

Original article

Functional endoscopic sinus surgery improved asthma symptoms as well as PEFR and olfaction in patients with nasal polyposis

Background: Nasal polyposis is a disease known to be associated with asthma. The management is anti-inflammatory, with topical and oral corticosteroids as the first-line treatment. The effect of surgical treatment on lower airway inflammation has not been sufficiently studied.

Aim: The aim of this study is to investigate the effects of functional endoscopic sinus surgery (FESS) as well as fluticasone propionate nasal drops (FPND) 400 µg b.i.d. on nasal and lower airway parameters in asthmatics with nasal polyposis.

Methods: This was a prospective 21-week study of 68 patients with asthma and nasal polyposis, on the benefits of FESS on nasal (butanol test, subjective olfaction, peak nasal inspiratory flow, congestion, rhinorrhoea, and polyp score), and on the lower airway parameters (dyspnea, cough, mean daily peak expiratory flow rate (PEFR), and lung function tests). It also included a randomized, double-blind, placebo-controlled 14 weeks phase on FPND.

Results: Functional endoscopic sinus surgery significantly improved mean asthma symptom scores and daily PEFR and all nasal parameters including subjective and objective olfaction tests. This is the first study that shows the benefits of FESS on butanol tests in patients with nasal polyposis. We found no significant difference between topical treatment with FPND or placebo in the nasal or lower airway variables.

Conclusion: Functional endoscopic sinus surgery improved nasal and asthma symptoms in patients with nasal polyposis. Functional endoscopic sinus surgery could be considered early in the natural course of nasal polyposis with concomitant asthma, as well as a second-line treatment in nasal polyposis patients with a reduced sense of smell. The potential benefits of FPND 400 µg b.i.d. were probably overshadowed by FESS.

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Key words: asthma; fluticasone propionate nasal drops; functional endoscopic sinus surgery; nasal polyposis; olfaction.

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Nasal polyps, when found on the examination of the nose, are a sign of inflammation in the upper airway and can be associated with chronic bacterial infection, fungal infection, as well as with cystic fibrosis, ciliary dysfunction (1), Peutz-Jeghers syndrome (2), and *nasal polyposis*.

Nasal polyposis is a chronic eosinophilic inflammatory disease in the nasal and paranasal mucosa, considered a subgroup to chronic rhinosinusitis and a disease in itself (3), with an unknown etiology. Our definition of nasal polyposis is in accordance with that of chronic rhinosi-

nusitis with nasal polyposis, recently defined in a position paper, the European Position Paper on Rhinosinusitis and Nasal Polyps (3). Nasal polyposis affects up to 4% of the population (4–6), and presents a real challenge to the physician because of its severity (7). Nasal polyposis has been shown to be associated with asthma, in particular asthma associated with intolerance to aspirin and other nonsteroidal anti-inflammatory drugs (Samters triade) (8).

The symptoms of nasal polyposis, including nasal congestion, nasal discharge, reduction in or loss of smell (3) are associated with substantial impairment in quality of life (9, 10). In patients with nasal polyposis, asthma was found in 30% of those referred to ENT Departments, and in more than 70% of those referred to allergy departments (11). In patients with asthma, polyps were found in 7–15%, with the highest frequency in the age group above 50 years (11).

Abbreviations: AE, adverse event; FESS, functional endoscopic sinus surgery; FEV₁, forced expiratory volume in 1 s; FPND, fluticasone propionate nasal drops; GSK, GlaxoSmithKline; OCS, oral corticosteroids; PD₂₀, provocative dose causing a decrease of 20% in FEV₁; PEFR, peak expiratory flow rate; PNIF, peak nasal inspiratory flow.

The objectives of the management of nasal polyposis are: to reduce or eliminate polyps, open the nasal airway, improve or restore the sense of smell, prevent polyp recurrence, and improve patients' quality of life (12, 13). Medical treatment with topical and oral corticosteroids (OCS) is considered an Evidence Grade A treatment recommendation (3). Clinical studies in patients with nasal polyposis have shown that fluticasone propionate nasal drop (FPND) 400 µg b.i.d. has statistically significant and clinically relevant effects on polyp size as well as on nasal congestion (14). Surgical treatment, nasal polypectomy, and functional endoscopic sinus surgery (FESS) in nasal polyposis have not been sufficiently studied, and hence, have been proposed to be reserved for patients who do not satisfactorily respond to medical treatment. According to the European Position Paper on Rhinosinusitis and Nasal Polyps (3), predominantly positive effects have been reported in recent years from the studies on the effects of surgical treatment on asthma; but the level of evidence is low. Therefore, there is a general need for prospective randomized studies with high clinical impact upon the benefits of surgical as well as medical treatment of this patient group (3).

