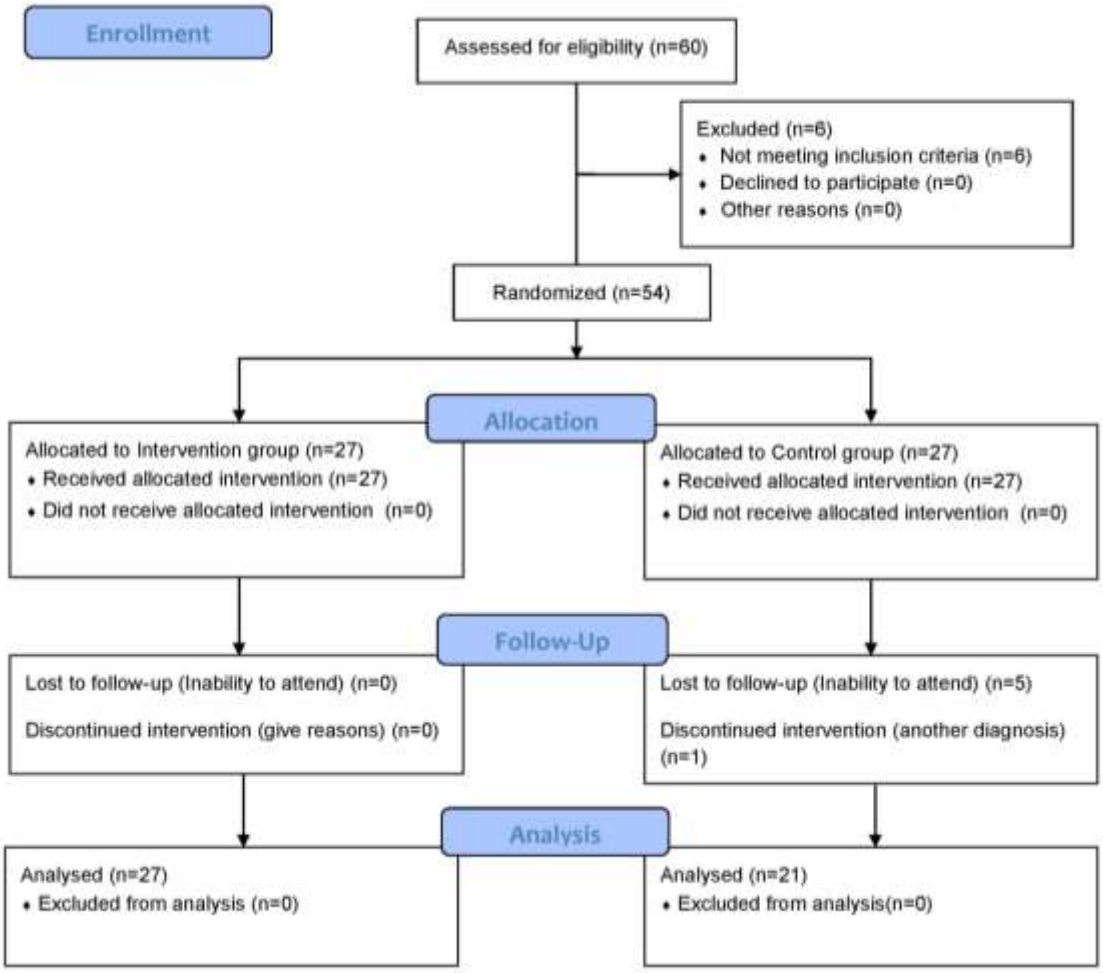

*Fig. 1.*Consort follow diagram showed the participants' allocation, follow-up, and analysis

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*Table 2.*Participants'Demographics and Baseline Evaluations

	All Participants	Intervention	Control	P-Value
CharacteristicNumber	48	27	21	
Sex, n(%)				
Male	34 (70.8)	19 (70.4)	15 (71.4)	0.936£
Female	14 (29.2)	8 (29.6)	6 (28.6)	
Age, mean(SD)	35.96 (7.39)	37.15 (7.63)	34.43 (6.95)	0.209*
Anosmia duration, mo mean (SD)	6.58 (3.74)	6.93 (3.66)	6.14 (3.89)	0.478*
Lund–Mackay score, mean (Std. deviation)	20.04 (3.05)	19.33 (3.22)	20.95 (2.60)	0.085*
I-SIT, mean (SD)	2.40 (2.60)	2.63 (2.44)	2.10 (2.83)	0.289*

I-SIT,Iran Smell Identification Test
£ Pearson chi-square
* Independent samples t test.

