ORIGINAL CONTRIBUTION

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Endoscopic Sinus Surgery improves olfaction in nasal polyposis, a multi-center study*

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SUMMARY

Background: *A positive effect of Endoscopic Sinus Surgery (ESS) as sole treatment on olfactory thresholds and sense of smell in patients with nasal polyposis has been questioned. The aim of this study was to test the hypothesis that ESS has a positive effect on sense of smell and olfactory thresholds in nasal polyposis.*

Methods: *Uncontrolled post-hoc analysis of a prospective study of 160 patients, ≥ 18 years, with bilateral nasal polyps that underwent ESS to treat bilateral nasal polyposis. The effect of ESS was assessed with an olfactory threshold test, a diary score and a smell and taste score, pre-, and post-ESS.*

Results: *All three effect measures were improved from pre-ESS to post-ESS. Olfactory threshold increased from 0.0 pre-ESS to 3.0 ($p < 0.001$), two weeks after surgery, and the smell diary score decreased from 3.0 to 1.7 during the same period ($p < 0.001$), i.e. improvement. The smell and taste score increased from 1.0 pre-ESS to 2.0 post-ESS ($p = 0.002$). Overall, the results were similar for patients with and without previous surgery, as well as for men and women.*

Conclusion: *ESS without concomitant medical therapy seems to improve both sense of smell and olfactory thresholds in patients with nasal polyposis in the short term.*

Key Words: smell, surgery, nasal polyps, anosmia, olfactory threshold test, sinus surgery

INTRODUCTION

Nasal polyposis, which affects up to 4% of the general population [1-3], is an inflammation of the sino-nasal mucosa with an unclear etiology and a tendency to recur. The inflamed mucosa prolapses into the nasal passages and often leads to nasal congestion and rhinorrhea. Impaired or absent sense of smell is also a common symptom of the disease. Although this symptom is a useful factor in identifying patients with nasal polyposis [4], the underlying mechanism of reduction in sense of smell is currently not understood [5]. Therapy of nasal polyposis involves a combination of medical and surgical treatments, depending on individual assessment. Intranasal and oral corticosteroids are first-line treatments, whereas Endoscopic Sinus Surgery (ESS) is reserved for medical treatment failure [6,7]. Several clinical studies have shown that intranasal corticosteroids alone, or combined with oral corticosteroids, can improve sense of smell in nasal polyposis [8-12]. Although some studies have shown that surgery has an effect on sense of smell [13,14], few clinical studies have reported an effect on the subjective sense of smell as well as olfactory thresholds in nasal polyposis after a combination of intranasal and oral corticosteroids together with ESS [7,15]. The positive effect of ESS as sole treatment on olfactory thresholds and sense of smell in patients with nasal polyposis has until recently been questioned. However, in an uncontrolled, prospective single-centre clinical study of patients with nasal polyposis and asthma, Ehnhage and co-workers showed a beneficial effect of ESS, without intranasal and oral steroids, on olfactory parameters [16].

The aim of this study was to test the hypothesis of a positive surgical effect on the sense of smell and olfactory thresholds in a large multi-centre study of patients with nasal polyposis.

MATERIALS AND METHODS

Study population

In total, 199 patients were recruited and screened from 10 Ear, Nose and Throat (ENT) clinics in Sweden. Patients were of both sexes, ≥ 18 years, with bilateral nasal polyps and fulfilling the criteria for surgery. Among exclusion criteria were polypectomy within the last six months prior to screening, unhealed nasal surgery/trauma, more than five polypectomies or an ongoing nasal infection. Asthmatic patients that had not experienced an asthma exacerbation after visit 1 (V1) were included if they were receiving a moderate, stable dose of inhaled corticosteroids, not exceeding beclomethasone 1000 μg/day or equivalent.

