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Response to Glucocorticosteroids Predicts Olfactory Outcome After ESS in Chronic Rhinosinusitis

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Objectives: Olfaction is frequently impaired in chronic rhinosinusitis with nasal polyps (CRSwNP) and often improves after endoscopic sinus surgery (ESS). Data about dynamics of olfactory changes after ESS are lacking, and little information is available concerning whether preoperatively administered glucocorticosteroids predict postoperative olfaction. Therefore, the aim of this study was to examine dynamics of olfaction after ESS in relation to the effect of preoperative administration of glucocorticosteroids in CRSwNP.

Methods: This prospective study included 52 CRSwNP patients (30 men, 22 women, mean age 54 ± 14 years) divided into a control group (n = 31) subjected to ESS without preoperative steroids and a treatment group (n = 21) receiving orally administered glucocorticosteroids preoperatively.

Self-ratings of olfaction and olfactory testing using the extended Sniffin' Sticks test battery (threshold, discrimination and identification [TDI] score) were performed. Olfaction was measured preoperatively; after termination of glucocorticosteroid treatment (only treatment group); and 2 weeks, 1 month, and 3 months postoperatively.

Results: After glucocorticosteroids, TDI score significantly improved in 57% of patients, and olfactory function remained unchanged in 43%. In addition, improvement in TDI score after steroids and 3 months postoperatively were significantly correlated ($r = 0.66$, $P = 0.01$). Patients whose olfaction did not improve after glucocorticosteroids did not benefit from surgery. Regarding postoperative olfactory dynamics, TDI score reached its maximum 1 month postoperatively and decreased again approximately 3 months after surgery.

Conclusion: Glucocorticosteroids improved olfaction in CRSwNP comparable to surgery. In addition, changes in relation to steroids predicted olfactory outcome postoperatively. Regarding the olfactory dynamics, it could be demonstrated that olfactory function increased 1 month after surgery and decreased 3 months postoperatively.

Key Words: Olfaction, chronic rhinosinusitis, nasal polyps, glucocorticosteroids, anosmia.

Level of Evidence: 2

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INTRODUCTION

Chronic rhinosinusitis (CRS) has a prevalence of 11% in Europe.[1] Olfactory dysfunction is a cardinal diagnostic symptom of this condition, affecting approximately 65% to 80% of patients.[2,3] In turn, this impacts quality of life by affecting food/drink enjoyment and environmental hazard avoidance systems.[4–7] Three main causes for the reduced olfaction in CRS are discussed: 1) a mechanical obstruction of the olfactory cleft (OC) by polyps/edematous mucosal tissue that decreases the access of the odorants to the olfactory cleft; 2) receptor-level dysfunction due to interference from inflammatory cytokines; and 3) remodeling of the olfactory neuroepithelium due to chronic inflammation.[8–11]

Compared to CRS without nasal polyps (CRSsNP), CRS with nasal polyps (CRSwNP) is associated with a higher frequency/degree of olfactory impairment.[2,12] Treatment of CRS is first conservative[13]; if this approach fails to relieve the symptoms, a well-established surgical method—endoscopic sinus surgery (ESS)—should be considered. For this method, polypoid tissue is removed, which increases the access of odorants to the OC and helps reduce the inflammatory burden on the sinunasal mucosa.[14] Hence, surgery has the potential to improve olfaction of CRS patients. In recent literature, the improvement rate after ESS varies widely from no improvement or even deterioration to a 13% to 97% improvement rate.[15–17] Accordingly, it is challenging to predict postoperative olfactory outcome. The current study aimed at examination of the dynamics of olfaction after ESS in relation to the effect of preoperative administration of glucocorticosteroids in CRSwNP patients. Using this approach, information on

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the predictive value of steroids in terms of olfactory outcome of surgery also can be provided.

MATERIALS AND METHODS

Fifty-two CRSwNP patients (30 men, 22 women, mean age 54 ± 14 years [23–77 years]) treated at the University Clinic of the Crimean State Medical University, Simferopol, Ukraine, from March 2012 to March 2013 were included in the present study. Exclusion criteria were aspirin intolerance; contraindications to the application of systemic steroids; and disorders that have a strong effect on the sense of smell, for example, Parkinson's disease or major renal dysfunction. Prior to their inclusion, all patients underwent a complete otorhinolaryngological examination including nasal endoscopy and X-ray of paranasal sinuses. Following detailed explanations on potential risks and benefits of the study, all patients provided written consent prior to participation in the study. The study was performed according to the ethical principles for medical research involving human subjects of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the University of Simferopol, Ukraine.

