

Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery

Albertien A.C. Aukema, MD,^a Paul G.H. Mulder, PhD,^b and Wytse J. Fokkens, MD, PhD^c Rotterdam and Amsterdam, The Netherlands

Background: Steroid treatment is the mainstay of therapy for nasal polyps and rhinosinusitis. Oral steroids have considerable systemic side effects, and nasal sprays do not sufficiently reach the middle meatus, where polyps originate. Nasal drops might be a more useful formula to deliver steroids into the middle meatus. **Objective:** We sought to investigate whether treatment with fluticasone propionate nasal drops (FPNDs) can reduce the need for surgery, as measured by signs and symptoms of nasal polyposis and chronic rhinosinusitis, in patients who are on the waiting list for functional endoscopic sinus surgery (FESS). **Methods:** Fifty-four patients (28 male) with severe nasal polyposis, chronic rhinosinusitis, or both indicated for FESS were included in a 12-week, double-blind, placebo-controlled study. Use of intranasal steroid spray was stopped at least 4 weeks before randomization. Signs and symptoms were recorded before, during, and at the end of the study period. At the end of the study, a computed tomographic scan was performed, and the need for operation was reassessed by using a standardized scoring method.

Results: FESS was no longer required in 13 of 27 patients treated with FPNDs versus 6 of 27 in the placebo group ($P < .05$). Six patients from the placebo group dropped out versus 1 from the FPND group. Symptoms of nasal obstruction, rhinorrhea, postnasal drip, and loss of smell were reduced in the FPND group ($P < .05$). Peak nasal inspiratory flow scores increased significantly ($P < .01$). Polyp volume decreased in the FPND group ($P < .05$), and computed tomographic scores improved in both groups ($P < .05$).

Conclusion: Treatment with FPNDs in patients indicated for FESS can reduce the need for surgery. (*J Allergy Clin Immunol* 2005;115:1017-23.)

Key words: Nasal polyps, rhinosinusitis, fluticasone propionate, Nasules, steroid, local, treatment, adult, sinus surgery, computed tomography

Abbreviations used

CT: Computed tomography
FESS: Functional endoscopic sinus surgery
FPANS: Fluticasone propionate aqueous nasal spray
FPND: Fluticasone propionate nasal drop
PNIF: Peak nasal inspiratory flow
VAS: Visual analogue scale

Nasal polyps and chronic rhinosinusitis have long been known as chronic inflammatory diseases of the nasal mucosa. The cause is yet unknown, and both diseases appear to be extremes of one entity, with most patients showing a mix of polyps and chronic rhinosinusitis. Treatment has long been aimed at surgery, removing polyps and diseased mucosa and restoring aeration of the mucosa and sinuses. However, polyps have a strong tendency to recur, and therefore repeated surgery is often needed. An infectious component is often present for which antibiotic treatment might be needed, but the inflammatory reaction is most prominent in both diseases.^{1,2} Systemic anti-inflammatory treatment with a short course of high-dose prednisolone has resulted in subjective and objective improvement, with involution of nasal polyps, especially in the frontal and sphenoid sinuses, but recurrence was seen after 5 months.³ Therefore long-term treatment, preferably without systemic side effects, would be more adequate. Intranasal corticosteroids have become widely used during the last decades, having the advantage of local action without the systemic side effects of steroids. Earlier studies have already demonstrated the beneficial effects of intranasal corticosteroid treatment on polyp volume, peak nasal inspiratory flow (PNIF), and symptom scores.^{4,5} Lund et al⁴ have demonstrated that fluticasone propionate aqueous nasal spray (FPANS) can reduce polyp size and symptoms caused by nasal polyps, but in this study no effect on need for surgery was noted. Nasal sprays, however, do not sufficiently reach the middle meatus, from which polyps originate, whereas nasal drops do.⁶ Thus more effective treatment would be expected with the use of nasal drops. Betamethasone drops have effectively been used for the treatment of nasal polyps, but there was considerable suppression of the hypothalamic-pituitary-adrenal axis.⁷ Recently, fluticasone propionate nasal drops (FPNDs),

From the Departments of ^aOtorhinolaryngology and ^bEpidemiology and Biostatistics, Erasmus University Medical Centre, Rotterdam, and ^cthe Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam. Supported by GlaxoSmithKline.