Aim

This prospective 21-week study investigated the effect of FESS and FPND or placebo on the lower and upper airway in patients with nasal polyposis and asthma. The variables evaluated were both subjective and clinical.

Patients and methods

Patients

Eighty-two patients, 19 years of age or older (range: 19–78 years), with a diagnosis of nasal polyposis and asthma were recruited from the outpatient clinic at the ENT Department of the Karolinska University Hospital, Huddinge, Stockholm, Sweden from January 2002 to September 2004 (Table 1). The patients were required to have bilateral nasal polyps, upon endoscopic examination and asthma, diagnosed by history and lung function tests, judged by a pulmonologist. For complete inclusion and exclusion criteria see Table 2. Investigators were instructed not to change the asthma medical treatment throughout the study. No nasal polyp surgery within the last 6 months was allowed. Aspirin sensitivity was not an exclusion criterion, and specific history was not investigated. No aspirin provocation test was performed. Medications prohibited during the prestudy wash-out period were intranasal, ocular, intramuscular, intra-articular, oral, intravenous or rectal corticosteroids, high-potency dermatologic corticosteroids, nasal cromones, anti-histamines, hydroxyzine, oral, nasal, and ocular decongestants. Oral corticosteroids had a 1 month wash-out period prior to visit 1. The same medications were prohibited during the treatment phase, except for nasal or oral decongestants on one occasion of maximum 5 days. Subjects were excluded if there was an asthma exacerbation that had to be treated with OCS.

Table 1. Baseline characteristics

| | Mean; Median (min.–max.) or n (%) | |
|-------------------------------------|-----------------------------------|----------------------|
| | Placebo + FPND | FPND |
| Age, years* | 52; 55 (24–78) | 51; 55 (19–73) |
| Male* | 28 (66.7) | 21 (52.5) |
| Smoker* | 3 (7.3) | 3 (7.5) |
| Skin prick test positive* | 18 (42.9) | 15 (41.7) |
| Number of surgeries (>2)* | 6 (14.6) | 8 (20.5) |
| Symptom score shortness of breath | 0.8; 0.8 (0.0–3.0) | 0.6; 0.3 (0.0–3.0) |
| Symptom score cough | 0.6; 0.1 (0.0–2.7) | 0.6; 0.6 (0.0–2.0) |
| FEV ₁ % of predicted | 82; 85 (44–112) | 86; 86 (40–120) |
| FEV ₁ > 80% of predicted | 27 (65.9) | 28 (71.8) |
| PEFR | 429; 422 (197–629) | 434; 418 (254–666) |
| PD ₂₀ FEV ₁ | 896; 355 (60–3520) | 1147; 1164 (36–3520) |
| Polyp score | 2.2; 2.0 (1.0–3.0) | 2.3; 2.0 (1.0–3.0) |
| Symptom score congestion | 1.8; 2.0 (0.0–3.0) | 1.9; 2.0 (0.0–3.0) |
| Symptom score rhinorrhoea | 1.0; 1.0 (0.0–3.0) | 1.1; 1.0 (0.0–3.0) |
| Symptom score sense of smell | 2.3; 3.0 (0.0–3.0) | 2.2; 3.0 (0.0–3.0) |
| Butanol test | 2.0; 0.0 (0.00–7.00) | 2.4; 0.00 (0.00–7.0) |
| Budesonide or equivalent, µg* | 661; 800 (100–1600) | 598; 400 (0–1600) |

*Inhaled Steroid Obtained at visit 1. All other characteristics were collected after wash-out (visit 2).

Table 2. Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|--|--|
| Age ≥18 years | Unfit for general anesthesia Polypectomy within last 6 months |
| Bilateral nasal polyps | Illness or medication that may interfere with the study Idiosyncratic reaction to corticosteroids |
| Asthma | Prohibited medication within wash-out period Participated in clinical trial within 30 days |
| Capable of recording daily symptom scores in diary | Pregnant or lactating women Women of child bearing potential not using adequate anti-contraceptive method |
| Capable of complying with dosing regimen | Study personnel or patients related to study personnel Patients not to be enrolled more than once |

Methods

Study design. This was a prospective 21-week single-centre study (visits 1–6) performed at the ENT and Pulmonary Departments of the Karolinska University Hospital. A randomized, double-blind, placebo-controlled phase of 14 weeks was included (visits 1–5). Between visits 5 and 6, all the patients received FPND. Thus, we define the two arms as the FPND group and the placebo + FPND group, respectively (Figs 1 and 2). The primary endpoint of this study was the change in the lower airway symptom scores (dyspnea and/or cough) after FESS, compared with before FESS.

