RHINOLOGY

The treatment efficacy of nasal polyposis on olfactory functions, clinical scoring systems and inflammation markers

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Abstract

Objective The aim of this study was to investigate the effect of the medical and the surgical treatment on the olfactory functions, clinical scoring systems and inflammation markers in patients with nasal polyposis. In addition, the secondary aim was to investigate the correlation between those investigated parameters.

Subjects and methods A total of 30 patients, who completed the standardized medical and surgical treatment and also came to 3 months of follow-ups regularly after the surgery, were included in the study. The Sniffin' Sticks olfactory tests, radiological and the endoscopic stagings, liver-expressed chemokine (CCL16) and endothelin (ET) levels and sino-nasal outcome test-22 (SNOT-22) were performed at the initial and at the end of the study.

Results The current study had four major findings: (1) significant improvement in odor functions after treatment was determined; however, the majority of the patients had been already hyposmic. (2) In addition, significant improvement was found in ET and CCL16 levels, SNOT-22 results, and radiologic and endoscopic stagings at the end of the study. (3) However, there was no correlation between the olfactory functions and the investigated parameters. (4) There was a positive correlation between polyp recurrence and ET levels.

Conclusion The standardized medical and surgical treatment provided a significant improvement in the olfactory functions. However, only one patient (3.3%) had become normosmic at the end of the study.

Keywords Nasal polyposis · Sniffin' sticks · Steroid treatment · Endoscopic sinus surgery · Endothelin · CCL16 · SNOT-22

Introduction

Chronic rhinosinusitis has a high prevalence. The disease has a significant impact on quality of life and health expenditures, and the recent data have reported the prevalence rates of up to 19.7% in Europe and up to 16% in the United States [1, 2].

Chronic rhinosinusitis (CRS) is accompanied by chronic symptoms such as nasal congestion, nasal discharge, olfactory dysfunction and facial pain. The disease is a chronic inflammation of the sinonasal mucosa, which may result in nasal polyposis development. However, chronic rhinosinusitis with nasal polyps (CRSwNP) is a complex and long-lasting inflammation of the nasal mucosa. In addition, CRSwNP is actually a heterogeneous disease that exists on a versatile spectrum of inflammatory pathology, which is thought to be generally an eosinophilic inflammation. A great deal of studies has focussed on eosinophilic mediators in nasal polyp tissue, and demonstrated that different cell types generate these mediators. However, an ideal biomarker which is easy to obtain and has a high sensitivity and specificity for CRSwNP is already in question [3].

Liver-expressed chemokine (LEC/CCL16) is synthesized from the liver and has been shown to be induced by IL-10. CCL16 is chemotactic to monocytes and lymphocytes [4, 5]. As known, the histamine receptor, named type 4 (H4), is expressed selectively by eosinophils and mast cells. CCL16 is thought to be a new functional ligand for H4 and to have a role in the elimination of eosinophils [6]. In addition, it has been reported that endothelin (ET) activates various inflammatory cells including macrophages and mast cells and exacerbates some allergic reactions [7]. Statistically significant

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correlations were found between ET and sino-nasal outcome test-22 (SNOT-22) with tomographic and endoscopic staging of the patients with CRSwNP [8]. However, CCL16 has not been investigated in the CRSwNP patients.

Thus, we aimed to investigate the efficacy of medical and surgical treatment for olfactory functions, radiologic and endoscopic stagings, CCL16 and ET levels, and SNOT-22 results in CRSwNP. In addition, our secondary aim was to investigate the correlations between those investigated parameters.

Materials and methods

All investigations were performed in accordance with the declaration of Helsinki on biomedical studies involving human subjects, and informed consent was obtained from all study subjects. The study was approved by the local Institutional Review Board (Ankara Numune Training and Research Hospital E-16-1127/28.12.2016). The study was conducted at Ankara Numune Training and Research Hospital, Otorhinolaryngology and Head and Neck Surgery Clinic between December 2016 and May 2018.

Patient selection

A total of 30 CRSwNP patients, who completed the medical and surgical treatment and also come to follow-ups regularly, were included in the study.

All the patients were diagnosed as CRSwNP and any of them had a history of previous sinonasal or nasal surgery. Any patient with a treatment history of systemic or intranasal corticosteroid therapy within 3 months was not included in this study. In addition, exclusion criteria included patients with active infection, smoking, severe septum deviation, use of nasal decongestant or antihistamine, cranio-facial abnormalities such as cleft lip/palate, malignancy, head trauma, neurologic, endocrine and psychiatric disorders.

Clinical and laboratory evaluations

After a detailed medical history was taken from all subjects in the study group, a complete otolaryngological examination was performed. The patients diagnosed with CRSwNP by nasal endoscopy and paranasal sinus computed tomography (CT) were included in the study.