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Reprint requests: Albertien A. C. Aukema, MD, Department of Otorhinolaryngology, Erasmus MC Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: aaukema@hotmail.com.

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TABLE I. Inclusion and exclusion criteria

Inclusion criteria	Age 18-70 y Recent CT scan with a score of ≥ 3 on one side Prior treatment corticosteroid spray ≥ 3 mo Requirement for surgical intervention on the basis of standardized scoring method Written informed consent
Exclusion criteria	Systemic steroids ≤ 4 wk before the study Intranasal medication other than trial medication Recent rhinosurgery (≤ 6 wk before visit 1) Serious-unstable concurrent disease Cystic fibrosis Medication affecting nasal mucosa (eg, cyclosporine) Pregnancy or possibility to become pregnant during study Inability to attend all visits or follow instructions

Nasules (GlaxoSmithKline, Brentford, Essex, United Kingdom), have become available for the treatment of polyposis. These have a low bioavailability and fixed dosage volume to achieve controlled administration.⁸ Nasal corticosteroid drops have shown decreases in polyp volume and symptoms, as well as increases in PNIF.⁹

This double-blind placebo-controlled study with FPNDs was set up to evaluate the effect on signs and symptoms in patients who are on the waiting list for functional endoscopic sinus surgery (FESS) and to determine whether treatment can postpone or prevent the need for surgery.

METHODS

Patients

Patients with polyposis, chronic rhinosinusitis, or both who were on the waiting list for FESS were screened for enrollment. Indications for surgery were complaints of decreased nasal passage, rhinorrhea, and loss of smell in combination with operable lesions on computed tomography (CT). Inclusion and exclusion criteria are displayed in Table I. Patients had all been treated with adequate dosages of intranasal corticosteroid spray for at least 3 months without a satisfactory result. The local medical ethics committee approved the study, and all patients provided informed consent before enrollment.

Medications

FPNDs, 400 μ g, or placebo was delivered in Nasules containing 0.4 mL for 1-time use. Nasules are designed to release one half of the content when squeezed once. Patients and investigators were blinded to the contents throughout the study. Patients used Nasules once daily at night. They were instructed to lie on their back with their head hanging down in a vertical position over the edge of the bed while administering half of the content to each nostril. They then remained in this position for 2 minutes. Patients were told to start with the left nostril one day and the right nostril the other day and alternate. At visit 2, the method of administration was verified by the investigator, ensuring sufficient vertical head position. All distributed Nasules were returned used or unused and counted later by a different investigator.

Study design

The study design is displayed in Fig 1. All investigations were carried out by one investigator (AA). In short, intake was done during

visit 1. A recent CT scan was scored, and subjective and objective measurements were made. Patients were instructed in how to use Nasules and a practice package placebo-Nasules was distributed. Intranasal steroids had been stopped at least 2 weeks before intake, hence at least 4 weeks before randomization at visit 2. After 2 weeks, they returned for visit 2, encompassing subjective (visual analogue scale [VAS]) and objective (PNIF and polyp size) measurements and nasendoscopy. Double-blind randomization to FPNDs or placebo took place after the investigator had observed and approved the administration method. Medications were numbered by means of computerized randomization and were assigned in numeric order. At visits 3 and 4, 2 and 6 weeks into the medication period, respectively, subjective and objective measurements were repeated, including nasendoscopy. At visit 5, after 12 weeks of treatment, a final CT scan was performed, and all subjective and objective measurements were done. In the intent-to-treat population, the need for FESS was assessed by using a standardized table (described later) and clinical observation. Randomization codes were not disclosed until a year after all patients had finished the study.

