

Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis and nasal polyps 1 year after functional endoscopic sinus surgery

M. D. Dijkstra*, F. A. Ebbens†, R. M. L. Poubon* and W. J. Fokkens†*

*Department of Otorhinolaryngology, Erasmus MC, Rotterdam, The Netherlands and †Department of Otorhinolaryngology, Academic Medical Center, Amsterdam, The Netherlands

Summary

Background Local corticosteroids are widely used in the treatment of nasal polyps and chronic rhinosinusitis both before and after nasal surgery. Their efficacy after functional endoscopic sinus surgery (FESS) has not been fully established by placebo-controlled trials.

Objective This double-blind placebo-controlled randomized study was performed in order to investigate whether fluticasone propionate aqueous nasal spray (FPANS) reduces the recurrence rate of nasal polyps and chronic rhinosinusitis during the first year after FESS.

Patients and methods The trial looked at 162 patients aged 18 years and older requiring FESS for chronic rhinosinusitis or nasal polyps. After FESS combined with peri-operative systemic corticosteroids, patients were randomized and given FPANS 400 µg b.i.d., FPANS 800 µg b.i.d. or placebo b.i.d. for the duration of 1 year. Patients were withdrawn from the trial (but still included in the study for statistical purposes) if there were recurrent or persistent diseases, defined as progressive regrowth of nasal polyps, recurrent signs and symptoms of chronic sinusitis combined with abnormalities on computed tomography scan and persistent complaints for at least 2 months after FESS.

Results A significant reduction of symptoms was seen after FESS. After 1 year, 46 patients had been withdrawn from the trial because of recurrent diseases and 32 patients because of persistent symptoms. No differences in the number of patients withdrawn because of recurrent or persistent diseases were found between the patients treated with FPANS and patients treated with placebo. We were also unable to find a positive effect of FPANS compared with placebo in several subgroups such as patients with nasal polyps, high score at FESS or no previous sinus surgery.

Conclusion This placebo-controlled study does not show that treatment with FPANS up to 1 year after FESS had a positive effect compared with placebo.

Keywords glucocorticoids, nasal mucosa, nasal polyps, otolaryngology, paranasal sinus diseases, sinus surgery

Submitted 3 October 2003; revised 28 November 2003; accepted 17 May 2004

Introduction

The aetiology, pathophysiology and therapy of chronic rhinosinusitis and nasal polyps are largely unknown [1–3]. Both diseases are thought to be based on inflammation of the nasal mucosa caused by viral, bacterial or fungal infection, allergy or aspecific hyper-reactivity. Inflammation of the mucosa causes oedema and secretion of mucus leading to blockage of the paranasal sinuses. This makes bacterial superinfections possible and therefore a continuation of the inflammatory process that may lead to the formation of nasal polyps. Of patients with nasal polyps, 65% have sinusitis and

chronic sinusitis often leads to the formation of nasal polyps [4]. Several authors therefore consider nasal polyps and chronic sinusitis to be different forms of a single disease.

One of the few published consensus articles about the treatment of chronic sinusitis states that medical treatment should be started first [5]. Antibiotics based on a sinus culture are prescribed during an adequate period of time (10–14 days) in order to reduce infection in combination with nasal decongestives and local or systemic corticosteroids in order to reduce oedema, inflammation and hyper-reactivity. However, treatment is based more on personal preferences than on placebo-controlled studies [1]. Four studies have investigated the effect of nasal corticosteroids on rhinosinusitis [6–8]. A recent study [8] show a significant reduction of symptoms of recurrent acute sinusitis by the addition of a nasal corticosteroid spray compared with treatment with antibiotics alone. When medical treatment of chronic sinusitis fails, functional endoscopic sinus surgery (FESS) is the current treatment of

Correspondence: W. J. Fokkens, Department of Otorhinolaryngology, Academic Medical Center, PO Box 22700, 1100DE Amsterdam, The Netherlands.