Upon study entry, patients were randomly assigned to one of two groups: Group 1, the control group, was comprised of patients (n = 31; 20 men, 11 women; mean age 57 ± 13 years) who underwent surgical treatment only (polypectomy, uncinectomy, middle meatal antrostomy, partial ethmoidectomy, and transoral endoscopical operation of the radiologically opacified maxillary sinus(es)). Group 2, the treatment group, was comprised of patients (n = 21; 10 men, 11 women; mean age 49 ± 14 years) who received a short course of oral prednisolone therapy at the preoperative stage (starting with 40 mg daily, tapered off every second day by 5 mg), 1 to 4 weeks after which the same surgical treatment was performed. Patients did not receive topical steroids from at least 2 weeks before the chemosensory assessment. From the third week of the postoperative period, patients of both groups received mometasone furoate (50 μg/spray) as two sprays in each nasal side once daily.

Olfactory Test

All patients underwent birhinal, orthonasal olfactory assessment using the extended "Sniffin' Sticks" test battery (Burghart GmbH, Wedel, Germany).[18] They also rated their olfactory function using a 10-point visual analogue scale (VAS). Olfactory function was evaluated preoperatively (test 1) after termination of the course of oral steroids (for patients of the treatment group, test 1A), 2 weeks postoperatively (test 2), 1 month (test 3), and 3 months (test 4) after ESS (see Fig. 1).

The "Sniffin' Sticks" battery comprises tests for odor threshold (THR), odor discrimination (DIS), and a 16-item odor identification test (ID). The Sniffin' Sticks are based on odors presented in felt-tip pens that are released by removal of the pen's cap. The tip of the pen is positioned approximately 2 cm in front of the participant's nostrils for about 3 seconds.

THR was determined for (the rose-like) phenyl ethyl alcohol with 16 stepwise dilutions starting at a 4% solution (dilution ratio 1:2 in propylene glycol). THR was measured using the single-staircase technique based on a three-alternative forced-choice task (3AFC), and the subjects score ranged from 1 to 16. DIS was assessed over 16 trials. For each individual discrimination task, three pens were presented: two containing the same odor and the third containing a different, target odor (3AFC task). ID was assessed presenting 16 common odors with four verbal descriptors in a multiple forced-choice format (3 distractors and 1 item describing the target odor). The interval between odor presentations was approximately 20 seconds. A total score (THR-DIS-ID: threshold, discrimination and identification [TDI]) was calculated: a score as ≥30.5, <30.5, and ≤16.5 indicated normosmia, hyposmia, and functional anosmia (in the following indicated as "anosmia"), respectively.[17] A clinically significant change in olfactory function was defined as a decrease or increase in TDI score by 6 or more points.[19]

Visual Analogue Scale

Participants reported their self-perception of their ability to smell using a VAS (length 10 cm) ranging from 0 "no olfactory function" (left-hand end) to 10 "excellent olfactory function" (right-hand end). Patients are asked to put a mark on this scale corresponding to their subjective olfactory function. The distance in centimeters from the starting point to the mark corresponds to the individual VAS score.

Surgical Intervention and Postoperative Care

All patients underwent ESS with general anesthesia. In the postoperative period, all patients received standard therapy consisting of antihistamines (cetirizine 10 mg once daily for 1 week), vasoconstrictive (naphazoline 1% for 7 days) and oily drops in the nose, a hemostatic agent (etamsylate 12.5% 2 mL intramuscularly 4 times daily for 2 days), and intranasal steroid-containing ointments (hydrocortisone 1% on a gauze stripe for 10 minutes on both sides once daily for 3–5 days). Information about symptoms and duration of patients' disorder were recorded.