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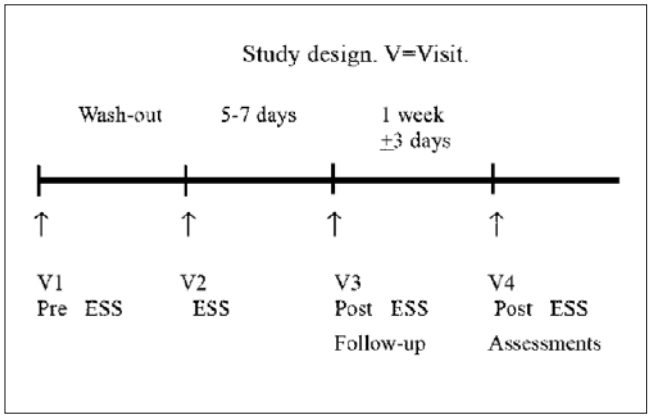

Figure 1. A schematic presentation of the study design.

Study Design

This is an uncontrolled post-hoc analysis of a prospective study [17]. A schematic presentation of the study design is shown in Figure 1.

Following entry assessments at V1, qualifying patients entered a washout phase of varying duration determined by washout periods for concomitant drug(s). Oral, intravenous, rectal, intranasal or ocular corticosteroids were not allowed for at least 3 weeks pre-ESS at visit 2 (V2). No oral, intravenous, rectal, intranasal, ocular corticosteroids or antibiotics were allowed at any time during this study period. As in Swedish clinical practice, nasal saline was allowed from V1 to visit 4 (V4). Between V2 and V4, lavage with nasal saline was recommended twice daily using a device (Nasoklar® Yogaprosess AS, Oslo, Norway). Nasal examination and endoscopy of the nasal cavity was performed at all study visits (V1, 2, 3, 4). Prior to performing endoscopy, a topical anesthetic and a decongestant were used. A polyp score was graded for each nasal cavity on a 0 to 3-point scale (0 = no polyps; 1 = polyps in the middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate; 3 = large polyps reaching to or below the inferior border of the inferior turbinate or polyps medial to the middle turbinate) [17, 18].

During the study the severity of nasal symptoms of polyposis, nasal congestion and sense of smell were individually scored. The patients recorded their symptoms in the diary once daily, and at each visit the patient and physician performed a joint evaluation that was entered into the Case Report Form.

At V2, patients underwent ESS, which included the removal of polyps and usually uncinectomy with anterior ethmoidectomy. If the posterior cells and sphenoid were involved, surgery was continued posteriorly with posterior ethmoidectomy and sphenoidotomy. For patients who had previously undergone FESS, the extent of surgery depended on clinical findings, and in some cases removal of polyps was sufficient. V3 was a post-ESS visit for nasal debridement. At V4, the assessments were performed again in order to compare the difference effect pre and post-ESS.

This study was approved by an independent ethics committee/institutional review board and the Swedish Medical Products Agency prior to enrollment of patients. All patients gave written informed consent to participate in the study. The study was conducted in accordance with the regulatory requirements, Good Clinical Practice, and the ethical principles of the Declaration of Helsinki, as adopted by the World Medical Assembly, 1964 (and subsequent revisions).

Olfactory threshold test

The effect of ESS was assessed with a butanol olfactory threshold test, performed prior to decongestant at V1 and V4 as described by the Connecticut Chemosensory Clinical Research Center [19]. The test uses aqueous dilutions of 1-butanol (n-butyl alcohol) as the odorant. The highest concentration (4%) in deionized water is called dilution step 0, and then the solution is diluted by successive factors of 3 to step 13. The test solutions were presented in squeezable polyethylene bottles. Testing began with a low concentration of butanol dilution and a blank. The subject had to decide which smelled the strongest. If the answer was wrong, the concentration was increased; if the answer was correct, the subject was given a bottle containing a solution with the same concentration and a blank. Five correct answers in a row were regarded as the olfactory threshold. The steps of butanol concentrations were divided into a scale that describes the level of sense of smell: 0-2 = anosmia, 3-6 = hyposmia, and 7-13 = normosmia [16].

Diary score of sense of smell

Sense of smell was recorded once each day by the subject in a diary, and at each visit the subject and investigator performed a joint evaluation that was entered into the CRF. Sense of smell was individually scored on a 0 to 3-point scale ranging from 0 = no signs/symptoms, 1 = slightly impaired, 2 = moderately impaired to 3 = severe symptoms or complete lack of sense of smell.