E-mail: w.j.fokkens@amc.uva.nl

choice for improving aeration of the sinuses and giving the mucosa the opportunity to recover.

There is some consensus that the best way to treat nasal polyps is by a combination of nasal or systemic corticosteroids and surgery in case of progressive disease [9, 10]. There is no consensus about the treatment of chronic sinusitis and nasal polyps after FESS. Often antibiotics or systemic or local corticosteroids are given in order to reduce the risk of recurrent disease. Only one placebo-controlled study shows a positive effect of nasal corticosteroids on the recurrence rate of nasal polyps after (FESS) [11]. In this study, however, there is a recurrence rate of nasal polyps of 87% in the placebo group, which seems exceptionally high, compared with 46% in the corticosteroid group. Four studies show a positive effect of nasal corticosteroids after polypectomy [12–15]. There are no studies investigating the efficacy of the post-operative use of nasal corticosteroids in patients with chronic rhinosinusitis. As the data on post-operative treatment of chronic rhinosinusitis and nasal polyps are limited, this double-blind placebo-controlled randomized study was performed in order to investigate whether fluticasone propionate aqueous nasal spray (FPANS) reduces the recurrence rate of nasal polyps and chronic rhinosinusitis during the first year after FESS.

Patients and methods

Patients

From October 1994 to December 1997, all patients who fulfilled inclusion criteria (Table 1) were recruited for the study. Diagnosis of chronic rhinosinusitis was made on the basis of symptoms of rhinosinusitis (blockage, rhinorrhoea, facial pain) for at least 12 weeks, confirmed by abnormalities on computed tomography (CT) scan persisting after therapy. Diagnosis of nasal polyps was based on nasendoscopy. The medical ethics committee of the Erasmus University Medical Centre Rotterdam approved the study.

General assessment

A full history and an ENT history were taken, a general physical examination and an ENT examination including nasendoscopy were performed and blood analysis, including an allergy test (Phadiatop), was carried out.

Symptoms

Symptoms were scored using visual analogue scales (VASs). Blockage, rhinorrhoea, anosmia, epistaxis, facial pain, headache and total symptoms were scored.

Nasendoscopy

Nasendoscopy was performed with a 30° Storz nasendoscope (Karl Storz GmbH, Tuttlingen, Germany) after local anaesthesia and decongestion with novesin and xylometazoline. The following nasendoscopy findings were recorded: secretion, oedema and polyps. The left and right anterior ethmoid, ostiomeatal complex and maxillary sinus were evaluated separately.

CT scan of the paranasal sinuses

A CT scan of the paranasal sinuses was scored according to Lund/Mackay [16] (0 = no opacification, 1 = partial opacification, 2 = total opacification, ostiomeatal complex open = 0, closed = 2. The maximum score was 24). The minimum required CT scan score was 2 (e.g. obstruction of one ostiomeatal complex).

Study design

On day 1, the evening before FESS, a 2-week course of systemic corticosteroids (40 mg prednisolone, tapered in 2 weeks) was started in all patients to cover for patients who needed peri-operative systemic corticosteroids for obstructive pulmonary disease. The next day FESS was performed. After surgery, patients had ethmoidal packing for 1 week. After removal of the ethmoidal packing, patients started taking study medication according to their randomization number. Study medication consisted of either FPANS 400 µg bd or FPANS 800 µg bd or placebo bd (double blind) using a randomization code generated by the statistics department of the Erasmus University Medical Centre Rotterdam. Randomization to treatment groups was equal.

Study medication was taken for 1 year after FESS or until withdrawal from the trial. Terfenadine 120 mg max bd was prescribed as rescue medication for allergic symptomatology. During 11 post-operative visits, VAS scores and nasendoscopy findings were recorded and a CT scan was made when necessary. Figure 1 shows the study design.