*Table 3.*The between-group Analysis of I-SIT by Treatment Group

Group	Before Treatment	Before Surgery	3 Months After Surgery	Group and Time Interaction*
I-SIT, mean (SD)				
Intervention	2.63 (2.44)	5.85 (2.46)[A]	18.93 (1.14)[A]	0.802
Control	2.10 (2.83)	5.62 (2.83)[A]	18.43 (1.36)[A]	
All participants	2.40 (2.60)	5.75 (2.68)	18.71 (1.25)	<0.001

A: No statistical significance between intervention and control groups based on the independent samples t-test (P>0.05).
B: Statistical significance between the intervention and control groups based on the independent samples t-test (P≤0.05).
I-SIT: Iran Smell Identification Test.
*Mixed ANOVA

Of 48 patients, 34 were menand 14were women, aged 20 to 50 years, with a mean of 35.96 ± 7.39 years, anosmia duration of 6.58 ± 3.74 months, Lund–Mackay score of 20.04 ± 3.05, and baseline I-SIT of 2.40 ± 2.63. Patients in the intervention group were 19 men and 8 women, with a mean of 37.15 ± 7.63 years, anosmia duration of 6.93 ± 3.66 months, Lund–Mackay score of 19.33 ± 3.22, and baseline I-SIT of 2.63 ± 2.44.Patients in the control group, were 15 men and 6 women, with a mean of 34.43 ±6.95 years, anosmia duration of 6.14± 3.89 months, Lund–Mackay score of 20.95±2.60, and baseline I-SIT of 2.10± 2.83. No significant differencewas observed between the 2 treatment groups regarding the demographic and patients' baseline characteristics all with p>0.05.The course of outcome measures during study follow-up is demonstrated in Table 3.

The I-SIT score improved toward the end of the study in all participants, reaching to 5.75 ±2.68 after oral therapy, and 18.71 ± 1.25 three months after surgery (Fig. 2).

There was a significant time interaction in the assessment of I-SIT (F (1.36) =1392.8, p<0.001). This implies that the ascending trend of I-SIT in the course of the trial was significant. In either treatment group, a similar improvement was observed. The I-SIT was 5.85±2.46 and 5.62 ± 2.83 after oral steroid therapy and 18.93 ±1.14 and 18.43 ± 1.36 three months after surgery in the intervention and control groups, respectively (Fig. 3).

No significant differencewas observed between the 2treatment groups regarding the I-SIT in both times, both with p>0.05. The interaction effect of time and group was not significantly different when evaluating the I-SIT (p=0.802) implying that the behavior of our 2treatment groups did not differ regarding the changes of I-SIT.

The changes in I-SIT in the study period are demonstrated in Table 4. Post hoc comparisons showed a significant improvement in I-SIT in both groups and in all participants, regardless of grouping in all evaluated timespans (ie, baseline to after oral therapy, baseline to 3 months

