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Nasal septal deviation and olfactory dysfunction: septoplasty and autoplalelet mesoconcentrate

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Background: Nasal septal deviation (NSD) prevalence rates in the general population range between 75% and 89.2%. The disease results in disorders of the ear, throat and nose, olfactory dysfunction (OD) in the form of hyposmia or anosmia, nasolacrimal duct obstruction, and, consequently, chronic dacryocystitis and low quality of life. Surgery for NSD (septoplasty) can be followed by postoperative anosmia. The three-year COVID-19 pandemic worsened the histories of candidates for septoplasty and the prognosis for surgical outcome in terms of restoration of smell. The methods available for the treatment of OD require close cooperation of specialties like ophthalmology, otorhinolaryngology and neuropathology. Cell-therapy technologies and application of platelet-rich plasma (PRP) seem to be promising in the treatment of NSD and OD.

Purpose: To improve the efficacy of septoplasty for patients with NSD-associated OD through the use of autoplalelet mesoconcentrate (APMC).

Material and Methods: One hundred and fifty-five individuals underwent examination and treatment. These included 22 apparently healthy volunteers aged 25 to 34 years (group 1 or control group), 47 patients with NSD-associated OD only aged 24 to 33 years (group 2 or archival group), 44 patients with NSD-associated OD only aged 23 to 35 years (group 3), and 42 patients with NSD-associated OD and a history of COVID-19 aged 23 to 36 years (group 4). Ten of the patients of group 4 had nasolacrimal duct obstruction.

Results: Our magnetic resonance imaging (MRI) studies found that olfactory bulb volume was 27.2% and 54.5% decreased in groups 3 and 4, respectively, compared to healthy volunteers. A procedure for obtaining at least 24 ml of APMC was described. A 4-mm diameter endoscope (Karl Storz, Germany) was used to perform septoplasty under general endotracheal anesthesia in groups 2, 3 and 4. Application of APMC after endoscopic septoplasty in patients presenting with NSD-associated OD, a history of COVID-19 contributed to the normalization of olfactory bulb volume, reduction in postoperative complication rate, and restoration of the sense of smell and quality of life. Application of APMC after endoscopic septoplasty in patients presenting with NSD-associated OD, a history of COVID-19 and nasolacrimal duct obstruction, contributed to restoration of nasolacrimal duct patency, thus preventing chronic dacryocystitis.

Keywords:

nasal septal deviation, septoplasty, COVID-19, olfactory dysfunction, nasolacrimal duct obstruction, autoplalelet mesoconcentrate

Introduction

Nasal septal deviation (NSD) is a common condition, with prevalence rates in the general population ranging between 75% and 89.2% [1, 2]. The disease results in difficulties with nasal respiration and the development of chronic rhinitis; disorders of the paranasal sinuses (PNS), Eustachian tube and middle ear; inflammation of the pharynx, larynx, and lower respiratory tract; olfactory dysfunction (OD) in the form of hyposmia or anosmia; nasolacrimal duct obstruction; and stress, depression and low quality of life. The nasal cavity mucosa is a reflexogenic zone from which the effects on the bronchopulmonary system, cardiovascular system and central nervous system (CNS) are produced [3].

Surgery for NSD (septoplasty) is one of the most commonly performed procedures within otorhinolaryngology and can be followed by postoperative anosmia of 6 to 12 month duration [1, 3].

The three-year COVID-19 pandemic worsened the histories of candidates for septoplasty and the prognosis for surgical outcome in terms of restoration of smell. Lechien and colleagues [4] demonstrated that, in the first 2 months, 79.5% of COVID-19 patients may expect to have complete recovery of their olfactory function. In addition, two years post-COVID-19, 29.8% of COVID-19 patients reported persistent OD [5].

To date, no specific method of treatment for OD is available. Cell-therapy technologies seem to be promising in the treatment of NSD and OD. This is particularly related to applications of platelet-rich plasma (PRP), with platelet counts several times higher than normal. PRP is applied for improved tissue regeneration and angiogenesis, and reduced scarring, and as a topical antiseptic [6].