The study protocol, the patient information, and consent forms, were reviewed and approved by the local independent ethics committee of the Karolinska Institute (Dnr 234:00) and the Swedish Medical Products Agency (MPA 151:384/01) prior to the enrollment of patients.

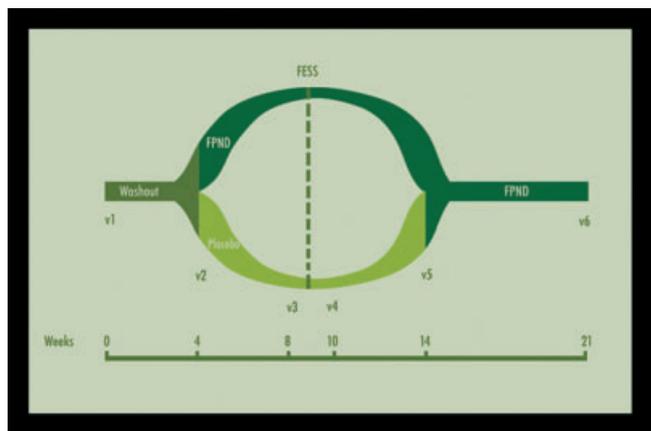


Figure 1. Study design. At visit 1, patients were evaluated by a pulmonologist and an ENT physician, and at visit 2 patients were randomized to FPND or placebo. Prior to surgery (FESS), patients were examined at visit 3 with postsurgical follow-up (nasal debridement) at visit 4. After visit 5, all patients received FPND treatment until visit 6 (end of study).

Treatment

Topical treatment. After a 4-week wash-out of nasal steroids at visit 2, the patients were randomized to either placebo or FPND 400 µg b.i.d for 10 weeks. Both placebo and FPND were produced by GlaxoSmithKline (GSK) Australia, and packed in Bad Oldesloe,

GSK Germany. The following batches were used throughout the study: Batch MR633560 (Dec. 31, 2002, Mar. 31, 2003) and MR63560-1 (Jul. 31, 2004).

Surgical treatment. The majority of FESS was performed by one of six ENT surgeons performing surgery in this study. All patients were under general anaesthesia. The procedure was tailored to the extent of the disease, with the removal of polyps, uncinectomy, exploration of ethmoidal bulla, and additional ethmoidal exploration, as indicated by clinical and CT scan findings. For subjects who had previously undergone FESS, the extent of surgery depended on clinical findings, and in some cases simple removal of polyps was sufficient.

Diary cards

Symptoms, PEFR, and as needed asthma medication. From the screening visit 1 to the end of the study, visit 6 (except visits 3–4), patients were asked to record symptom scores on a daily basis before going to bed, the morning and evening peak expiratory flow rate (PEFR, Personal Best®, Health Scan Products Inc., Cedar Grove, NJ, USA), as well as the daily use of short-acting β₂-agonists taken as needed. We calculated the mean daily symptom scores, the mean daily PEFR, and the mean number of inhalations with short acting β₂-agonists from the diary cards of the last 7 days prior to visit 2 (baseline recordings), and compared with the scores of the last 7 days prior to visits 3, 5, and 6. Adherence to the study treatment was reported in the nasal symptom score diary by the patients.

Nasal symptoms scores. Patients graded the symptoms of nasal congestion and rhinorrhoea, respectively, on a 0–3 scale (0 = no symptoms; 1 = mild symptoms/tolerable; 2 = moderate symptoms/still tolerable; 3 = severe symptoms/affects daily activity). The sense of smell was also graded on a 0–3 scale (0 = normal; 1 = mild reduction; 2 = moderate reduction; 3 = absent sense of smell).

Asthma symptoms score. Patients were asked about their asthma symptoms on a separate page: shortness of breath and cough. The symptoms were graded on a 0–3 scale (0 = no symptoms; 1 = mild symptoms/tolerable; 2 = moderate symptoms/still tolerable; 3 = severe symptoms/affects daily activity).

As needed β₂-agonists for asthma. Patients were instructed to use short-acting β₂-agonists as a needed asthma medication, and to register the number of inhalations in the diary. The frequency of inhalations was graded as follows: 0 inhalations = 0 points; 1–2 inhalations = 1.5 points; 3–5 inhalations = 4 points; > 5 inhalations = 5 points.

Clinical assessments

PNIF. Prior to a decongestant at visits 2, 3, 5, and 6, the best of three peak nasal inspiratory flow (PNIF) attempts was recorded, using an In-check™ Portable Inspiratory Flow-meter (Clemont Clark Int. (CCI), Harlow, UK).