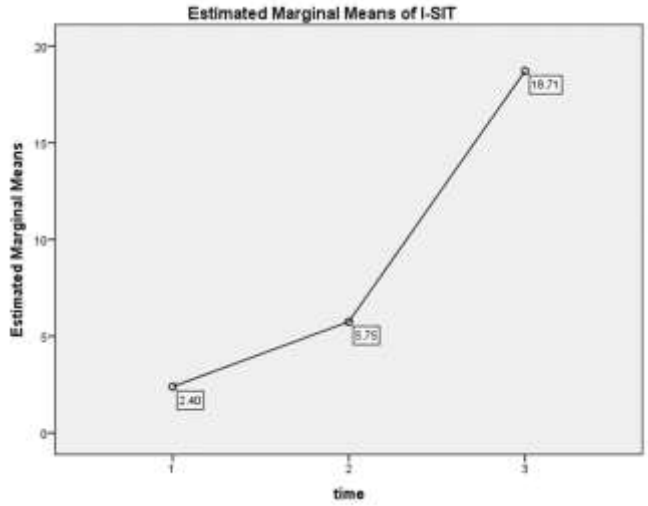

*Fig. 2.*I-SIT Score Course in All Participants

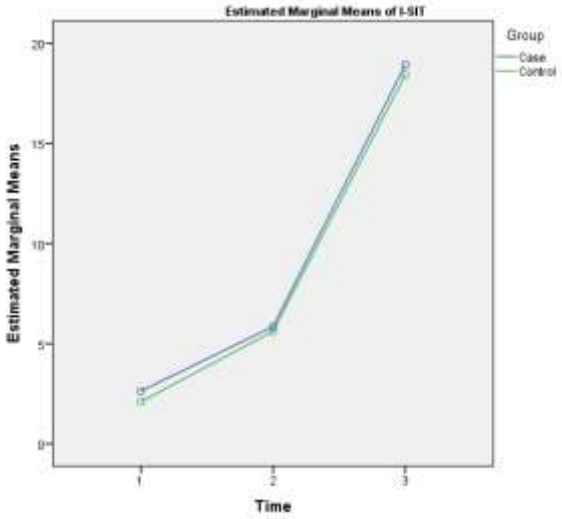

*Fig. 3.*I-SIT Score Course in Either Group

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*Table 4.*The Post Hoc Analysis of the I-SIT in theTreatment Group

Outcome	Baseline Compared with Before Surgery	Baseline Compared with3 Months after Surgery	Before SurgeryCompared with3 Months after Surgery
I-SIT, mean difference (P-value*)			
TENS	-3.22 (0.24)[B]	-16.30 (0.52)[B]	-13.07 (0.50)[B]
tDCS	-3.52 (0.28)[B]	-16.33 (0.59)[B]	-12.81 (0.57)[B]
All participants	-3.35 (0.18)[B]	-16.31 (0.39)[B]	-12.96 (0.37)[B]

A: No statistical significance (P>0.05)
B: Statistical significance. (P≤0.05)
I-SIT: Iran Smell Identification Test
*All Pvalues were <0.001 based on the paired sample ttest.

after surgery, and after oral therapy to 3 months after surgery).

Discussion

Despite the various use of PRP in the otorhinolaryngology field, especially during maxillofacial interventions, few studies evaluated its effects as an alternative treatment method in the management of anosmia. In this randomized controlled trial study, we evaluated the efficacy of intranasal PRP injection in the management of anosmia in patients with sinonasal polyposis. According to the findings of the present study, the I-SIT score improved in either the intervention or the control group toward 3 months after the FESS. Although this improvement was significant in both groups, there was no significant difference between the patients receiving PRP with the control group. This implies that PRP injections did not affect the recovery of OD in patients with sinonasal polyposis.

The first study on this subjectwas conducted in 2016, (18) including4 intranasal injections of PRP in the olfactory area (3 injections 4 weeks apart, and the 4th, 3 months after the previous injection) in 5patients with severe anosmia. Of these 5 patients, 4 had a history of viral rhinitis and 1 had a history of trauma to the nose and the forehead. All patients reported an improvement in olfactory function after PRP injections. After the final injection, 4 of them reported complete smelling recovery, while the last patient mentioned that their olfactory function almost returned and not completely. Based on the results of this study, the administration of PRP in the olfactory region can be a promising treatment as a last resort for stimulating the olfactory system in patients with complete anosmia. It should be noted that the mentioned study evaluated the olfactory function using subjective measures and not objective methods. Moreover, the effect of PRP in the treatment of chemically induced anosmia was evaluated in an animal model (12). The PRP injection was associated with better improvement in olfactory function (evaluated via food-finding test), lower epithelial damage, and greater epithelial thickness. It was concluded that the PRP has curative effects on olfactory functions, but further human studies are required before considering PRP as a treatment in patients with anosmia.Furthermore, the effects of single PRP injection in patients with OD longer than 6 months were assessed (23). They included 7 patients with nonsinonasal OD who were nonresponsive to standard cares (ie,budesonide nasal irrigationsand olfactory training). All patients reported subjective improvement in their smell immediately after PRP injections. Three-month improvement was observed only in patients with moderate OD (Sniffin' Sticks olfactory test (TDI) of >16 and <30) and PRP was not effective in patients with anosmia (TDI<16).