Withdrawal from trial because of recurrent or persistent disease

Patients were to be withdrawn from the trial (but not from the study) in case of recurrent or persistent disease, defined by progressive regrowth of nasal polyps, recurrent complaints of chronic rhinosinusitis combined with signs of rhinosinusitis at nasendoscopy and abnormalities on CT scan, or persistent complaints of rhinosinusitis for at least 2 months after FESS.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Signs and symptoms of nasal polyps or chronic rhinosinusitis requiring FESS	Use of systemic corticosteroids or other medication influencing nasal mucosa during the study
Abnormalities on CT scan confirming diagnosis of nasal polyps or chronic sinusitis	Significant structural anatomical abnormalities of the nose persisting after FESS ± septoplasty
Eighteen years and older	History of ASA intolerance
Written informed consent	Pregnancy, cystic fibrosis, serious concurrent disease
	Rhinoplasty in the past 6 weeks

FESS, functional endoscopic sinus surgery.

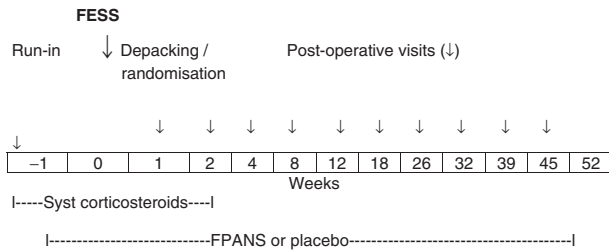


Fig. 1. Study design.

Withdrawal because of adverse events or poor compliance

Patients were also withdrawn from the trial in case of adverse events requiring medication influencing nasal mucosa (systemic corticosteroids) or in case of poor patient compliance.

Functional endoscopic sinus surgery

Every patient underwent FESS in accordance with the extent of the disease [17]. The ostiomeatal complex was opened and if necessary the operation also included the ethmoidal, frontal or sphenoidal sinuses. In cases of severe septal deviation, septoplasty was performed as well. During FESS, the extent of disease was scored. Obstruction, pus, polyps or abnormal mucosa in a sinus each scored 1 point. When a sinus was completely full with polyps, 2 points were scored. Anterior and posterior ethmoid, frontal, maxillary and sphenoidal sinuses and the ostiomeatal complex were scored separately. Four points per sinus were possible. Blockage of each ostiomeatal complex scored 2 points as well. The maximum possible score was 52 points. On the basis of symptoms, nasendoscopy findings and findings during FESS, patients were diagnosed as having nasal polyps or chronic rhinosinusitis or both.

Statistics

Log rank testing was used to determine significant differences in time preceding withdrawal per treatment group. The effect of FESS was determined by Wilcoxon-signed ranks testing. Cox regression analysis was used to measure relative recurrence rate ratios. $P < 0.05$ was considered a significant difference.

Results

Patients

A total number of 162 acetyl salicylic acid tolerant patients participated in the trial (92 men and 70 women). The average age was 41 years (range, 18–78). Fifty-three patients (33%) had a history of chronic obstructive pulmonary disease, 44 patients (27%) were allergic to inhalation allergens and 57 patients (35%) smoked. ENT history revealed previous FESS in 59 patients, no previous nasal surgery in 59 patients, septoplasty in 12 patients and some other form of sinus surgery (e.g. polypectomy, antral washing) in 32 patients. Hundred and forty patients had used nasal corticosteroids previously: 50 had used nasal corticosteroids within 2 months before FESS.

Symptoms

The mean total symptom score (VAS) in the placebo group was 72 ($SD \pm 22$), 70 in the FPANS 400 μ g group ($SD \pm 20$) and 70 in the FPANS 800 μ g group ($SD \pm 22$). Median pre-operative symptom scores for the total patient group were: blockage 59, rhinorrhoea 34, anosmia 50, facial pain 50, headache 53 and epistaxis 2, and median total symptom score was 74 (scale, 0–100).