Statistical Processing of Data

Results were analyzed using SPSS 25.0 (SPSS, Inc., Chicago, IL). All data are presented as mean ± standard deviation (SD). The results were considered significant at $P < 0.05$. The normality of the distribution of all data obtained was estimated using the Kolmogorov-Smirnov test. If data were not normally distributed, appropriate nonparametric tests were used. To compare the results of, for example, different groups or different time points, we used Student t test, one-way analysis of variance (ANOVA), and nonparametric tests by Wilcoxon or Mann-Whitney. The association between olfactory function, age, duration of disease, and the patients' ratings were investigated by calculating Pearson correlation coefficients. To assess the influence of various factors on the change in the olfactory capacity of patients of

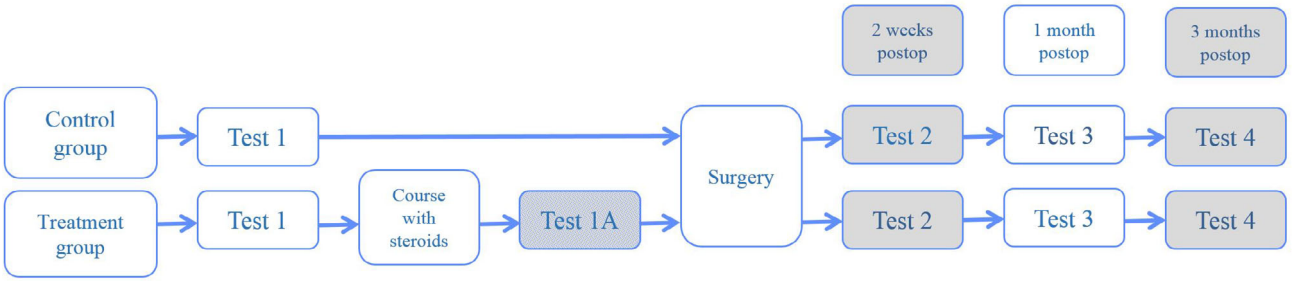

Fig. 1. Study design. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

the two groups in the postoperative period, a repeated measures ANOVA was performed.

RESULTS

A total of 52 patients were examined in the present study; of those, 51 underwent ESS. One of the 52 patient experienced significant olfactory improvement and resigned surgery after taking a course of oral steroids. Thus, 31 patients from the control group and 20 patients from the treatment group underwent follow-up during the postoperative period.

Self-Ratings of Olfactory Function

Forty-four of the 52 patients (85%) reported a decreased smell function. Based on the Sniffin' Sticks test, 43 of the patients were found to be hyposmic and functionally anosmic (further termed anosmic), and one was normosmic. Eight patients (15%) rated their olfactory function as normal; however, hyposmia was found in four, and one was anosmic.

The mean VAS score (maximum score: 10) was 2.27 ± 2.39. In 50% of cases, the VAS score did not exceed 1. Still, self-ratings correlated with the preoperative TDI score (r = 0.75, n = 52, $P < 0.001$).

Sniffin' Sticks Test

During the baseline examination, anosmia was seen in 34 (65%) patients, hyposmia in 14 (27%) patients, and normosmia in 4 (8%) patients (Hummel et al.[17]). Olfactory function (TDI score) of the two groups (treatment and control group) was not statistically different preoperatively (16.6 ± 6.8 vs. 15.1 ± 7.6; Mann-Whitney test, $P = 0.25$). Age and duration of the disorder did not significantly correlate with the TDI score before surgery (r = −0.25, $P = 0.07$ and r = −0.21, $P = 0.14$, respectively). Figure 2 shows the relationship between the VAS scores and Sniffin´ Sticks scores.

The Effect of Systemic Steroid Therapy on Olfaction

The course of steroid therapy improved olfactory function (see also Fig. 3). The TDI score was clinically significantly improved (by 6 or more points of the TDI-score) in 12 (57%) patients (improvement by 10.4 ± 3.5); olfactory function did not change for the remaining nine patients (43%). No major side effects of prednisolone were observed.

Following the systemic steroid therapy, 20 patients from the treatment group also underwent surgery. The changes in the TDI score at 1 and 3 months after the operation were statistically not significantly different from results obtained directly prior to surgery (test 1A) (Table I). In addition, in comparison to baseline measurements (test 1), there was a correlation between improvement in TDI score after steroid therapy (difference TDI1A – TDI1) and improvement in TDI score 1 months and 3 months after surgery (difference TDI3 – TDI1 and TDI4 – TDI1) (r = 0.66, $P = 0.01$ and r = 0.46, $P = 0.04$, respectively).