"Experience of smell and taste" score

Interference with daily activities was recorded with an "Experience of smell and taste" score [18]. The assessment was performed at V1 and at V4 as subjective judgments made by the patients and reviewed by the investigator with respect to experience of smell and taste, assessed as "Almost not at all", "Fairly" or "Very well".

Statistical analyses

All patients who underwent ESS and had pre-surgery and post-surgery data were included in the statistical analyses. Since this is a post-hoc analysis, the variables studied did not serve as the basis of the sample size determination. For the daily recorded diary scores, the patients mean values across the pre-surgery and post-surgery periods were analyzed. Descriptive statistics included number of patients, minimum, 25% percentile, median, 75% percentile and maximum value. The statistical analy-

Table 1. Demographic data for 54 women and 106 men included in a study investigating the effect of Endoscopic Sinus Surgery (ESS) on sense of smell and olfactory thresholds.

	Women			Men			Overall total
	Previous surgery	No previous surgery	Total	Previous surgery	No previous surgery	Total	
N	32	22	54	53	53	106	160
Age (years); median (range)	50 (17-76)	46 (19-69)	48 (17-76)	53 (23-80)	48 (19-72)	50 (19-80)	50 (17-80)
Number of previous surgeries; median (range)	1 (1-4)	---	1 (0-4)	2 (1-6)	---	0 (0-6)	1 (0-6)
Polyp score sum right+left; median (range)	4.5 (2-6)	5 (2-6)	5 (2-6)	5 (3-6)	5 (2-6)	5 (2-6)	5 (2-6)
Congestion score; median (range)	2 (1-3)	2 (1-3)	2 (1-3)	2 (0-3)	2 (1-3)	2 (0-3)	2 (0-3)
Smokers; N (%)	4 (12.5%)	1 (4.6%)	5 (9.3%)	6 (11.3%)	5 (9.4%)	11 (10.4%)	16 (10.0%)

A polyp score was graded for each nasal cavity on a 0 to 3-point scale (0 = no polyps; 1 = polyps in the middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate; 3 = large polyps reaching to or below the inferior border of the inferior turbinate or polyps medial to the middle turbinate).

ses of changes were performed using the Wilcoxon signed-rank test, at a two-sided significance level of 0.05.

RESULTS

Patient characteristics

Overall, 199 patients were screened of which 160 patients (54 women and 106 men) qualified for surgical treatment. The age distribution and the percentage of smokers were similar for men and women. Moreover, there were no obvious differences between men and women, or between patients with or without previous surgery, with respect to polyp and congestion scores (Table 1).

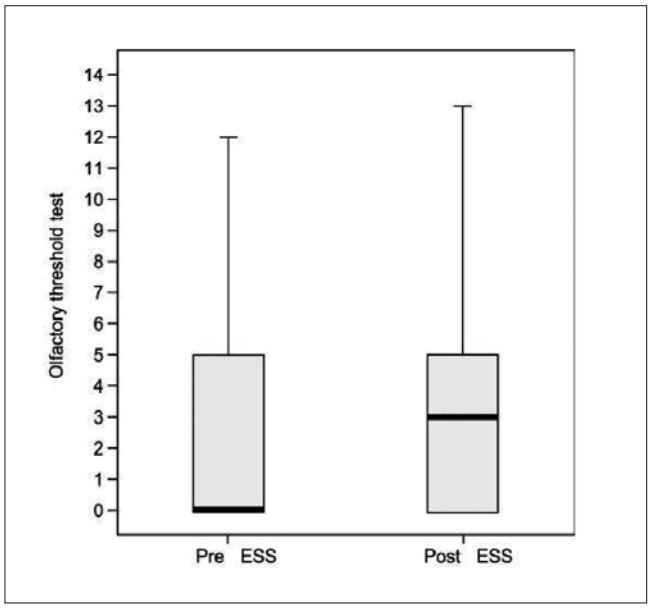

Figure 2. Olfactory Threshold test pre-ESS and post-ESS (n = 158). Box-whisker plots. Data are presented as median, 25% and 75% percentiles, minimum and maximum values. The change from Visit 1 to Visit 4 was statistically significant, $p < 0.001$.