After the first examination, the patients, who underwent endoscopy and CT scans, performed Turkish translation of SNOT-22 scale [9] and Sniffin' Sticks olfactory tests. In addition, a blood sample was taken for the measurement of inflammatory marker levels (ET, CCL16). Moreover, eosinophil levels were counted with routine hemogram, and total IgE levels were determined.

Table 1 Lund–Mackay radiologic staging of nasal polyposis

Radiological grading sinus systems	Right	Left
Maxillary	0–2	0–2
Anterior ethmoids	0–2	0–2
Posterior ethmoids	0–2	0–2
Sphenoid	0–2	0–2
Frontal	0–2	0–2
Osteomeatal complex	0 or 2	0 or 2
Total	0–12	0–12

Scoring: for all sinus systems: 0 = no abnormalities, 1 = partial opacification, 2 = total opacification. For the osteomeatal complex: 0 = not occluded, 2 = occluded

Table 2 Lund–Kennedy endoscopic scoring of nasal polyposis

Characteristics	Right	Left
Polyps: 0 = no polyps, 1 = polyps in middle meatus only 2 = beyond middle meatus		
Edema: 0 = absent, 1 = mild-moderate, 2 = severe		
Discharge: 0 = no discharge, 1 = clear, thin discharge 2 = thick and purulent discharge		
Scarring: 0 = absent, 1 = mild, 2 = severe		
Crusting: 0 = absent, 1 = mild, 2 = severe		

Olfactory testing

Sniffin' Sticks olfactory tests have been performed as described in the literature [10–13]. Odorants were presented in commercially available felt-tip pens (Burghart GmbH, Wedel, Germany) [10–13]. The olfactory testing comprised three tests: an odor threshold test (testing by means of a single staircase procedure), an odor discrimination test (three-alternative forced choice), and an odor identification test (four-alternative forced choice) [10–13].

The results of each component of the olfactory testing were analyzed separately. Overall, olfactory function was expressed as the sum of the scores of the three individual tests (i.e., odor threshold, odor discrimination, and odor identification), which is called the TDI score [10–13]. In this study, TDI scores below 16.5 were accepted as functional anosmia and TDI scores above 30.3 as normosmia. TDI scores between 16.5 and 30.3 were categorized as hyposmia [10–13].

Endoscopic staging of the patients was made according to the Lund–Kennedy staging system and the staging of paranasal sinus CTs' was made according to the Lund–Mackay staging system [14] (Tables 1, 2).

After the initial investigations, the same standard medical treatment was started for patients with CRSwNP, who had

no contraindicated disease for systemic steroid treatment. Oral prednisolone was started in decreasing dose for 15 days. 15 days oral steroid treatment was planned as: 5 days 40 mg/day, 5 days 20 mg/day, 5 days 10 mg/day doses. In addition to oral steroid, nasal steroid fluticasone propionate (2×2 puff) was given to each patient during the pre-operative and postoperative follow-up period. In addition, combined antihistamines Levocetirizine Dihydrochloride + Montelukast Sodium were given to each patient for the preoperative and postoperative 3-month follow-up period.

After 15 days of medical treatment, the patients were evaluated whether they were candidates for endoscopic sinus surgery or not. While determining the surgical criteria, we modified the study of Rudmik et al. [15]. Our surgical criteria decisions were based on: (1) Endoscopic Lund–Kennedy Score > 1 (monitoring polyp in the middle meatus) and (2) SNOT-22 score > 20 after 15 days of medical treatment.

Patients who had no indication for surgery in 15th day control were excluded from the study. As a result, 30 patients, between 27 and 61 years of age, underwent endoscopic sinus surgery. Postoperative follow-up period was planned as weekly for the first postoperative month and monthly follow-ups were planned after the first month from surgery. At the end of the third month of the follow-up after endoscopic sinus surgery, endoscopic staging, CT staging and Sniffin' Sticks olfactory tests were renewed. In addition, serum CCL16 and ET levels were measured.

Statistical analysis

The research data were evaluated by SPSS 16.0 statistical package program. Descriptive statistics were presented as frequency distribution and percentage for categorical variables and as mean ± standard deviation for the variables specified by measurement. Paired T test and correlation analysis were used as statistical methods. Statistical significance was accepted as $p < 0.05$.

Results

The study was concluded with 30 patients (8 female, 22 male) who completed the medical treatment with attendance to the regular follow-ups and underwent endoscopic sinus surgery. The average age was 45.6 ± 9.82 years. According to Sniffin' Sticks olfactory test, the mean TDI score was 14.1 ± 6.45 at the beginning of the study, whereas the mean TDI score was 20.9 ± 5.00 at the end of the study. The improvement in the TDI scores of the patients was statistically significant ($p < 0.001$). The results from the subtests of Sniffin' Sticks olfactory testings are shown in Table 3.