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Material and Methods

One hundred and fifty-five individuals underwent examination and treatment. These included 22 apparently healthy volunteers aged 25 to 34 years (group 1 or control group), 47 patients with NSD-associated OD only aged 24 to 33 years (group 2 or archival group), 44 patients with NSD-associated OD only aged 23 to 35 years (group 3), and 42 patients with NSD-associated OD and a history of COVID-19 aged 23 to 36 years (group 4). Ten of the patients of group 4 had nasolacrimal duct obstruction. There were no significant differences in age, gender, nasal cavity disorder or PNS disorder among the groups.

In patients of group 4, COVID-19 infection was verified by a positive SARS-CoV-2 ribonucleic acid (RNA) polymerase chain reaction (PCR) test via a nasal swab. The time between OD onset and a routine pre-septoplasty examination ranged from 3 to 6 months.

Informed consent for clinical, imaging, laboratory and therapeutic measures was obtained from all patients.

The study followed the ethical standards stated in the Declaration of Helsinki and the United Nations Educational, Scientific and Cultural Organization (UNESCO) Universal Declaration on Bioethics and Human Rights.

Inclusion criteria for healthy volunteers were informed consent; no history of nasal or PNS disease or trauma; and no clinical signs of damage to or inflammation in the nasal mucosa or PNS at the time of examination.

Inclusion criteria for patients were informed consent; NSD; OD (anosmia); difficulties with nasal respiration, possibly as severe as no nasal respiration; nasal obstruction; poor quality of sleep; inadequate respiration during physical activity; nasal dryness; and snoring.

Exclusion criteria for patients were acute or exacerbation of chronic inflammation in the nasal mucosa or PNS; history of cranial trauma or surgery of the nasal cavity or PNS; severe decompensated comorbidity; taking neuroleptics; history of nasal mucosa toxicity or body toxicity; smoking; alcohol or drug addiction; or no informed consent.

Olfactory function (OF) was objectified with the Sniffin Sticks test (SST; Burghardt®, Wedel, Germany), including threshold (T), discrimination (D) and identification (I) subtests [7]. The composite score of olfactory threshold, odor discrimination, and odor identification was calculated as the total threshold-discrimination-identification (TDI) score, which was ≤ 15 for functional anosmia, ≥ 30 for normosmia, and in between for hyposmia.

All imaging was performed using a 1.5-T magnetic resonance imaging (MRI) scanner with a 12-channel head coil as described previously [8]. Syngo MMWP software (Siemens Medical Solutions, Forchheim, Germany) was used to determine the volume of the right and left olfactory bulbs (OBs).

The Nasal Obstruction Symptom Evaluation (NOSE) scale [9] consists of 4 items: nasal congestion (nasal blockage), trouble breathing, trouble sleeping, and being unable to get enough air during exercise, each scored using a 5-point (0-4) Likert scale (not a problem; very mild problem; moderate problem; and severe problem). A result was considered positive if the total score did not exceed 4.

In group 1, MRI of the facial skeleton and the SST were performed only once. Patients in groups 3 and 4 underwent an MRI before septoplasty and at 6-7 months after septoplasty. In addition, they had assessment with the NOSE scale and SST and endoscopy of the nasal cavity before septoplasty and at day 10-14 and months 1, 3, 6-7, and 12 after septoplasty.

A 0-degree 4-mm diameter endoscope (Karl Storz, Germany) was used to perform endoscopic nasal cavity examination and septoplasty under general endotracheal anesthesia in groups 2, 3 and 4.

Operative technique

The operative field was prepared, and the nasal septal mucosa was locally anesthetized with 1% lidocaine with epinephrine (1:200,000) to facilitate dissection of the mucoperichondrium.

A semipenetrating incision facilitates surgical manipulations at the nasal floor and medial crura of the alar cartilage and was used as a major approach. The nasal mucosal lining was carefully lifted away from the septum simultaneously with developing the mucoperichondrial and mucoperiosteal tunnels. After an incision was made and dissection of the mucoperichondrium and mucoperiosteum was performed on the side of deviation, the type of septoplasty performed depended on the type of nasal septal deformity.