Olfactory threshold test

The median olfactory threshold increased from 0.0 pre-FESS to 3.0 approximately 2 weeks after surgery ($p < 0.001$; Figure 2). The results were similar when performing separate analyses for patients with (median 0.0 pre-ESS vs 0.0 post-ESS, mean 1.4 vs 2.3; $p = 0.003$) and without (2.0 vs 4.0, mean 3.0 vs 4.0; $p = 0.003$) previous surgery. Moreover, the same effect was found for both men (1.0 vs 3.0; $p < 0.001$) and women (0.0 vs 3.0; $p = 0.048$). In the study, 15/63 patients (that could decrease with two or more steps) deteriorated with more than 2 steps on the threshold test from visit 1 to 4, while 48/158 patients improved with more than 2 steps. Improvement was seen in subjects with a history of asthma (n = 53, median 0.0 to median 0.0; mean 1.7 to mean 2.4; $p = 0.12$ [n.s.]) and in subjects without a history of asthma (median 1.0 to median 4.0; mean 2.4 to 3.6; $p < 0.001$). Improvement was seen in subjects with a history of aspirin intolerance (n = 24, median 0.0 to median 0.0; mean 0.6 to mean 1.3; $p = 0.04$) and in subjects without a history of aspirin intolerance (median 1.0 to median 4.0; mean 2.5 to mean 3.5; $p < 0.001$).

Diary scores for sense of smell

The sense of smell score assessed by the patient at each visit decreased (i.e. improved) from 3.0 pre-ESS to 1.7 approximately 2 weeks after surgery ($p < 0.001$; Table 1; Figure 3). Again, similar results were found for patients with (median 3.0 pre-FESS vs 2.0 post-FESS; $p < 0.001$) and without (2.2 vs 1.2; $p < 0.001$) previous surgery, as well as for men (2.8 vs 1.7; $p < 0.001$) and women (3.0 vs 1.7; $p < 0.001$). Improvement was seen in subjects with a history of asthma (median 3.0 to median 2.0; $p < 0.001$) and in subjects without a history of asthma (median 2.4 to median 1.4; $p < 0.001$). Improvement was seen in subjects with a history of aspirin intolerance (median 3.0 to median 2.3; $p < 0.001$) and in subjects without a history of aspirin intolerance (median 2.7 to median 1.4; $p < 0.001$).

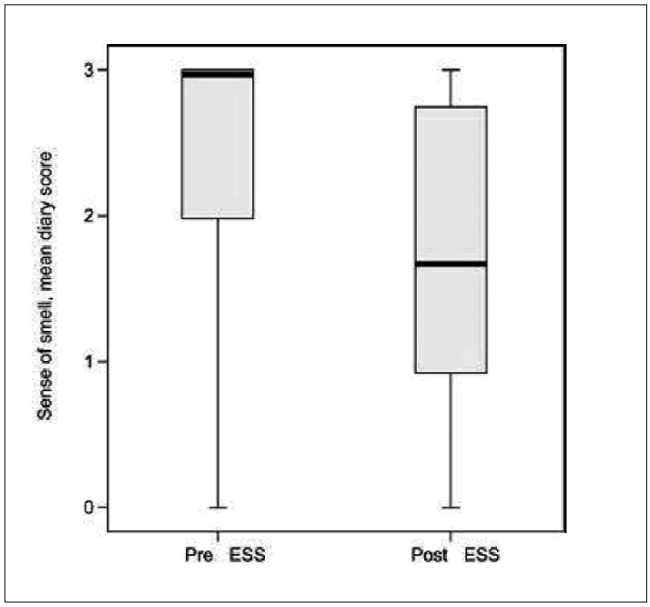

Figure 3. Diary Sense of Smell score pre-ESS and post-ESS (n = 144). Box-whisker plots of period mean values. Data are presented as median, 25% and 75% percentiles, minimum and maximum values. The change from Visit 1 to Visit 4 was statistically significant, $p < 0.001$. 0 = no signs/symptoms, 1 = slightly impaired, 2 = moderately impaired to 3 = severe symptoms or complete lack of sense of smell.