Butanol threshold test of the olfactory function. Prior to a decongestant at visits 2, 3, 5, and 6, the olfactory threshold was determined using butanol in dilutions ranging from 4% to 0.000008%. The olfactory threshold was identified when the subject was able to distinguish the same butanol concentration from a blank control on five consecutive attempts (15, 16). The grading of this test is: normal olfactory function when the threshold is 7–14, hyposmia 3–6, and anosmia 0–2.

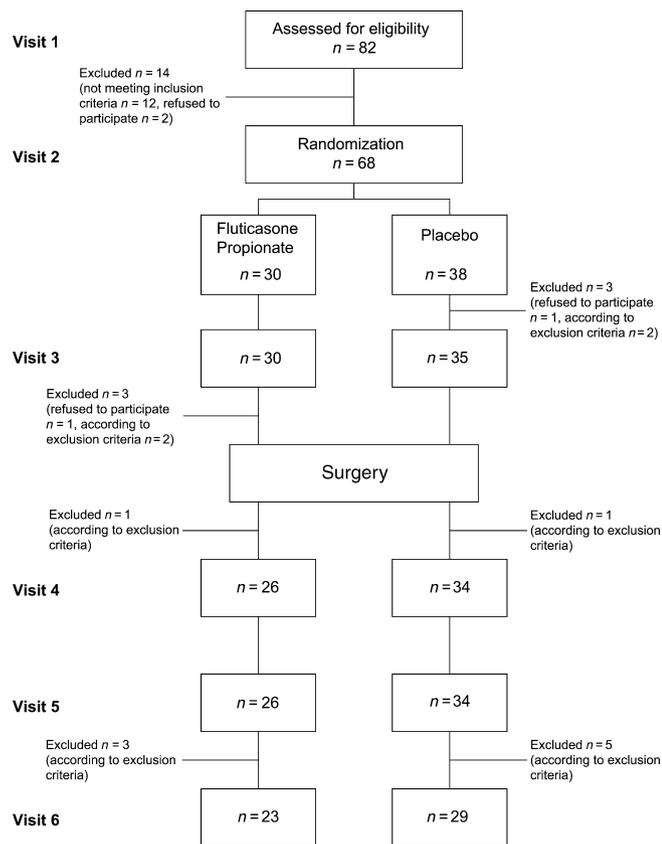


Figure 2. Study flow chart.

Nasal endoscopy. Nasal endoscopy was performed by otorhinolaryngologists on all visits and was scheduled after PNIF and butanol threshold test. The nasal cavity was decongested prior to endoscopy with Lidocaine hydrochloride + Nafazoline, 34 + 0.17 mg/ml (colored). The nasal polyp size was scored on a 0–3 scale (16) (0 = no polyps; 1 = polyps in the middle meatus, not reaching below the inferior border of middle turbinate; 2 = polyps reaching below the inferior border of the middle turbinate, but not the lower border of the inferior turbinate; 3 = polyps reaching lower than the inferior border of the inferior turbinate and/or medial to the middle turbinate).

Pulmonary function and bronchial histamine sensitivity. Lung function was measured as forced expiratory volume in 1 s (FEV₁) at visits 1, 2, 3, and 5 using a spirometer (Spirolab[®]; MIR, Rome, Italy), according to the standards laid down by the American Thoracic Society (17).

The bronchial responsiveness was measured with histamine inhalation challenge, and performed provided FEV₁ was 80% of predicted normal or more at visit 1, and not lower than 70% of predicted normal at visits 2, 3, and 5. Short-acting and long-acting β_2 -agonists were not allowed for 8 and 24 h, respectively, and anti-histamines were not allowed for 5 days prior to the challenge at visit 1. The challenge was performed by the use of a dosimeter-controlled jet nebuliser (Spira Elektro 2TM; Respiratory Care Center Ltd, Hemeenlinna, Finland) as previously described (18). Briefly, inhalation of diluent was followed by incremental doses of histamine phosphate (prepared at Norrlands University Hospital Pharmacy, Umeå, Sweden) administered at 3-min intervals. Three concentrations (1, 8 and 64 mg/ml) and 2, 4, and 8 breaths were used to create increasing doses (range: 14–3520 μ g). The test was terminated when FEV₁ had fallen at least 20% from the postdiluent baseline, or the maximum cumulative dose of histamine had been reached (7027 μ g). After the challenge, the patient was observed until FEV₁ had returned to within 90% of baseline. The histamine provocative dose causing a decrease of 20% in FEV₁ (PD₂₀FEV₁) values were calculated from the log-dose response curves by linear interpolation (18).