Deformed bone and cartilage fragments were resected and removed, leaving a caudal and dorsal strut for support. Endoscopic guidance was used.

Bone and cartilage fragments were crushed into submicron (0.1-1.0- μm) fragments with a tissue crusher.

The cartilage graft was placed between the leaves of the mucosa membrane and secured with transfixion (4-0 Vicryl Rapide) sutures.

Interrupted stitches were used to close the incision, and transfixion sutures were placed on the nasal septum at the nasal valve.

Conchoplasty was additionally performed if indicated. The inferior nasal concha mucosa was infiltrated with 1% lidocaine with epinephrine (1:200,000). The nasal concha mucosa was dissected medially from the bony septum. Submucosal coblation of the cavernous plexus was performed. Nasal scissors were used to remove excessive nasal mucosa from the bone base of the posterior aspect of the inferior turbinate. Homeostasis was achieved with cold plasma coblation.

As a final step, septal silicone splints were placed in the nasal cavity and fixed with Surgipro 3-0 sutures, with an Epistaxis Nasal Dressing placed in the inferior nasal

meatus to the tight/left of the splints, and a U-shaped transseptal suture was applied.

On day 10-14 after surgery, the splints were removed, and a 400-ml sample of venous blood was obtained by venipuncture from each patient using a peripheral venous catheter (Vasofix®, B.Braun, Melsungen, Germany). Catheter size ranged from 22G (0.9 mm) to 18 G (1.3 mm) and depended on the pattern of the patient's peripheral venous network. Blood was collected into vacuum blood collection tubes using a Sarstedt multi-adapter system (Sarstedt, Nümbrecht, Germany). Blood to anticoagulant ratio was 9:1. Given a short preservation period for APMC, 3.8% acid-citrate-dextrose (ACD) was used as an anticoagulant.

Two-stage centrifugation was used to yield APMC. After the first-stage centrifugation at 2000 g for 13 min using a Universal 320R Centrifuge (Hettich, Tuttlingen, Germany), plasma was separated from erythrocytes and leucocytes to prevent a cytotoxic effect of the products formed as a result of breakdown of these cells. After the second-stage centrifugation using an RS-6MTS centrifuge, the platelet sediment was separated from platelet-poor plasma (PPP).

A 120-mm needle (Sterican, B. Braun, Melsungen, Germany) was used for separating fractions after centrifuging. Plasma from collection tubes was transferred to a syringe (at average, 16-22 ml of plasma was transferred from eight tubes to a syringe).

Thereafter, the precipitate was filtrated and, with a platelet level achieving 1×10^9 platelet/ml, the platelets were collected into cryotubes and frozen in liquid nitrogen for obtaining growth-factor containing lysate.

A day thereafter, the lysate was thawed at $+37^\circ\text{C}$ and initially centrifuged at 2,500 rpm for 10 min, and precipitated fibrin was removed. A second centrifugation was performed at 3,200 rpm for 3 min. The growth factor rich substance was resuspended in the buffer solution to obtain at least 24 ml of APMC.

A 10% solution of calcium chloride injection at an amount of 0.2 ml per 1 ml of APMC was applied to activate platelet degranulation. APMC was dehydrated in standard sterile Petri dishes by squeezing a sterile gauze sponge to obtain a transparent elastic homogeneous structure several times greater than initial cartilage fragments.

Cartilage microfragments were reliably fused with each other by fibrin polymer threads to allow for sufficient transparency and elasticity: an implant could withstand a load of 50-70g without changes in structural integrity and shape.

APMC was used postoperatively, after removal of splints. Each nostril was to be sprayed with APMC two times, thrice a day, for 10 days, and then two times, twice a day, for 10 days. In 6 months, if required, each nostril was to be sprayed with APMC two times, thrice a day, for four days, and then two times, twice a day, for 14 days.

Microsoft Excel 2010 (license number 02260-018-0000106-48794) i Statistica 6.1 (serial number

AGAR909E415822FA) were used for statistical analysis of quantitative data, and mean and standard deviation values were calculated.