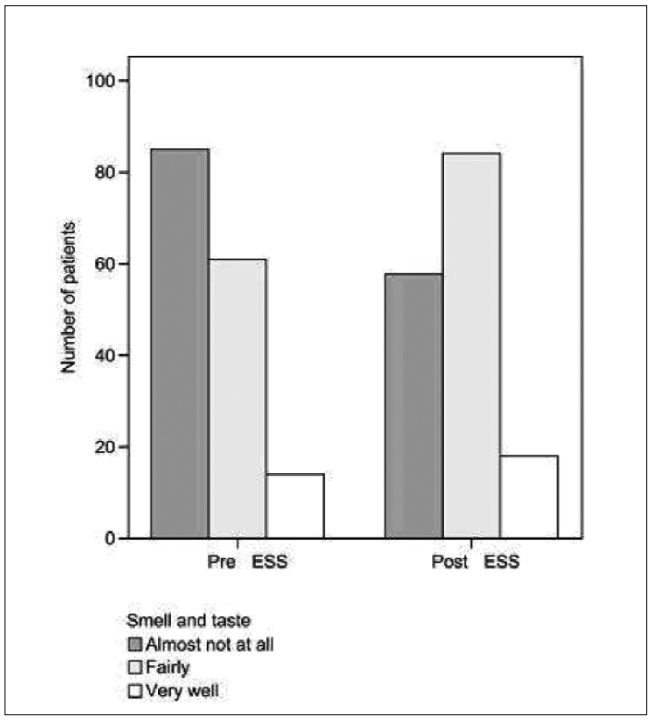

Figure 4. Quality of Life, Experience of Smell and Taste (n = 160). Number of patients by response alternative. The change from Visit 1 to Visit 4 was statistically significant, $p = 0.002$.

"Experience of smell and taste" score

The "experience of smell and taste" score increased from 1.0 pre-FESS to 2.0 approximately 2 weeks after surgery ($p = 0.002$; Figure 4). The increase was more marked among patients with previous surgery (median 1.0 pre-FESS vs 2.0 post-FESS; $p = 0.010$) than among patients without previous surgery (2.0 vs 2.0; $p = 0.07$). Moreover, even though the effect was similar for both genders (1.0 vs 2.0 for both men and women), statistical significance was reached for men ($p = 0.005$) but not for women ($p = 0.15$). Improvement was seen in subjects with a history of asthma (median 1.0 to median 2.0; $p = 0.42$ [n.s.]) and in subjects without a history of asthma (median 1.0 to median 2.0; $p < 0.001$). Improvement was seen in subjects with a history of aspirin intolerance (median 1.0 to median 2.0; $p = 0.08$) and in subjects without a history of aspirin intolerance (median 1.0 to median 2.0; $p = 0.006$).

DISCUSSION

Our clinical study shows, for the first time in a large multicenter trial, that ESS alone improves both sense of smell and olfactory thresholds in patients with nasal polyposis with or without asthma. This finding further indicates that ESS could reduce anosmia and hyposmia in nasal polyposis.

Most previous prospective clinical studies on the effects of ESS on sense of smell and olfactory thresholds in nasal polyposis have been confounded by the lack of control for concomitant medications, absence of information on medical treatment, or by a study design that included co-treatment with intranasal and/or oral steroids [7,15,20-26]. This has made it impossible to differentiate the effects of ESS from medical treatment.

Blomqvist et al. [7] used prednisolone 10 days followed by nasal steroids for 1 month after which 32 patients were randomized to surgery on one or the other side. Mean polyp score was more than 2.5 (out of 3) at baseline and mean olfactory threshold 3.5, measured with the same methods as in our study. Three months post-ESS the threshold increased to a maximum of 5.0 compared to the change from 0.0 to 3.0 in 2 weeks in our study. In a recent prospective study on effects of ESS on odour identification, the authors found a beneficial effect of ESS in nasal polyposis [27]. Interestingly, they also found a positive correlation between the severity of polyposis prior to surgery and olfactory improvement. However, it is unclear how many patients used intranasal steroids. Furthermore, Pade and Hummel [16] only could identify supra threshold olfaction as they were using the odour identification tool in "Sniffin Sticks". Their finding that olfaction deteriorates in 5% of patients with septoplasty or sinus surgery is something to consider whenever making decisions about surgical intervention. In our mixed population of anosmics and hyposmics, 15 patients (23% of those that could deteriorate more than 2 steps) deteriorated from baseline.