VAS

Symptoms were scored on a VAS of 0 to 100 mm, with 0 mm being "no complaints whatsoever" and 100 mm being "worst imaginable complaints." Six VAS scores concerning the following symptoms were noted: rhinorrhea, mucus in the throat, nasal blockage, loss of smell, and twice the score of facial pain. Only patients with a cumulative score of 200 mm or more on these 6 scales were included in the study. Headache was also scored but not included in the inclusion criteria because it is generally not related to sinus problems. Facial pain (ie, in the area where no hair grows and around the eyes and nose) was counted twice because this symptom was considered most bothering. At each clinical visit, patients were asked to indicate the severity of their symptoms.

Objective measurements

The nasal passage was assessed with PNIF by using a Youlten Peak Nasal Inspiratory Flow Meter (Clement Clark International Ltd, Aired house, Essex, United Kingdom). The highest score of 3 maximal inspiratory efforts through the nose was noted.

A CT scan of the nose and paranasal sinuses was performed before the study in all patients; almost all were made less than 3 months before visit 1. In most patients, a CT scan was made at the end of the study. The CT scan was scored with the system proposed by Lund and Mackay (Table II).¹⁰

Polyp size was estimated by the investigator after nasendoscopy, indicating the volume of the middle and inferior meatus to the left and right that was occupied by polyp tissue on a VAS.

Standardized table

At the end of the study, the necessity of FESS was reassessed in 2 ways: a standardized table (Table III), taking into account patients' symptoms and CT score, and a clinical evaluation. The table was designed to provide an objective tool to decide whether surgery was indicated. In a normal situation we decide on surgery if there is a lesion to remove and if the patient has complaints. These 2 items are translated into a table: total VAS symptom score and CT score. There is an area in which no hard yes or no can be provided (shown in the table with an asterisk). In these cases decision on surgery was made on purely clinical grounds, as in the normal situation.

Statistics

Statistical analyses were performed with SPSS for Windows, version 9.0, and SAS, version 6.12. Treatment effects were estimated by comparing the outcome variables in the FPND group with those in

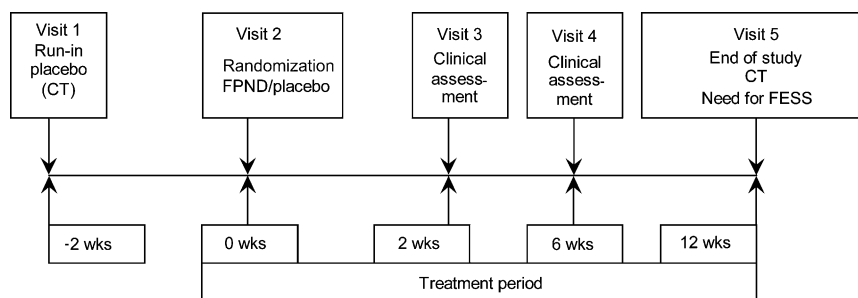


FIG 1. Study design.

TABLE II. CT scoring table

For each sinus	Score both sides
Maxillary	0 = No abnormality 1 = Partial opacification 2 = Complete opacification
Anterior ethmoid	
Posterior ethmoid	
Sphenoid	
Frontal	Max = 20 points 0 = Open 2 = Obstructed
Subtotal	
Ostiomeatal complex	Max = 24 points
Total	

TABLE III. Standardized scoring table

Indication for FESS?	CT score = 0	CT score = 1 or 2	CT score ≥ 3
0 < total VAS symptom score ≤ 100	No	No	No
100 < total VAS symptom score ≤ 200	No	No	*
Total VAS symptom score > 200	No	*	Yes

*"Undecided": indication for surgery was dependent on clinical findings.

the placebo group. Three repeated measurements of the outcome variables during treatment were considered simultaneously; the baseline measurement at the start of treatment was included in the analysis as a given covariate. Mixed-model ANOVA for repeated measures was used to estimate the effect of treatment, time, and their interaction on the outcome variable adjusted for the baseline value of that outcome variable. The treatment-by-time interaction allowed the treatment effect to vary (eg, increase or decrease) in time. In this analysis no structure was imposed on the (co)variances of the residual error term. Baseline-adjusted mean levels and differences between the treatment groups and their SEs and CIs were estimated.