Results

MRI of the facial skeleton with measurements of the volume of the right and left olfactory bulbs were performed patients of groups 3 and 4 and volunteers of group 1 (Table 1). Olfactory bulb volume was 27.2% and 54.5% decreased in patients in groups 3 and 4, respectively, compared to healthy controls, and this difference was significant ($P < 0.05$). Six to seven months after septoplasty, in patients in groups 3 and 4 olfactory bulb volume increased by 14.5% and 38.4%, respectively.

In a systematic review and meta-analysis [11], descriptive analysis found that 55.6% and 43.5% of patients with COVID-19 infection and OD had morphological abnormalities of the olfactory bulb and olfactory nerve, respectively, while 60.0% had abnormal olfactory bulb volumes. In addition, olfactory bulb MRI findings in COVID-19 patients on days 7-40 after the diagnosis of COVID-19 included edema, small volume and abnormal morphology and atrophy of olfactory bulbs [11]. In the above studies, patients with NSD were not separated in a special group. The investigations in the current study were conducted at 3 months after a negative test for COVID-19 and later. They confirmed a reduced olfactory bulb volume in patients with NSD plus OD with or without a history of COVID-19, and demonstrated the reversibility of this phenomenon after application of APMC. Ku and colleagues [12] noted a phenomenon of a reduction in olfactory bulb volume in OD with subsequent restoration of olfactory bulb volume due to therapeutic olfactory training.

In the current study, the NOSE scale was used to assess preoperative and postoperative degrees of nasal obstruction and evaluate disease-specific quality of life before and after treatment (Table 2).

There was no significant difference in NOSE scale score between the groups, with the mean scores for each item being higher than 3, before septoplasty. At day 7 after septoplasty, patients reported increased scores for nasal congestion, trouble breathing, trouble sleeping, and being unable to get enough air during exercise, compared

Table 1. Volume of olfactory bulbs (mm^3)

Group	Measurement time point	Volume of olfactory bulbs	
		Left	Right
1	-	70.3±2.1	68.9±2.2
3	Before septoplasty	51.2±2.4	49.8±2.3
	6-7 months after septoplasty	58.6±2.2	56.3±2.1
4	Before septoplasty	30.7±2.6	27.1±2.5
	6-7 months after septoplasty	42.5±2.4	38.4±2.3

to pre-surgery (baseline) scores. No significant difference between patient groups was observed at this time point. The obtained results depended on the postoperative course. Symptom severity is associated with the reactive and repair processes in the nasal cavity mucosa. At one month after septoplasty, NOSE scale scores decreased compared to day 7 in all groups, and there was a significant difference between groups 2 and 3, and between groups 3 and 4, in the NOSE scale score. In addition, at 3 months and 6 months after septoplasty, NOSE scale scores decreased in all groups, and there was a significant difference between groups 2 and 3, and between groups 2 and 4, in the NOSE scale score. At 12 months after septoplasty, no complaints regarding nasal respiration was reported by patients in any group, and mean NOSE scale scores in patients of groups 2, 3 and 4 indicated no nasal obstruction, with no significant difference among these groups.

The TDI scores were calculated for all groups. The mean TDI score in practically healthy subjects was seen at 35.9 ± 1.4 , indicating normosmia, whereas the mean TDI scores in patients of groups 2, 3 and 4 indicated anosmia (Table 3). There was no significant difference in the TDI score between the groups before septoplasty. At days 10-14 after septoplasty, TDI scores in patients of groups 3 and 4 increased by 41.0% and 128.0%, respectively, compared to baseline values, with these differences being significant ($P < 0.01$). An increase in the TDI score in patients of group 2 at days 10-14 compared to baseline was, however, not significant ($P > 0.01$). At 1, 3 and 6 months, TDI scores in patients of groups 3 and 4 increased by 53.8% and 74.3%; 21.0% and 48.6%, and 12.6% and 21.0%, respectively, compared to previous time point values ($P < 0.01$). Patients in group 2 exhibited a persistent delayed recovery of sense of smell at 3 and 6 months and an increase in the TDI score ($P < 0.01$). At 12 months, there was no significant difference in the TDI score between the groups.