Prior to the treatment, 11 patients were hyposmic and 19 were functional anosmic. However, after treatment, 4 patients were determined as functional anosmic, 1 patient as normosmic and 25 patients as hyposmic.

Table 3 Descriptive statistics of Sniffin' Sticks olfactory testing before and after the treatment

	Beginning of the study	3 Months after the endoscopic sinus surgery	*p* value*
Odor threshold	1.5 ± 2.6	4.4 ± 2.0	< 0.001
Odor discrimination	6.0 ± 2.7	8.8 ± 2.3	< 0.001
Odor identification	6.5 ± 2.7	7.6 ± 2.6	0.057
TDI	14.1 ± 6.1	20.9 ± 5.0	< 0.001

*(*T* test in dependent groups)

TDI Sum score of odor threshold, odor discrimination and odor identification scores

The mean endoscopic scores were 8.5 ± 1.7 at the beginning of the study and 2.8 ± 1.9 at the end of the study, and there was a statistically significant difference ($p < 0.001$) (Table 4).

The mean Lund–Mackay was 17.8 ± 3.9 at the beginning of the study, whereas it was scored as 6.7 ± 3.3 at the end of the study and the difference was statistically significant ($p < 0.001$) (Table 4).

The mean SNOT-22 was 44.8 ± 19.2 at the beginning of the study, and 17.4 ± 16.6 at the end. There was a significant difference between the symptom scorings before and after treatment ($p < 0.001$) (Table 4).

We did not find any correlation between Sniffin' Sticks odor testing scores with endoscopic, CT scoring and SNOT-22 symptom score performed both at the beginning and at end of the study.

The mean ET levels were found to be 13.6 ± 3.6 at the beginning of the study and 4.4 ± 1.1 at the end of the study. There was a significant difference between ET levels before and after treatment ($p < 0.001$) (Table 5). We found significant positive correlation between initial ET levels and posttreatment blood eosinophil levels (*p*: 0.018, *r*: 0.4).

In addition, the mean CCL16 levels were 444.2 ± 77.6 at the beginning of the study and 362.1 ± 91.6 at the end of the study. There was a significant difference in CCL16 level before and after treatment ($p < 0.001$) (Table 5).

No significant correlation was found between the odor tests with CCL16 and ET levels both at the beginning and at the end of the study. In addition, we did not find significant correlation between inflammatory markers and total IgE levels.

Recurrence of the polyp was detected in seven patients at the end of postoperative third month. When we performed a correlation analysis for the relationship among nasal polyp recurrence, ET and CCL16 levels, we found that there was no significant relationship among nasal polyp recurrence, initial ET level and initial CCL16 level. In addition, there was no correlation between nasal polyp recurrence and postoperative CCL16 level, whereas we found a significant

Table 4 Comparison of endoscopic, tomographic disease scores and SNOT-22 scores before and after treatment

	Beginning of the study	3 Months after the endoscopic sinus surgery	p value*
Lund–Mackay right	9.0 ± 2.21	3.16 ± 1.64	< 0.001
Lund–Mackay left	8.83 ± 2.03	5.53 ± 2.12	< 0.001
Lund–Kennedy right	4.26 ± 0.86	1.43 ± 1.0	< 0.001
Lund–Kennedy left	4.23 ± 0.89	1.43 ± 1.04	< 0.001
SNOT-22	44.80 ± 2.19	17.4 ± 16.6	< 0.001

*(T test in dependent groups)

SNOT-22: sino-nasal outcome test

Table 5 Comparison of ET and CCL16 levels before and after treatment

	Beginning of the study	3 Months after the endoscopic sinus surgery	p value*
Endothelin	13.6 ± 3.6	4.4 ± 1.1	< 0.001
CCL16	444.2 ± 77.6	362.1 ± 91.6	< 0.001

*(T test was performed in dependent groups)

Table 6 Correlation of endothelin and CCL16 levels at postoperative third month with polyp recurrence (r value was shown only for statistically significant data)

Recurrence of polyps	r	p*
Endothelin	0.483	**0.017**
CCL16		0.9

Pearson correlation ($p < 0.05$ was accepted as statistically significant and written in bold)

positive correlation between nasal poly recurrence and post-treatment ET levels (p: 0.007, r: 0.483) (Table 6).

Discussion

The current study had four major findings: (1) significant improvement in Sniffin' Sticks olfactory testing scores was observed at the end of the third month follow-up of patients after appropriate medical and surgical treatment; however, the majority of the patients had been already hyposmic. (2) In addition, significant improvement was found in ET and CCL16 levels, SNOT-22 results, and radiologic and endoscopic stagings at the end of the study. (3) However, there was no correlation between the olfactory functions and the investigated parameters. (4) Moreover, there was a positive correlation between polyp recurrence and final ET levels, and also a significant positive correlation was found between initial ET levels and post-treatment blood eosinophil levels, whereas such correlations was not found for CCL16.