None of those nine patients for whom the course of steroids was ineffective experienced a clinically significant change of olfaction 3 months after surgery (mean

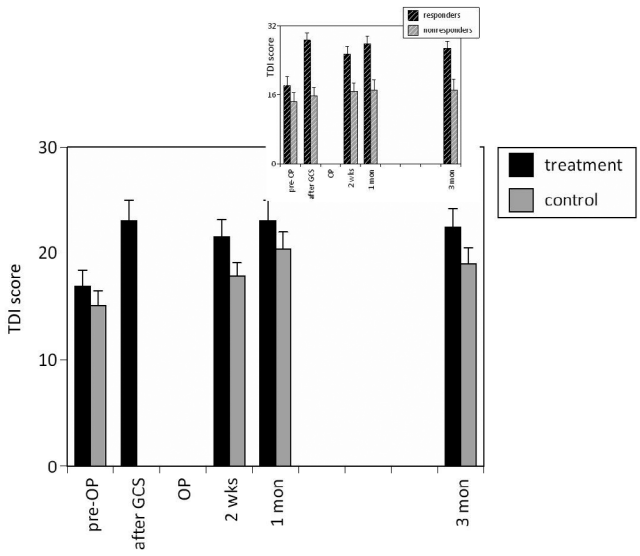

Fig. 2. Scatter plot shows the relationship between the VAS score and the TDI score preoperatively (r = 0.57). TDI = threshold, discrimination and identification; VAS = visual analogue scale.

TDI increase TDI4 – TDI1A ± SD = 1.5 ± 3.0, standard error of the mean [SEM] = 1.0). The scores TDI1A and TDI4 of these 9 patients showed a strong positive correlation (r = 0.9, $P = 0.001$) and did not significantly differ in paired t test ($t = -1.45$, $P = 0.19$). Of the 11 patients who both had a clinically significant improvement in olfaction after steroids and underwent surgery, one experienced a further clinically significant improvement of olfaction 3 months after surgery (TDI4 – TDI1A = 6.75), and two experienced a clinically significant deterioration (TDI4 – TDI1A = −15 and – 8.75,

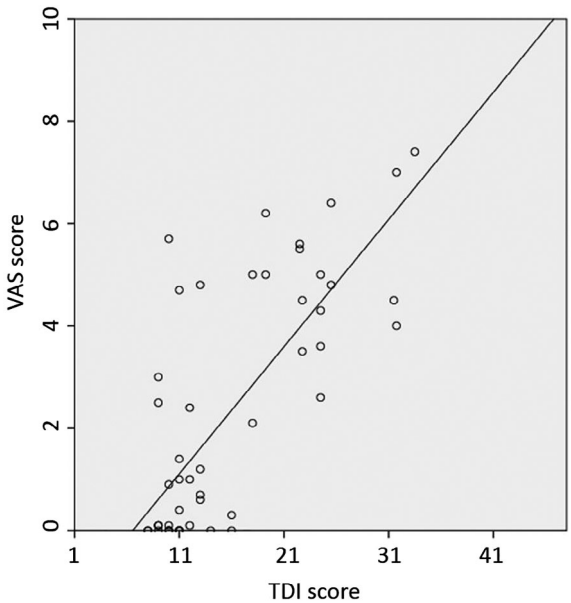

Fig. 3. The dynamics of the results of olfactory testing (TDI score; mean, SEM) for the treatment (black) and control (gray) group. The insert shows the results from the treatment group, separately for responders to GCS (black hatched bars) and nonresponders (gray hatched bars). GCS = glucocorticosteroids; SEM = standard error of the mean; TDI = threshold, discrimination and identification.

respectively). The mean change of the TDI score (TDI4 – TDI1A) for these 11 patients was −2.1 (SD 6.3, SEM 1.9). The scores TDI1A and TDI4 of these 11 patients showed no significant correlation (r = 0.4, $P = 0.23$) and did not significantly differ in paired t test ($t = 1.1$, $P = 0.3$).

Eight of 11 patients (73%) with a clinically significant improvement after the course did not experience any additional significant change after the surgery.