Table 4 compares groups of patients in numbers and rates of postoperative complications. Rates of complications after endoscopic septoplasty for group 2 (the

Table 2. NOSE scale scores before and after seproplasty

Measurement time point	Групи		
	2	3	4
Before septoplasty	13.96±2.05	15.39±1.65	15.76±1.53
	$P_{2-3} > 0.05$	$P_{3-4} > 0.05$	$P_{2-4} > 0.05$
7 days after septoplasty	15.72±0.92	14.83±0.84	15.54±0.85
	$P_{2-3} > 0.05$	$P_{3-4} > 0.05$	$P_{2-4} > 0.05$
1 month after septoplasty	10.24±0.63	6.21±0.52	11.03±0.61
	$P_{2-3} < 0.05$	$P_{3-4} < 0.05$	$P_{2-4} > 0.05$
3 months after septoplasty	5.11±0.41	2.45±0.31	2.79±0.34
	$P_{2-3} < 0.05$	$P_{3-4} > 0.05$	$P_{2-4} < 0.05$
6 months after septoplasty	3.35±0.46	1.64±0.32	1.45±0.32
	$P_{2-3} < 0.05$	$P_{3-4} > 0.05$	$P_{2-4} < 0.05$
12 months after septoplasty	1.07±0.17	0.48±0.06	0.42±0.08
	$P_{2-3} > 0.05$	$P_{3-4} > 0.05$	$P_{2-4} > 0.05$

Note: P, significance of difference

archival group), group 3 (patients with NSD-associated OD only treated with APMC) and group 4 (patients with NSD-associated OD and a history of COVID-19 treated with APMC) were 100%, 100% and 100%, respectively, at days 10-14; 55.3%, 15.9% and 42.9%, respectively, at month 1; and 25.5%, 4.5% and 11.9 %, respectively, at month 3.

Of note, since APMC is prepared in autologous blood, APMC treatment exhibited no undesirable side effects (like allergic reactions or foreign body response) on our patients, which is in agreement with findings of others [13]. It is also noteworthy that application of APMC after endoscopic septoplasty in patients presenting with NSD-

Table 3. Sniffin Sticks test (SST) threshold, discrimination and identification (TDI) scores before and after septoplasty

Parameter	Groups			P_{2-3}	P_{3-4}	P_{2-4}
	2	3	4			
Before septoplasty	11.6±1.9	11.2±1.5	4.6±1.5	>0.05	>0.05	>0.05
10-14 days after septoplasty	12.9±1.9	15.8±1.5	10.5±1.6	>0.05	<0.05	>0.05
1 month after septoplasty	19.2±1.4	24.3±1.7	18.3±1.5	>0.05	>0.05	>0.05
3 months after septoplasty	22.7±1.3	29.4±1.5	27.2±1.7	<0.05	>0.05	<0.05
6 months after septoplasty	26.5±1.5	33.1±1.4	32.9±1.7	<0.05	>0.05	<0.05
12 months after septoplasty	33.4±1.8	34.1±1.4	34.5±1.8	>0.05	>0.05	>0.05

Note: P, significance of difference

Table 4. Numbers and rates of post-septoplasty complications

Complication	Group					
	2		3		4	
	number	rate	number	rate	number	rate
7 days						
<i>Anticipated feelings and symptoms</i>						
Headache	21	44.7	17	38.6	15	35.7
Painful breathing	19	40.4	16	36.4	13	31.0
Serosanguinous fluid	47	100.0	44	100.0	42	100.0
Crusting	47	100.0	44	100.0	42	100.0
Total	47	100.0	44	100.0	42	100.0
<i>Complications</i>						
Residual NSD	3	6.4	1	2.3	1	2.4
Parforated septum	4	8.5	1	2.3	1	2.4
Bleeding	3	6.4	1	2.3	1	2.4
Hematoma	4	8.5	3	6.8	1	2.4
Infection	3	6.4	1	2.3	1	2.4
Synechia	-	-	-	-	-	-
Total	17	36.2	7	15.9	5	11.9
1 month						
<i>Anticipated feelings and symptoms</i>						
Headache	1	2.1	-	-	-	-
Painful breathing	-	-	-	-	-	-
Serosanguinous fluid	1	2.1	-	-	-	-
Crusting	-	-	-	-	-	-
Total	2	4.3	-	-	-	-
<i>Complications</i>						
Residual NSD	3	6.4	1	2.3	1	2.4
Parforated septum	4	8.5	1	2.3	1	2.4
Bleeding	-	-	-	-	-	-
Hematoma	-	-	-	-	-	-
Infection	-	-	-	-	-	-
Synechia	-	-	-	-	-	-
Total	7	14.9	2	4.5	2	4.8