Statistical methods. All randomized patients were included in the statistical analyses, according to the intent-to-treat principle. For continuous variables and ordinal variables including symptom scores, changes from visit 2 to each subsequent visit were calculated, and between-groups comparisons were performed applying Wilcoxon–Mann–Whitney tests. Changes within groups were analyzed with Wilcoxon sign-rank tests. For the study of correlations, Spearman's rank-correlation coefficients were calculated. All statistical analyses were performed at a two-sided significance level of 0.05. Data are expressed as median (range). The power analysis was based on a frequency of improvement in the placebo group of 30% and in the treatment group of 60%, which implied that 78 patients should be studied to achieve a power of 80%, so that the null hypothesis ($p_1 = p_2$) will be falsified at a 5% significant level.

Safety. Safety variables included adverse events (AE), vital signs, and the results of physical examinations. Details of all the reported AEs were recorded throughout the study, with severity graded as mild, moderate, or severe. The relationship between AEs and the assigned treatment on the basis of the judgment of the investigator was considered: not, possibly, probably, or definitely related to the study medication or surgery. Vital signs were measured and physical examinations were carried out at visits 1, 5, and 6.

Results

Baseline data

For baseline characteristics see Table 1. All but one patient were on inhalation steroids at the beginning of the study. Thirty-seven patients (15 in the FPND group and 22 in the placebo + FPND group) performed histamine inhalation challenge provided FEV₁ was 70% of the predicted values at visits 2, 3, and 5.

Efficacy

Subjective and clinical variables before FESS (visit 3). *Nasal variables:* Within the FPND group, there was a statistically significant improvement in the symptom of the nasal congestion (median and range): –0.2 (–2.7 to 0.9), ($P = 0.005$), and PNIF, 15 (–40 to 120) ($P = 0.019$). Within the placebo + FPND group, no statistically significant improvement was seen for nasal congestion: 0 (–1.7 to 1.2) ($P = 0.14$) or PNIF: 10 (–60 to 90), ($P = 0.21$). However, between the FPND group and the placebo + FPND group, no statistically significant differences were found for these variables ($P > 0.05$). Regarding other variables (sense of smell, rhinorrhoea, butanol threshold test, polyp score), there were no statistically significant differences between treatment groups compared with visit 2 (Fig. 3).

Lower airway variables: There were no statistically significant differences within or between the FPND and placebo + FPND groups (visit 2 vs visit 3) for pulmonary function, bronchial histamine sensitivity, or diary card data (Fig. 4).

Subjective and clinical variables after FESS (visits 5 and 6). *Nasal variables – visit 5:* Changes in the following nasal variables showed statistically significant improvements (median and range) at visit 5 as compared with before surgery (visit 2) (Fig. 3).

The FPND group:

Congestion: –1.88 (–3.0 to 0.00) $P < 0.001$
 Rhinorrhoea: –1.0 (–2.29 to 0.29) $P < 0.001$
 PNIF: 40 (–20 to 180) $P < 0.001$
 Sense of smell: –1.00 (–3.00 to 0.80) $P < 0.001$
 Butanol threshold test: 2.00 (–3.00 to 8.00)
 $P = 0.004$

The placebo (+ FPND*) group:

Congestion: –1.95 (–3.0 to 0.20) $P < 0.001$
 Rhinorrhoea: –0.95 (–3.00 to 0.43) $P < 0.001$
 PNIF: 30 (–30 to 150) $P < 0.001$
 Sense of smell: –0.65 (–2.00 to 0.60) $P < 0.001$
 Butanol threshold test: 0.50 (–5.00 to 10.00)
 $P = 0.002$

*This is a placebo group at visit 5.