To our knowledge, the only other clinical study with evidence of sole effects of ESS on sense of smell and olfactory thresholds in nasal polyposis was also conducted in Sweden, with a prospective design and in a single centre setting [16]. Our study was multi-center, post hoc in design, but was larger (n = 160) as compared with the study from Ehnhage et al. (n = 68). The patient population was somewhat different in the Ehnhage et al. study, as concomitant asthma was an inclusion criterion. Still, both median nasal polyp and congestion score [2] and olfactory thresholds (0) at baseline were identical with our study, measured by the same scoring system and olfactory assessment. Five weeks after ESS the median olfactory threshold had improved from 0 to 4.

In our study, we noted an effect of ESS on olfactory threshold (from 0 to 3) as soon as 2 weeks post-ESS, even though at this time point the cavity is not totally healed. The slightly better result of the Ehnhage et al. [16] study could be a result of observation time.

Danielides et al. [22,26] have studied ESS in 116 patients with concomitant medical treatment and found an odour threshold increase already at 1 month. Others have studied olfactory threshold as an outcome, but used somewhat different surgical techniques, which makes results hard to compare [24,28]. Litvack et al. [23] have reported significant improvement in olfactory scores after ESS in 14 anosmics with nasal polyposis at 6 months, which sustained at 12 months. However, they used a smell identification test, not a threshold test.

The strengths of our study are that it is - to date - the largest clinical study on sole effects of ESS on sense of smell and olfactory thresholds and that there was no concomitant medical treatment for at least 3 weeks before ESS and up until the assessments at 2 weeks post surgery. The only nasal treatment allowed was nasal lavage, which does not have an evidence-based effect on sense of smell or olfactory thresholds in nasal polyposis [29]. Another strength is that the butanol test of olfactory thresholds is a validated method [17].

A weakness of the test is that it is time and staff consuming and therefore not a useful tool in clinical practice. Our classification of olfactory threshold scores into “normal”, “hyposmia” and “anosmia” with specific ranges of scores is not validated. Also, the sensitivity is only 86%, which could be criticized. The reliability is, on the other hand, 92%. The two subjective assessments used in our study are not validated and patients’ subjective assessment of olfactory impairment has been shown to be inaccurate. On the other hand, our subjective scores point in the same direction as our test data.

A general weakness with our study design is that it was a post-hoc analysis without a control group and that we only have data on olfaction without influence of concomitant medication two weeks after ESS. The short follow-up was a result of the design of the randomized, controlled trial [17].

The mechanisms behind the effect of ESS in improving sense of smell and olfactory thresholds are not clear. Surgical “debulking” could lead to increased passage of odorants into the narrow space where olfactory epithelium is situated. The effect may also be due to a decreased inflammation in the mucosa due to removal of polypoid masses filled with inflammatory cells and mediators with subsequent reduction of inflammatory load. Reducing anosmia and hyposmia in patients with nasal polyposis is an important aim in the treatment of the disease, as sense of smell is a prevalent symptom that reduces the quality of life [21,30].

With our study results, two clinical studies with limited follow-up now indicate a positive effect of ESS by itself on sense of smell and olfactory thresholds in nasal polyposis with moderate nasal congestion.

Additional randomized controlled trials are needed to assess the effects of oral corticosteroids on olfactory thresholds in patients with nasal polyposis.

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POTENTIAL CONFLICTS OF INTEREST

Dr Stjärne has received honoraria from Schering-Plough and GlaxoSmithKline for educational activities and has received honoraria for consulting on advisory boards for Schering-Plough, GlaxoSmithKline and Novartis.

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