Complication	Group					
	2		3		4	
	number	rate	number	rate	number	rate
14 days						
<i>Anticipated feelings and symptoms</i>						
6	12.8	4	9.1	2	4.8	
3	6.4	3	6.8	1	2.4	
5	10.6	3	6.8	1	2.4	
1	2.1	1	2.3	-	-	
15	31.9	11	25.0	4	9.5	
<i>Complications</i>						
3	6.4	1	2.3	1	2.4	
4	8.5	1	2.3	1	2.4	
2	4.3	1	2.3	-	-	
1	2.1	-	-	-	-	
1	2.1	-	-	-	-	
4	8.5	1	2.3	-	-	
26	55.3	7	15.9	2	4.8	

Note: NSD, nasal septal deviation

Table 5. Hospital stay after septoplasty

Parameter	Group		
	2	3	4
Mean number of bed days	6.9±1.5	6.1±1.2	7.2±1.6
P	P ₂₋₃ >0.05	P ₃₋₄ >0.05	P ₂₋₄ >0.05

Note: P, significance of difference

associated OD, a history of COVID-19 and nasolacrimal duct obstruction, resulted in the restoration of nasolacrimal duct patency and prevented the development of chronic dacryocystitis.

There was no significant difference ($p > 0.05$) in hospital stay after septoplasty among groups 2, 3 and 4 (Table 5).

APMC is plasma with a platelet concentration of 3.0 to 3.5 times greater than normal plasma. In a healthy person, the platelet concentration in blood is around (1.5-4.0) x 10⁵ cells/μL. The activating effect of APMC is initiated at a platelet concentration ranging from 7 x 10⁵ to 1 x 10⁶ cells/μL. No activating effect of APMC has been observed at a platelet concentration lower than 7 x 10⁵, and no evidence has been reported that a platelet concentration exceeding 1 x 10⁶ cells/μL promotes subsequent tissue regeneration. AMCT with a platelet concentration of one million cells per microliter corresponds to a volume of native plasma of 5 ml [13].

Platelet growth factors of AMCT are peptides capable of stimulating cell growth and division: platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), and insulin-like growth factor (IGF). The number of growth factors in a cell is genetically determined. They exert effects on the receptors of the cell membranes of stromal stem cells with a high degree of affinity for target gene, triggering the regeneration mechanism of any connective tissue. It is FGF and IGF that are involved in osteosynthesis and osteoconduction. Therefore, AMCT can activate reparative regeneration of bone and surrounding tissues [13].

There are many ways to obtain PRP, and each of which has its own parameters and results. For example, it is possible to obtain a clinically effective product in 35-40 minutes [14]. However, despite repeated discussions of the need to standardize the methods for obtaining PRP [13,14], there are no specific practical recommendations in the framework of evidence-based medicine.

Conclusion

Our MRI studies found that olfactory bulb volume was 27.2% and 54.5% decreased in group 3 (patients with NSD-associated OD only) and group 4 (patients with NSD-associated OD and a history of COVID-19) respectively.

Application of APMC after endoscopic septoplasty in patients presenting with NSD-associated OD, a history of COVID-19 and nasolacrimal duct obstruction, contributed to the normalization of olfactory bulb volume, reduction in postoperative complication rate, and restoration of nasolacrimal duct patency, the sense of smell and quality of life.

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Disclosures

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