At an individual level, olfactory function at 3 months after surgery compared with the condition after steroid therapy was clinically significantly reduced (for more than 6 points on the TDI score) in two out of 20 patients and significantly increased in one patient. In the remaining 17 patients, the sense of smell compared with the condition after a course of steroid therapy did not change significantly.

There was no significant difference between the change of the TDI score in the treatment group after the course of steroids (TDI1A4 – TDI1) and the TDI score in the control group 3 months after the operation (TDI44 – TDI1) (6.5 ± 5.5 vs. 4.0 ± 5.2, respectively; $t = 1.70$, $P = 0.10$).

Postoperative Dynamics in the Olfactory Function

The means of the TDI scores for both groups preoperatively (TDI1), as well as 2 weeks (TDI2), 1 month (TDI3), and 3 months (TDI4) postoperatively, are shown in Table I. TDI scores of the control group increased significantly after the operation, reaching a maximum 1 month postoperatively ($P < 0.001$). Three months after the operation, average olfactory function exhibited a slight decrease (Fig. 2). Wilcoxon test for paired samples showed that TDI1 was significantly different from all postoperative test results in both groups. Importantly, TDI1 and TDI1A (before and after systemic steroid treatment) were significantly different from each other ($P < 0.001$). However, there were no significant differences between TDI1A and TDI3 and between TDI1A and TDI4 (after prednisolone treatment vs. TDI1 and 3 months after surgery) (Table I).

Across all patients of both groups, 1 month postoperatively the TDI score increased by 5.6 ± 4.9 points. On an individual level, 1 month postoperative olfactory function improved clinically significantly in 24 patients (47%). Three months after surgery, across all patients the TDI score was found to be increased by 4.6 points ± 5.1 in comparison to baseline. On an individual level, 3 months after the operation the sense of smell was still clinically significantly improved in 15 patients (29%).

There was no significant correlation of the overall improvement of TDI score 3 months after treatment for patients of both groups with the age of patients (r = −0.16, $P = 0.27$). The improvement did not differ significantly between men and women ($t = 0.3$, $P = 0.77$). However, there was a weak but significant negative correlation of this improvement with the duration of the disease (r = −0.35, $P = 0.012$), meaning that the improvement was more pronounced the shorter the duration of the disorder.

TABLE I.
Comparison of TDI Scores Obtained at Various Sessions (*P* value, Wilcoxon test for paired samples), Separately for Treatment and Control Group.

Treatment Group	TDI1	TDI1A	TDI2	TDI3
TDI1 (baseline)				
TDI1A (after GCS)	<0.001			
TDI2 (2 weeks after surgery)	0.001	0.36		
TDI3 (1 month after surgery)	<0.001	0.77	0.032	
TDI4 (3 months after surgery)	0.001	0.97	0.12	0.95

Control Group	TDI1	TDI2	TDI3
TDI1 (baseline)			
TDI2 (2 weeks after surgery)	0.002		
TDI3 (1 month after surgery)	<0.001	0.001	
TDI4 (3 months after surgery)	<0.001	0.19	0.042

GCS = glucocorticosteroids; TDI = threshold, discrimination and identification.

DISCUSSION

The present investigation produced three major results: 1) systemic glucocorticosteroids improved olfactory function in CRSwNP patients comparable to the effect of ESS; 2) olfactory function increased after surgery; 3) patients who did not respond to preoperative systemic steroids did not respond to subsequent ESS in terms of olfactory outcomes.

CRSwP is associated with decreased olfactory function.[6,20–23] More than 90% of our study population were diagnosed with olfactory dysfunction; of those, more than two-thirds were functionally anosmic. These findings are in line with previous research.[16,24–27]

Regarding postoperative olfactory function 1 month after ESS, olfaction improved in 24 patients (47%). Interestingly, there was a negative correlation between duration of the disorder and postoperative TDI score increase. This highlights that it seems to be advantageous regarding olfactory function to intervene in an early stage of CRSwNP.[28,29] Regarding the effect of glucocorticosteroids, it could be demonstrated that olfactory function improved. This is in line with recent reviews indicating subjective and objective improvement of olfactory function after oral steroid administration.[13,30]

In the present study, we confirm that a short course of oral steroids significantly improved olfactory function to a degree comparable to surgery. These results are in line with other research that could show preoperative use of systemic steroids in patients with CRSwP led to a significantly higher improvement of smell compared to placebo.[31] Our findings may be explained by reducing inflammation in the nasal cavity and the size of the polyps, thereby facilitating odorants to reach olfactory cleft.