Computed tomography scan of the paranasal sinuses

CT scans showed at least blockage of one ostiomeatal complex. The median CT scan score was 10 (range, 2–24). The median CT scan score in the placebo group was 12, 11 in the FPANS 400 μ g group and 10 in the FPANS 800 μ g group.

Functional endoscopic sinus surgery

During FESS, the extent of disease was scored. The median score was 9 (range, 0–45). The median score in the placebo group was 12, 8 in the FPANS 400 μ g group and 10 in the FPANS 800 μ g group. On the basis of symptoms, nasendoscopy findings, and findings during FESS, 55 patients were diagnosed as having nasal polyps and 94 patients were diagnosed as having chronic sinusitis. Thirteen patients were classified as having both nasal polyps and chronic sinusitis. In the placebo group, 21 patients were diagnosed as having nasal polyps, 28 as having chronic sinusitis, and seven as having both nasal polyps and chronic sinusitis. In the FPANS 400 μ g group, 13 patients were diagnosed as having nasal polyps, 36 as having chronic sinusitis and four as having both nasal polyps and chronic sinusitis. In the FPANS 800 μ g group, 21 patients were diagnosed as having nasal polyps, 30 as having chronic sinusitis and two as having both nasal polyps and chronic sinusitis.

Effect of treatment with fluticasone propionate aqueous nasal spray

After FESS, there was a significant reduction in symptoms of nasal polyps and chronic rhinosinusitis. The median total symptom score in the placebo group two weeks after FESS was 24 compared with 78 before FESS. In the FPANS 400 μ g group, the median total symptom score after FESS was 31 compared with 70 before FESS and, in the FPANS 800 μ g group, the median total symptom score after FESS was 24 compared with 75 before FESS ($P < 0.001$). There was no significant difference between the placebo group and the FPANS 400 and 800 μ g groups (Wilcoxon-signed ranks testing).

No significant difference in the recurrence rate of nasal polyps and chronic rhinosinusitis could be found in the total patient group between the FPANS and placebo groups (Fig. 2). In the placebo group ($n = 56$), 32 patients were withdrawn from the trial. Twenty-two patients (39%) were withdrawn because of recurrent or persistent disease. In the FPANS 400 μ g group ($n = 53$), 34 patients were withdrawn from the trial. Twenty-seven patients (51%) were withdrawn because of recurrent or persistent disease and in the FPANS 800 μ g group ($n = 53$), 37 patients were withdrawn from the trial.

Twenty-nine patients (55%) were withdrawn because of recurrent or persistent disease (not significant). Compared with placebo, recurrence rate ratios were 1.22 in the FPANS 400 µg group (95% CI = 0.70–2.13) and 1.48 in the FPANS 800 µg group (95% CI = 0.86–2.56).

When patients with a high score during FESS were analysed separately, no significant difference was found between fluticasone and placebo either (Fig. 3a). In the placebo group, 14 patients (42%) were withdrawn from the trial because of recurrent or persistent disease, compared with nine patients (43%) in the FPANS 400 µg group and 19 (68%) in the FPANS 800 µg group. It was also not possible to identify any significant differences when patients with nasal

polyps (Fig. 3b) were evaluated separately from patients with chronic rhinosinusitis (Fig. 3c). In the placebo group of the patients with nasal polyps, seven patients (33%) were withdrawn from the trial because of recurrent or persistent disease. Four patients in the FPANS 400 µg group (31%) were withdrawn from the trial and this figure was 14 for the FPANS 800 µg group (58%). Thirteen patients in the placebo group of the patients with chronic rhinosinusitis (46%) were withdrawn from the trial because of recurrent or persistent disease, with 21 being withdrawn from the FPANS 400 µg group (58%) and 14 from the FPANS 800 µg group (47%). In addition, the results for patients without a history of sinus surgery (Fig. 3d) were no better after treatment with fluticasone compared with placebo. In the placebo group of these patients, seven patients (30%) were withdrawn from the trial because of recurrent or persistent disease, 12 were withdrawn in the FPANS 400 µg group (48%) and 12 from the FPANS 800 µg group (52%).