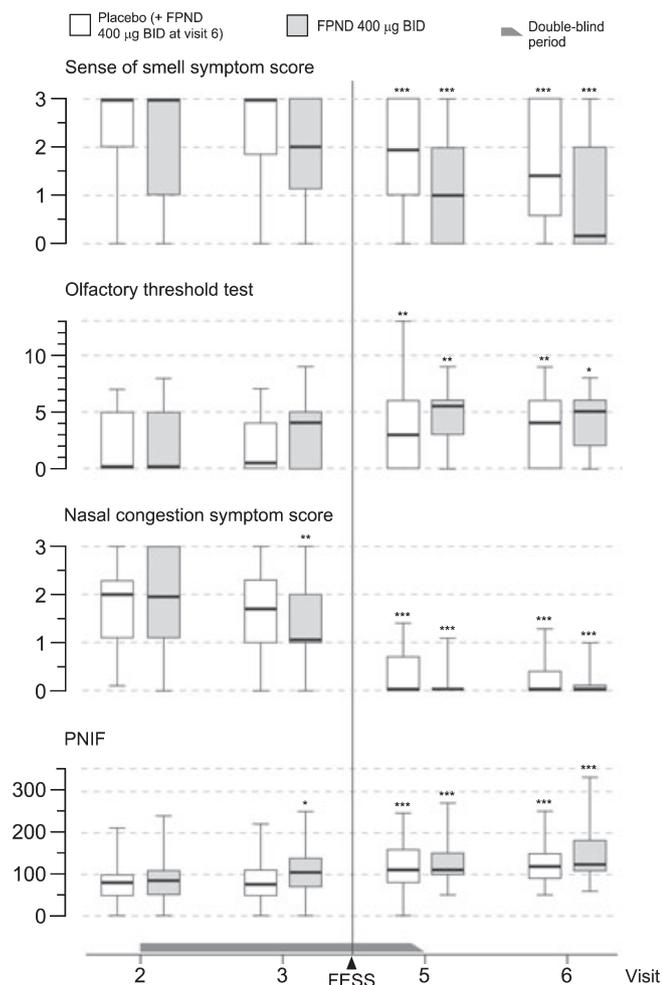


Figure 3. Nasal variables. FESS reduced nasal symptoms and improved olfaction as well as PNIF. Box-whisker plots by treatment group and visit. Data are presented as median, 25% and 75% percentiles, minimum and maximum values. Statistically significant changes within groups from visit 2 are indicated: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. There were no statistically significant differences between the two treatment groups.

Nasal variables – visit 6: These are the corresponding changes in the nasal variables at visit 6 as compared with before surgery (visit 2).

The FPND group:

Congestion: -1.81 (-3.00 to 0.00) $P < 0.001$
 Rhinorrhoea: -1.0 (-2.43 to 0.40) $P < 0.001$
 PNIF: 50 (-10 to 150) $P < 0.001$
 Sense of smell: -1.00 (-3.00 to 0.30) $P > 0.001$
 Butanol threshold test: 0.50 (-4.00 to 7.00)
 $P = 0.015$

The placebo + FPND group:

Congestion: -2.00 (-3.0 to 0.30) $P < 0.001$
 Rhinorrhoea: -1.00 (-2.43 to 0.40) $P < 0.001$
 PNIF: 50 (-20 to 150) $P < 0.001$

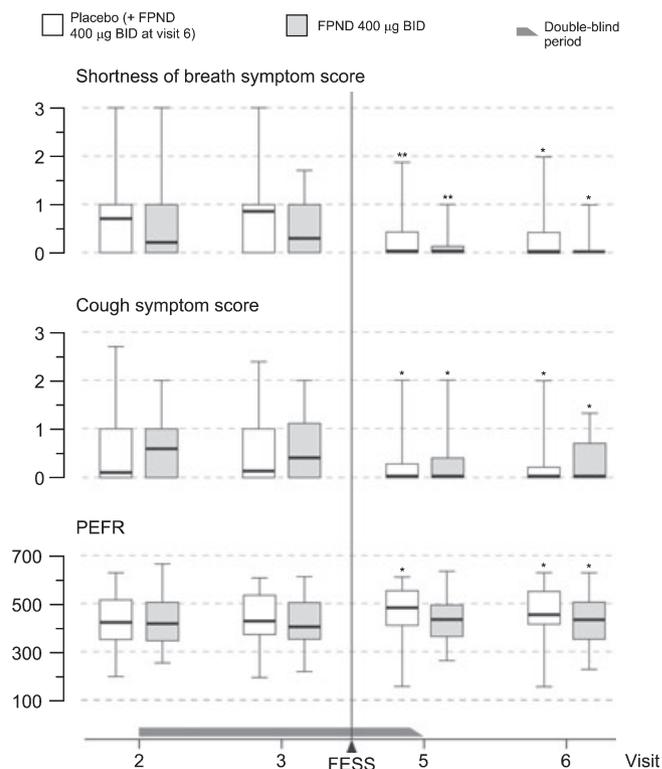


Figure 4. Lower airway variables. FESS reduced asthma symptoms and improved PEFR. Box-whisker plots by treatment group and visit. Data are presented as median, 25% and 75% percentiles, minimum and maximum values. Statistically significant changes within groups from visit 2 are indicated: * $P < 0.05$; ** $P < 0.01$. There were no statistically significant differences between the two treatment groups.

Sense of smell: -0.85 (-3.00 to 0.60) $P < 0.001$
 Butanol threshold test: 0.50 (-2.00 to 6.00)
 $P = 0.001$

However, there were no statistically significant differences in the changes in these nasal parameters between the FPND and the placebo + FPND groups at visit 5 as well as at visit 6.