For those variables that could not be analyzed with mixed-model ANOVA because of severe nonnormality of the residual error term, change from baseline was analyzed nonparametrically by categorizing it in 3 ordinal levels (worse, same, and better) and comparing this ordinal score between the treatment groups by using a χ^2 trend test per period. The Mann-Whitney test was used to test a difference in CT score between treatment groups at the end of the study. The Wilcoxon signed-ranks test was used to test changes in CT score from baseline in either treatment group. To test differences in proportion of subjects requiring FESS between the treatment groups, the Pearson χ^2 test was used.

All tests were performed with a significance level of .05.

The power analysis of this study was based on the need for FESS. With 27 patients per group, a difference of 40 percentage points in eventual need of FESS (60% in the placebo group and 20% in the FPND group) is detectable with 80% power, given a test size of 0.05 (2-sided).

RESULTS

Fifty-four patients (28 male patients; age range, 18-68 years; median age, 44 years) were randomized, 27 to FPNDs and 27 to placebo. Patients' characteristics are

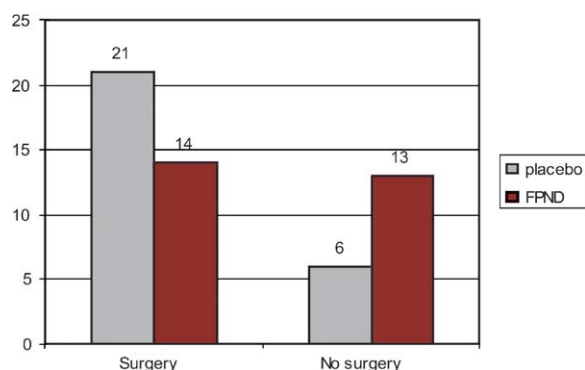
displayed in Tables IV and V. At the end of the study, 6 patients of the placebo group and 1 of the FPND group had dropped out. Of the placebo group, 5 patients dropped out because they had a lot of complaints and did not want to complete the study. Three were prematurely scheduled for FESS (2 after 6 weeks and 1 after 2 weeks of treatment). Two patients resumed intranasal corticosteroids (after 4 and 8 weeks of treatment). One patient received oral steroids from her pulmonologist because she did not tolerate inhaled steroids (after 8 weeks of treatment) and was scheduled for FESS as well. The one dropout in the FPND group failed to return for the last visit, despite repeated requests. At the second-to-last visit, he was not much improved compared with inclusion, and he finally underwent surgery. There were 2 serious adverse events. First, an exacerbation of frontal sinusitis leading to osteomyelitis occurred in a patient from the placebo group who had frontal osteomyelitis earlier. Hospital admission and treatment with intravenous antibiotics settled the disease. A relationship with trial medication seemed not to be plausible. Second, a prostate carcinoma was diagnosed in a patient of the FPND group. This lacked obvious relationship with the trial medication. Neither incident caused withdrawal of the patient. Nonserious adverse events that might have been related to the trial medication were reported by 6 patients: 3 had some degree of nose bleeding (all FPND group), 2 reported throat ache (1 on placebo and 1 on FPNDs), and 1 experienced pain in the nose after taking the (placebo) medication.

Indication for FESS

All patients who entered the study had indications for FESS. In the standardized table (Table III) all patients had

TABLE IV. Patients' characteristics per group

	Placebo (n = 27)	FPNDs (n = 27)
Median age (min-max)	47 (30-63)	41 (18-69)
Female	15 (56%)	11 (41%)
Current smokers	4 (15%)	2 (7%)
Former smokers	11 (41%)	11 (41%)
Atopic (increased specific serum IgE)	7 (26%)	5 (19%)

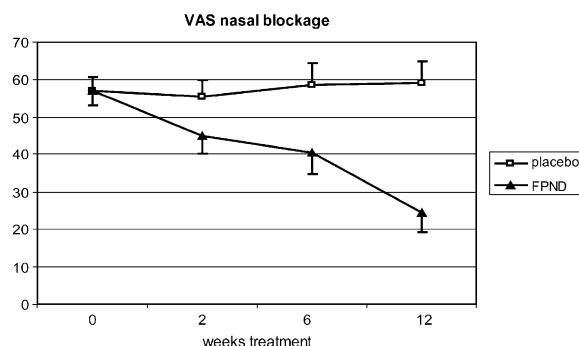
**FIG 2.** Number of finally performed FESSs.