The conduct of ESS did not lead to an additional significant improvement in smell either in patients for whom the systemic glucocorticosteroids (GCS) therapy was effective or in patients for whom it was ineffective. This confirmed recent work showing no major significant differences, at least short-term, in the results of the course of systemic GCS therapy and ESS for the first 4 months after the intervention.[32] Hence, the absence of a clinically significant effect on olfaction after short-course systemic steroids seems to predict that these patients will not benefit from surgery in terms of olfaction. This finding is in line with other recent research, which could demonstrate that patients who

showed an olfactory improvement greater than 50% after systemic corticosteroid before surgery had a better rate of olfactory recovery postoperatively.[33] However, the study by Rives et al. was based on VAS only for olfactory measurement, the results of which have to be treated with caution.[28]

Whether and how much CRS patients may benefit from steroids also seems dependent on CRS endotype with characteristics such as eosinophilia and the presence of nasal polyps. In general, it could be shown that several types of CRS; for example, CRS with a high degree of eosinophilia seem to have less benefit from ESS in general, although they seem to have higher benefit from preoperative glucocorticosteroid administration compared to other CRS types.[34] Also a meta-analysis failed to reveal significant differences in postoperative symptom score between steroid and nonsteroid groups of CRSwNP patients.[35]

In turn, when reduced olfactory function is the major complaint of the patient, the ineffectiveness of GCS therapy seems to predict with a high probability that CRSwP patients are not likely to respond to surgical treatment. In patients with olfactory impairment with nonobstructing polyps and in patients who cannot be operated on for various reasons, the course of GCS therapy followed by long-term therapy with topical steroids could be an alternative to surgical treatment.

Evaluation of further possible predictive factors of the olfactory outcome after ESS revealed that the effect of surgery was not dependent on patient sex or age; however, duration of the disease affected the postoperative increase in TDI score. Indeed, a positive outcome of surgery was more likely when the duration of the disorder was short. This confirms previous observations that point in the same direction.[28,29,36,37]

With regard to the postoperative dynamics of olfactory function, it could be demonstrated that ESS leads to a significant improvement in the sense of smell 1 month after surgery in only about half of the patients, and that olfactory function again decreased on average 3 months after surgery. Interestingly, 3 months after surgery only one-third of the patients retained a significant improvement in their sense of smell. The limited effect of ESS may be at least partly due to the inflammation-associated degenerative processes in the olfactory epithelium and also the olfactory cortex.[38] The current results are in contrast to Federspil et al., who found a significant increase in olfactory function between month 1 and 3 after surgery.[39] This may partly be explained by the pattern of use of nasal steroids in the present study. Because this was not controlled between months 1 and 3 after surgery, many patients may have abstained from the application of nasal steroids. Reasons to discontinue the postoperative use of topical steroids may include the following: 1) relief after the operation, 2) cost of the drug itself, or 3) unwillingness of long-term use of such drugs. Otherwise, the discrepancy between the present study and Federspil et al.[39] may relate to the surgery performed. In our group, the earlier recurrence of inflammation, and hence of olfactory dysfunction, could be explained by the fact that the ethmoid cells were not removed completely up to skull base as performed in ESS.

Regarding subjective assessment of olfactory function, most patients were aware of the decrease of their sense of smell. Still, before surgery five patients reported a normal sense of smell although they were hyposmic or even anosmic, and one patient reported very low olfactory function although normosmic. This is in line with previous work showing that the subjective evaluation of olfactory function does not necessarily correspond with measured olfactory function.[40,41] The findings emphasize the need for the measurement of olfactory function in addition to the subjective ratings.

We recognize that this study has following limitations: 1) missing stratification regarding the severity and phenotype of the CRS, 2) small cohort, 3) short follow-up period, and 4) treatment was not standardized according to the latest guidelines (e.g., EPOS 2012). Hence, research in a larger cohort for a longer time period is needed.

CONCLUSION

A short course of oral glucocorticosteroids improved olfactory function in CRSwNP patients comparable to the effect of surgical treatment. The olfactory response after administration of a systemic GCS therapy predicts the influence of sinus surgery on olfaction in CRSwNP.

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