There was no significant difference between the effect of fluticasone and of placebo on different symptoms or on the total symptom score. The incidence of epistaxis as a possible complication of treatment with local corticosteroids was not higher in the groups given FPANS.

Discussion

This study investigated the effect of FPANS on the recurrence rate of nasal polyps and chronic rhinosinusitis during the first year after FESS. In the literature, the recurrence rate of nasal polyps and chronic sinusitis after endoscopic sinus surgery is measured by many different methods ranging from telephone follow-up, quality of life questionnaires and VAS to objective nasendoscopy findings like visible polyps or pus. This makes

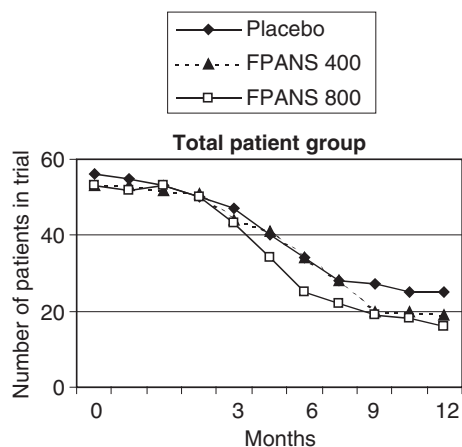


Fig. 2. Total number of patients still participating in the trial per treatment group. The horizontal axis shows the time (months, 0 = before functional endoscopic sinus surgery (FESS)). The vertical axis shows the number of patients per treatment group.

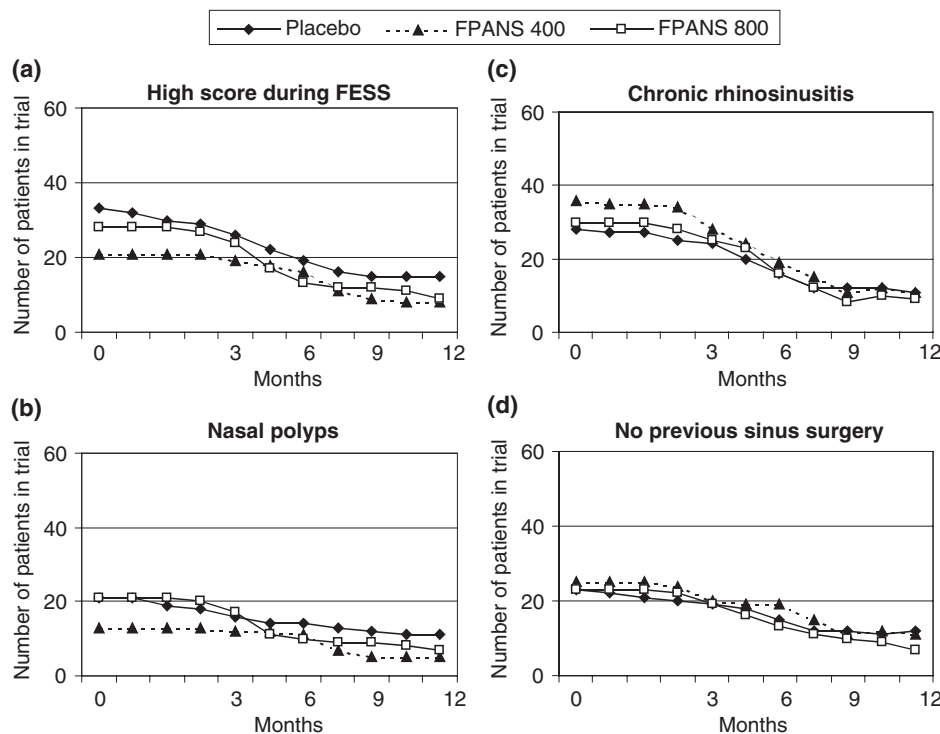


Fig. 3. Number of patients still participating in the trial per treatment group in several subgroups. The horizontal axis shows the time (months, 0 = before functional endoscopic sinus surgery (FESS)). The vertical axis shows the number of patients per treatment group: (a) patients with high scores during FESS; (b) patients with nasal polyps, (c) patients with chronic rhinosinusitis, (d) patients without previous sinus surgery.