a total VAS score of more than 200 and a CT score of 3 or more on one side. At the end of the study, need for FESS was reassessed by using the standardized table, but the final decision to perform surgery was made on clinical grounds on the basis of the opinion of the patient and the investigator, as well as that of the treating specialist, as is the usual practice. In the placebo group there were 6 dropouts, of which 3 underwent FESS shortly after dropping out. In the FPND group the one dropout underwent surgery when he finally returned to the clinic. In the placebo group one patient had no indication for FESS according to the standardized table on the basis of reduction of symptoms, and 16 still had indications for FESS. In 4 patients the result of reassessment was "undecided," which meant that the decision to operate was made on clinical grounds: 3 of these 4 patients did not need surgery. In the FPND group 9 patients had no more indications for FESS: 7 because their symptoms were diminished to less than 200 on cumulative VAS scales and 2 because their CT score was reduced to less than 3 points also. Eleven patients still had an indication for FESS, and 6 were "undecided." Four of these did not need FESS after clinical evaluation. Within the nondropout group, there were significantly more patients in the FPND group that had no FESS indication than in the placebo group ($P = .028$).

In the intent-to-treat population 13 patients in the FPND group did not undergo FESS but received open treatment with FPNDs. Fourteen patients in the FPND group did undergo FESS. In the placebo group only 6 patients did not undergo surgery, whereas 21 underwent FESS (Fig 2). This difference was significant ($P = .046$).

TABLE V. Number of previous sinus surgeries per group

Previous sinus surgeries	Placebo	FPNDs
0	3	6
1	11	6
2	8	5
3	1	4
≥4	4	6
	27	27

**FIG 3.** Nasal blockage: baseline-adjusted means with SEs as estimated by visit and treatment group by using mixed-model ANOVA.

VAS scores

The results below are based on mixed-model ANOVA, with the baseline measurement of the outcome variable at hand as a covariate. If the treatment-by-time interaction was significant, the significant treatment effects are presented per visit; otherwise, one overall effect estimate is presented.

Figs 3 to 5 represent the baseline-adjusted means with SEs of various outcome variables per treatment group and per visit, as estimated in the mixed-model ANOVA. Throughout the study, almost all recorded symptoms showed better results in the actively treated group than in the placebo group.

Nasal blockage (Fig 3). The treatment-by-time interaction was significant ($P = .020$): the treatment effect builds up over time. Mean scores in the FPND group were significantly lower at visits 4 and 5, with a mean of -18 (95% CI, -35 to -1.4 ; $P = .034$) and -34 (95% CI, -51 to -18 ; $P = .0001$), respectively, compared with those in the placebo group.

Rhinorrhea (Fig 4). No significant treatment-by-time interaction was seen ($P = .69$). The overall mean score in the FPND group was lower than in the placebo group (-16 ; 95% CI, -27 to -5.8 ; $P = .003$).

Facial pain (data not shown). There was no significant difference between groups concerning facial pain. Both groups tended to decrease from median around 50 to median about 30 (on a scale of 100), with a widespread range of facial pain ($P = .05$ at visit 5).

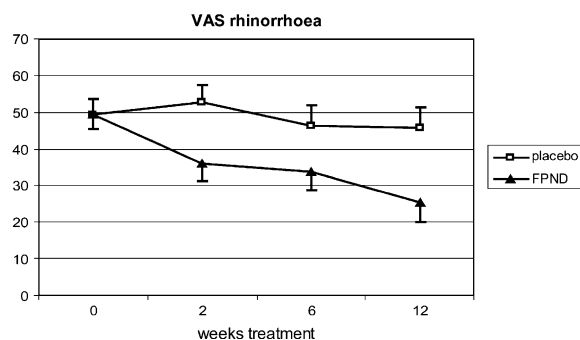


FIG 4. Rhinorrhea: baseline-adjusted means with SEs as estimated by visit and treatment group by using mixed-model ANOVA.