With this in mind, our work emphasis on sinonasal polyposis, the findings of the present study differed from the above-mentioned studies, and it implies that conservative treatments and FESS are still the best options in the treatment of anosmia in patients with sinonasal polyposis, and PRP injection showed no effect on the course of anosmia recovery in these patients.

Overall, the most frequent causes of anosmia are sinonasal pathologies, such as patients in present study. Inthispopulation, use of surgical and nonsurgical therapies related to the underlying factor, lead to the improvement of their olfactory function. The challenge of treating anosmia is greater in cases where the anosmia is caused by non sinonasal pathologies, in which the anosmia is associated with olfactory epithelial degeneration (24, 25). The lower layer of olfactory epithelium consists of basal cells capable of regeneration (26). These cells include 2 types of precursor cells: horizontal basal cells (HBC) and globose basal cells (GBC). While GBCs are always active and support the replacement of olfactory epithelial cells, HBCs are usually in a quiescent state and proliferate afterinjuries. Therefore, the activation of HBCscould be useful to improve the function of the olfactory system (27-31).

In recent years, various studies have been conducted to assess the use of growth factors for the activation of HBCs of the olfactory epithelium. Among them, statins induced olfactory neuronal regeneration and, therefore, improved degenerative anosmia. This improvement was the result of 2 mechanisms: (1) inflammation reduction; (2) activation of genes associated with cell growth and neurogenesis, leading to cell proliferation and neuro regeneration in the olfactory epithelium. Besides, intranasal application of the basic fibroblast growth factor (bFGF) reported to be effective. The BFGFis recognized as a multifunctional growth factor and prevents nerve cell apoptosis and causes neuronal sprouting, which can lead to olfactory epithelial regeneration(20). Ginkgo biloba was also associated with good anosmia recovery when combined with dexamethasone because of its antioxidant properties (32).

PRP has a high concentration of GFs and neurotropic factors, such as platelet-derived growth factor, insulin-like growth factor, neurotrophin-3, angiopoietin-1, and others. Thus, the a neuro regenerative and therapeutic effect is expected with its administration and could be used as an activator of basal cell regeneration in the treatment of an-

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osmia (33-37). According to previous studies, PRP not only could activate the olfactory system but also could create new receptors (12). Although PRP was associated with good results in non sinonasal anosmia, it was not effective in anosmia associated with sinonasal polyposis according to the findings of the present study.

In summary, based on the findings of the present study and comparing its results with prior researches, it could be concluded that PRP injection should be considered in cases where anosmia is caused by non sinonasal pathologies and olfactory epithelial degeneration is presented. The steroid application and surgical interventions are the best choices of treatment in patients with OD related to sinonasal polyposis.

Despite the strength of this study, which was the first randomized controlled trial to evaluate PRP in the treatment of anosmia, it has some limitations that should be addressed in further studies. This was a single-center study. We only used a semi-objective measure to assess anosmia. Given the proposed effect of PRP on olfactory epithelial regeneration, using methods of evaluating olfactory systems, including electro-olfactogram, odor-induced EEG changes, and evoked potentials, could be better measures of the PRP effectiveness (12, 18).

Conclusion

The standardized medical and surgical treatment of sinonasal polyposis provided a significant improvement in the olfactory functions. However, PRP injection as an adjuvant therapy showed no short-term effect on the recovery of olfactory function.

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Conflict of Interests

The authors declare that they have no competing interests.

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