There are studies showing that the elevation in ET level is specific for chronic rhinosinusitis with nasal polyps [8]. ET has been shown to activate various inflammatory cells, including macrophages and mast cells. In some studies, it

has also been shown that the level of ET is correlated with SNOT-22 [8]. In our study, there was a significant difference in ET levels in the pre- and post-treatment evaluations. However, the decrease in ET level after surgery was not correlated with tomographic staging, endoscopic staging and symptom scoring.

CCL16 is a new functional ligand for H4 and is thought to have an important role in the release of eosinophils [5–8]. Apart from our study, there is no study on the relationship between CCL16 and nasal polyps. In our study, there was a statistically significant decrease in serum CCL16 values between pre-treatment and postoperative third month. However, we did not find any correlation between blood eosinophil levels and total IgE levels with CCL16.

Although there was a significant improvement in pre- and post-treatment values for both ET and CCL16, this decrease was not correlated with improvement in the endoscopic, radiologic, symptom and olfactory scores. However, there was a positive correlation between postoperative third month ET levels and nasal polyp recurrence.

Several studies have shown that patients with a high preoperative Lund–Mackay score showed more improvement in symptoms after surgical or medical treatment. Patients with nasal polyps who were admitted with diffuse disease in CT staging were found to be at a higher risk of recurrence after endonasal surgery. CT scan scores have been suggested as the strongest predictor of the need for postoperative systemic medication [16–18]. However, in our study, no such correlation was found between CT scores and the other parameters that were studied such as SNOT-22 symptom scores, Sniffin' Sticks olfactory testing scores and endoscopic scores. We also did not find a correlation between CT scores and polyp recurrence.

Sinus surgery creates a change in the nasal airflow and at the same time leads to an improvement in the patient's olfactory abilities in most cases. However, odor loss occurring in nasal polyposis may be caused by conduction pathology, secondary to obstruction and also may be due to degenerative changes in the olfactory mucosa after surgery. In addition, local inflammation in the olfactory epithelium can also cause smell loss. In our study, we found no correlation between

olfactory functions and inflammatory markers, although significant improvement was observed in the olfactory functions and inflammatory marker before and after treatment.

In addition, patients with more severe disease had less improvement than expected in the olfactory sensations despite the surgical removal of obstructive polyps [19]. Especially in severe cases of CRSwNP, this lack of improvement supports the theory that a change in olfactory epithelium due to chronic inflammation may cause smell loss [20, 21].

In our study, a significant improvement was found between the initial and after postoperative third month Sniffin' Sticks olfactory testings scores in terms of odor threshold, odor discrimination and TDI scores. However, no significant difference was found in odor identification scores.

Studies show that surgery was effective in approximately 70–80% of patients with olfactory disorder among the patients with CRSwNP. However, the olfactory function does not improve in a significant number of patients after the surgery and the rate of olfactory dysfunction is found 8–34% and anosmia is observed in 1% of these patients [20–22]. It has been suggested that these losses are caused by neuronal damage or anatomical changes during surgery or by displacement of nasal olfactory mucosa with scar tissue. At the beginning of the study, 36.6% (11 patients) of the patients were hyposmic and 63.3% (19 patients) were functional anosmic. However, at the postoperative third month, only 1 patient (3.4%) was found to be normosmic, while 4 patients were functionally anosmic (13.3%) and 25 patients were hyposmic (83.3%).

In the study by Hummel et al., in the fourth month of post-surgery, the olfactory functions were improved in 23% of the patients, unchanged in 65% and worsened in 9%. In our study, we found that in the third postoperative month, 73.3% of the patients improved their olfactory functions and in 26.7%, these functions remained unchanged [23].

These findings suggest that the smell loss, resulting from conduction-type pathology in CRSwNP, may also be due to neuronal damage and toxins in the advanced stages of the disease. In the study of Kern et al., biopsies of 19 patients were found to have high levels of lymphocytes, macrophages and eosinophils [24]. These histological studies support that olfactory dysfunction in CRSwNP patients is caused by inflammation and damage in the olfactory epithelium, in addition to obstruction caused by polyps and nasal discharge. As a result, the improvement in the degree of smell at this stage may not be satisfactory [23–26].

Our study had some limitations. We did not have a control group, and we had a limited sample. Therefore, those factors prevent us from concluding definitive interpretations.

Conclusion

Although all the investigated clinical and radiological parameters were statistically improved after the standardized medical and surgical treatment, especially the improvement in odor functions did not seem to be sufficient. Eventually, only one patient (3.3%) had become normosmic at the end of the study. In addition, it was impossible to predict olfactory functions according to the Lund–Kennedy and the Lund–Mackay staging systems according to our results.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local Institutional Review Board (Ankara Numune Training and Research Hospital E-16-1127/28.12.2016).

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