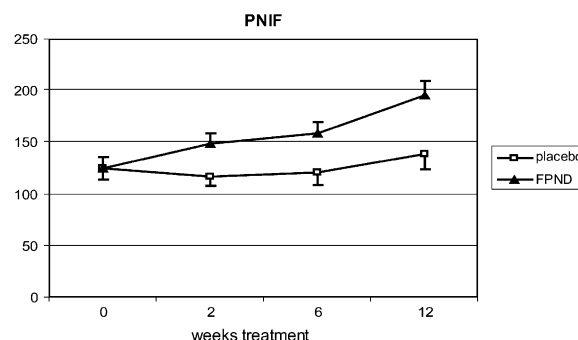


FIG 5. PNIF: baseline-adjusted means with SEs as estimated by visit and treatment group by using mixed-model ANOVA.

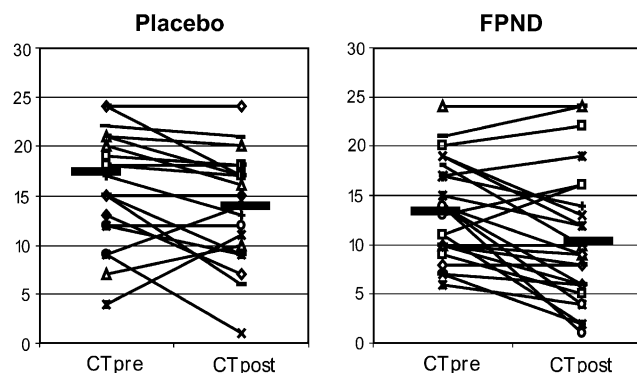


FIG 6. CT scores per subject before and after treatment. Bars represent median scores per group.

Mucus in throat (data not shown). No significant treatment-by-time interaction was seen ($P = .53$). The overall mean score in the FPND group was lower than that in the placebo group (-12 ; 95% CI, -22 to -1.1 ; $P = .031$).

Loss of smell (data not shown). There was a wide range in loss-of-smell reports. At visit 5, there was a reduction in loss of smell in the FPND group compared with that in the placebo group when corrected for baseline ($P = .004$).

Headache (data not shown). There was no significant difference between groups concerning headache. The degree of headache was low (median, <20 in both groups; $P = .76$).

Objective measurements

PNIF (Fig 5). No significant treatment-by-time interaction was seen ($P = .52$). The overall mean PNIF value was higher in the FPND group compared with that in the placebo group ($+41$; 95% CI, 17 - 66 ; $P = .001$).

Polyp volume (data not shown). No significant treatment-by-time interaction was seen ($P = .53$). The estimated polyp volume by the investigator was reduced in the FPND group compared with in the placebo group (overall mean of -24 ; 95% CI, -48 to -1.4 ; $P = .038$).

CT score (Fig 6). CT scores at both visits 2 and 5 in the FPND group were lower than in the placebo group (mean, 10.5 [SD 1.30] vs 14.2 [SD 1.29]; $P = .031$). However, the

change in CT score was not significantly different between the groups (mean, -2.92 [SD 4.48] in the FPND group vs -1.90 [SD 4.09] in the placebo group) but was significant compared with baseline values (FPNDs, $P = .005$; placebo, $P = .043$).

Posttreatment follow-up

Median follow-up time in the intent-to-treat population was 20 months, with 3 patients lost to follow-up (2 in the placebo group and 1 in the FPND group). Minimum follow-up time was 6 months. During this follow-up, 3 patients from the FPND group who had no FESS indications at the study's end had surgery after 6 months or more. One patient who had an indication for FESS did not undergo surgery. From the placebo group, 2 patients who had indications for FESS did not undergo surgery in our clinic: 1 refused surgery, and 1 was lost to follow-up. Hence during follow-up, 11 of 26 FPND-treated patients did not need FESS versus 6 of 21 placebo-treated patients.

DISCUSSION

This study was performed to evaluate the requirement for FESS, objectified by patients' symptoms on VAS and findings at CT scan after treatment of nasal polyps and chronic rhinosinusitis with intranasal corticosteroid drops.