Lower airway variables – visit 5: Changes in the following lower airway variables showed statistically significant improvements (median and range) at visit 5 compared with before surgery (visit 2) (Fig. 4).

The FPND group:

Shortness of breath: -0.05 (-3.0 to 0.10) $P = 0.001$
 Cough: -0.22 (-1.57 to 1.00) $P = 0.011$

However, PEFR: 6.0 (-40 to 102) $P = 0.103$, FEV₁: 0.04 (-0.35 to 1.19) $P = 0.619$, and PD₂₀: -48.00 (-1651.0 to 726.00) $P = 0.450$, did not improve significantly.

The placebo (+ FPND) group:*

Shortness of breath: -0.05 (-2.14 to 1.00) $P = 0.002$
 Cough: 0.00 (-1.71 to 0.90) $P = 0.020$
 PEFR: 19 (-87 to 94) $P = 0.010$

However, FEV₁: 0.08 (−0.51 to 0.67) $P = 0.128$, and PD₂₀: 59.50 (−1564.0 to 1153.00) $P = 0.243$, did not improve significantly. *This is a placebo group at visit 5.

Lower airway variables – visit 6 (no spirometry or bronchial histamine challenge test): Given below are the corresponding changes in the lower airway variables at visit 6 compared with before surgery (visit 2) were:

The FPND group:

Shortness of breath: −0.05 (−3.00 to 0.70) $P = 0.010$

Cough: 0.00 (−1.40 to 1.00) $P = 0.029$

PEFR: 20 (−129 to 96) $P = 0.022$

The placebo + FPND group:

Shortness of breath: −0.10 (−3.00 to 1.10) $P = 0.007$

Cough: 0.00 (−1.86 to 1.00) $P = 0.017$

PEFR: 11 (−45 to 123) $P = 0.031$

However, there were no significant differences between the two treatment groups in changes these lung function variables at visit 5 or visit 6.

As needed β_2 -agonists: There were no statistically significant changes in the use of needed β_2 -agonists within each treatment group or between the two treatment groups from visits 2 to 5.

Correlations: As a *post hoc* analysis, both study groups were included in the following correlation calculation to evaluate the statistically significant improvement in butanol threshold test in relation to the improvement in the subjective symptom sense of smell: as for the sense of smell vs butanol threshold test, statistically significant correlations were found at visits 2 ($R = -0.81$, $P < 0.001$), 3 ($R = -0.85$, $P < 0.001$), 5 ($R = -0.71$, $P < 0.001$), and 6 ($R = -0.71$, $P < 0.001$).

Safety. In this study, FPND was well-tolerated. Seventy-nine AEs, which may or may not have been related to the study medication or surgery, were reported in 40 of the 68 subjects included in the safety analysis. Twenty-two of these were FPND recipients (55%) and 18 were placebo + FPND recipients (45%). Fifty-five (70%) of the AEs were considered by the investigators to be of mild, 18 (23%) of moderate, and six (7%) of serious intensity. Of the five serious AEs reported, one was judged to be related to surgery. Three subjects in the FPND group and four in the placebo + FPND group were discontinued because of AEs, and in five of these seven patients, the reason for discontinuation was OCS treatment because of asthma exacerbation or onset of acute bacterial rhinosinusitis (Fig. 2).

The two most common causes for exclusion before randomization (between visits 1 and 2) were: severe nasal symptoms during the wash-out and no ethmoid polyps according to the presurgery CT-investigation (three patients respectively) (Fig. 2).

The two most common reasons for exclusion after randomization (visits 2–6) were: acute respiratory tract

infection, i.e. pneumonia, bacterial sinusitis, or asthma exacerbations leading to OCS treatment or inhibition of surgery, and too many missed doses of study medication (5 and 4 patients respectively) (Fig. 2).

Six patients in the FPND group and two in the placebo + FPND group reported nasal bleeding, and one of these were judged by the clinician to be related to FESS.

No clinically relevant changes in vital signs or physical examinations were noted in either of the treatment groups, and no death was reported during this study.

Discussion

In this prospective 21-week study, without a nonsurgical control, of 68 patients, we have found that FESS in patients with nasal polyposis and concomitant asthma had a statistically significant and clinically relevant effect on subjective and clinical nasal as well as on lower airway parameters.