It confirms the results of earlier studies, showing that FPNDs decrease the signs and symptoms of polyposis. Moreover, this study shows that treatment of nasal polyps with FPNDs, 400 μ g once daily, can reduce the need for surgery, as was not found in the study performed by Lund et al⁴ with FPANS, 200 μ g twice daily, in a comparable patient group. Our patients all had already received treatment with intranasal corticosteroid spray for at least 3 months before they entered the study. This suggests that FPNDs might be more effective than FPANS in reducing the need for surgery. The route by which medication is administered can explain this finding. Patients were in the head-down position when they used the drops and remained in this position for 2 minutes. Nasal sprays are mainly delivered at the nasal septum and anterior head of the inferior turbinate, and only a small portion reaches the middle meatus, where polyps originate.⁶ Nasal drops, however, if instilled in the right way (head down, roll to side, maintain position >1 minute), reach the middle meatus and ethmoid region.⁶ The dosage in this study (400 μ g once daily) was half the dosage that is now commercially available and advised (400 μ g twice daily). The study by Penttila et al¹¹ suggests that there is a dose-related response to FPNDs, with significantly better results in polyp decrease and PNIF scores with high dosages. Our study indicates beneficial effects and reduction in need for surgery already in lower doses of FPNDs. Further studies are needed to decide on optimal dosage.

Most of our patients had already undergone sinus surgery (Table V), suggesting that we are treating a relatively therapy-resistant population. On the other hand, if a proper ethmoidectomy has been performed, there is more chance for the medication to reach deep into the ethmoid and be more effective.

Symptoms rated by the patients were reduced for nasal blockage, rhinorrhea, mucus in the throat, and loss of smell, but symptoms of facial pain and headache were not different in both groups. Facial pain (ie, pain where no hair grows) was recorded separately to have an impression of pain caused by the sinuses, which might be influenced by treatment. Headache refers to pain where hair grows, not in the paranasal region, caused by other factors, but apparently treatment did not affect either of these pain symptoms. Kenny et al¹² report that there were several sinus symptoms correlating to severity of disease at CT scan but that both headache and facial pain are not reliable predictors of CT scan findings supporting the diagnosis rhinosinusitis. Our data contain facial pain scores that were not different between groups or before and after treatment and therefore will probably not interfere with the final outcome.

For scoring polyp size, we estimated polyp volume in the middle and inferior meatus on both sides. Johansson et al¹³ describe that reproducibility is poor with more observers but reasonable with one observer, which was the case in our study.

CT scores were obtained before and at the end of the study. Prestudy CT scans were not older than 3 months,

provided that symptoms had remained stable (ie, no antibiotic or systemic steroid treatment). These CT scans were often those that were seen at the visit when indication for the operation was set after a course of intranasal steroid spray for 3 months or more. This might explain why not only the FPND-treated group but also the placebo-treated group showed improvement in CT scores, the phenomenon of "regression to the mean." Patients were scanned and indicated for FESS at their worst episode; it can be expected that even without treatment, their CT scores would regress. However, this does not explain why the CT score in the FPND group was already better at the start of the study. One could argue that the FPND group represents a positive selection of the total study population incidentally, but the remaining signs and symptoms are evenly distributed between both groups. On the other hand, if CT scores are already low, a further improvement is less likely, but still a significant improvement was found in the FPND group.

Necessity for FESS was reassessed at the end of the study. All patients had indications for FESS at the start of the study because this was an entry criterion. The decision to perform FESS was ultimately based on clinical grounds and resulted in 13 of 26 patients undergoing surgery in the FPND group and 17 of 21 undergoing surgery in the placebo group. Only one patient in the FPND group had a low CT score without a low VAS score and had no surgery. It is observed that CT findings often do not correlate with subjective complaints of patients. This was seen in a prospective study correlating the Sino-Nasal Outcome Test-20 (SNOT-20) to CT findings by using the same scoring system that we did, and no correlation was found.^{14,15}

This study demonstrates the efficacy of FPNDs in reducing the need for surgery in patients with polyposis and chronic rhinosinusitis by using objective and subjective measurements. Future research should be done to evaluate the results of long-time treatment in further preventing surgery.

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