Early studies observed that surgery such as polypectomy, a removal of polyps from the nasal cavity only by a snare, could cause deterioration in lower airway disease (11, 19). Even in this millennium the question still remains about the possible benefits from surgery – which today has evolved to FESS, a functional endoscope-guided removal of nasal as well as ethmoid polyps with clearance of mucous drainage and aeration of the sinuses – in nasal polyposis patients with concomitant asthma. Batra et al. (20) reported a significant improvement in lung function (FEV₁) and a reduction in OCS use after FESS in 17 patients with nasal polyps and concomitant OCS-dependent asthma. In a series of 13 patients with nasal polyposis and concomitant asthma, Uri et al. (21) reported that FESS did not improve the asthma state in patients with massive nasal polyposis. However, a statistically significant decrease was documented for OCS and bronchodilator inhaler usage (21). In a subgroup of 35 patients with nasal polyposis and concomitant asthma, Ragab et al. (22) reported that FESS had a subjective and objective tendency for asthma improvement, however, statistically nonsignificant. Our interpretation is that, although the statistical power has been low, these findings point out the positive effects of FESS on asthma in nasal polyposis.

In this study, the largest of its kind to our knowledge, we have included patients with stable persistent asthma controlled on inhaled corticosteroids, but not requiring OCS, with concomitant nasal polyposis and symptom scores of various degrees.

In clinical practice, FESS is often reserved for patients with nasal polyposis who do not respond sufficiently well to full nasal medical treatment, irrespective of the lower airway status. We proceeded to surgery 4 weeks after treatment with either FPND or placebo, across the severity of nasal polyp size, obstruction, and symptoms, i.e. we have operated on the whole range of nasal polyposis patients, from severe to mild, our hypothesis

being that FESS is an anti-inflammatory treatment, and the effect in the upper airway results in the reduction in lower airway inflammation. Despite the fact that the asthma of the patients was well controlled with inhaled corticosteroids, we noted statistically significant improvements in mean and median asthma symptom scores, daily PEFR (Fig. 4) with no increase in the use of β_2 -agonists.

Given that all but one subject were on inhaled corticosteroids throughout the study and all displayed bronchial hyperresponsiveness to histamine in mild-to-moderate range, the lack of effect of FESS on this parameter and FEV₁ was perhaps not surprising. Direct challenges are also not very responsive to anti-inflammatory treatment, and may take longer time to show improvement.

We found that FESS, performed by a few ENT surgeons in our single center, had statistically significant effects on nasal-, as well as lower airway-, subjective- as well as objective parameters. There are only a few studies of high evidence level that have shown a significant effect on nasal subjective and objective parameters (16, 20, 22, 23), but still FESS is considered the preferred method in treating patients with nasal polyposis, not responding to optimized medical therapy. However, until now, no major study has been performed that demonstrates objective effects on the sense of smell after FESS in nasal polyposis (24). In this study, we found statistically significant improvements in both objective (butanol threshold test) as well as subjective parameters of olfactory function (Fig. 3), including a statistically significant correlation between the two after the endoscopic surgery. We believe that these findings of the olfactory effects are in accordance with the clinical impression of the most experienced sinus surgeons, and may be a new regime in treating anosmia/hyposmia in patients with nasal polyposis without using systemic steroids.

Earlier studies have shown that topical corticosteroid treatment, FPND, as well as Mometasone Furoate Nasal Spray, in nasal polyposis had statistically significant and clinically relevant effects on polyp size, congestion/obstruction, and sense of smell (14, 25). In the 14-week randomized, double-blind, placebo-controlled phase of our study, we did not find any statistically significant effects of FPND compared with placebo on any of the primary or secondary endpoints. However, as we could detect a statistically significant improvement within the FPND group in nasal congestion scores and PNIF already before FESS at visit 3, after only 4 weeks of treatment, these results indicate that FPND could have

an effect on these parameters although the treatment time was too short to reveal the differences between the groups. Consequently, our interpretation is that potentially long-term positive effects on upper and lower airway parameters by FPND were overshadowed by the effects of FESS. Four weeks of topical treatment was in our study probably too short a pre-FESS period (Fig. 1) to detect significant benefits of FPND 400 μ g b.i.d. on upper and lower airway parameters.

Conclusion

In conclusion, our prospective study supports the hypothesis that FESS has beneficial effects on asthma in patients with nasal polyposis. Functional endoscopic sinus surgery improved asthma symptoms as well as PEFR and olfaction. We believe that these data indicate that FESS could be considered early in the natural course of the disease with concomitant asthma, and a second-line treatment in patients with reduced sense of smell and nasal polyposis. In our study, a 4-week treatment period with FPND 400 μ g b.i.d. seems to be too short to have an effect on upper and lower airway inflammation. Functional endoscopic sinus surgery seems to be a potent anti-inflammatory treatment, and probably overshadows the effects of FPND.

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Conflict of Interests

After the end of this study Petter Olsson has been employed by Schering-Plough AB, Sweden.

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