it hard to compare results. Usually, symptoms are better than nasendoscopy findings [2, 18]. Danielsen and Olofsen [18] for example, demonstrated that only 40% of the patients with a good result after FESS for nasal polyps or recurrent or chronic sinusitis had normal mucosa at nasendoscopy, and Kennedy [2] described a subjectively good result after FESS in 97.5% of his patients whereas, at nasendoscopy, there was still evidence in 44.9% of residual disease. This study used VASs combined with nasendoscopy findings to determine recurrent or persistent disease. In addition, it was decided before starting the study to withdraw patients with recurrent or persistent disease at nasendoscopy from the trial, but not from the study, in order to be able to treat them with FPANS. As could have been expected, this resulted in a large number of withdrawals. Only 59 patients finished the trial. Forty-six patients (29%) were withdrawn from the trial because of recurrence of nasal polyps or chronic rhinosinusitis at nasendoscopy and 32 patients (20%) were withdrawn because of persistent complaints. It is hard to compare these results to the results described in literature, because there are no comparable placebo-controlled trials. After further treatment of withdrawn patients in our referral university clinic, good results were eventually obtained in 77% of the total patient group.

This study was, however, not performed to analyse our results after FESS but to evaluate the influence of local corticosteroid nasal spray after FESS. This study did not find any positive effect of FPANS compared with placebo. As the literature provides some evidence of a positive effect of local corticosteroids on the recurrence of nasal polyps [11–15], the group of patients with nasal polyps was analysed separately. However, in the separate nasal polyp group, no positive effect of local corticosteroids could be found either. In our referral university hospital we see many patients who are referred to us by other ENT surgeons, which means that we see many patients who have already had FESS followed by local corticosteroids without an acceptable result. This large group could possibly explain the lack of efficacy of local corticosteroids found in this study. However, the results for patients who had never undergone sinus surgery before were also no better with local corticosteroids than with placebo. Furthermore, there was no positive effect produced by local corticosteroids in patients with many symptoms at FESS. In our hospital, all patients with nasal polyps and chronic rhinosinusitis are treated with local corticosteroids, often in combination with a course of oral corticosteroids. Only those who do not respond well undergo operations, which means we operate on a selected patient group of non-responders to local corticosteroids. This might explain why there is also no positive response to local corticosteroids after FESS. Other explanations could be that a local corticosteroid spray is not able to reach the diseased area properly. This would explain why systemic corticosteroids often have a much better effect. A study is currently being conducted in our hospital to determine whether fluticasone propionate nasal drops produce better results. A challenging explanation would be that chronic inflammation causes irreversible mucosal changes that are completely resistant to corticosteroids. For this group of patients even FESS might no longer be enough because of irreversible damage to the mucociliary clearance system. In these cases, more radical surgery, with ethmoidectomy being

followed by complete removal of the lateral nasal wall (Denker's procedure), might be the only way to achieve an acceptable quality of life [19, 20].

Conclusion

This placebo-controlled study does not show a reduction in the recurrence rate for nasal polyps or chronic rhinosinusitis after treatment with FPANS compared with placebo 1 year after FESS. We were also unable to establish a positive effect of FPANS in several subgroups such as nasal polyps, high score at FESS or no previous sinus surgery. In the literature, there is no clear evidence of the efficacy of treatment with local corticosteroids after FESS either. More studies should therefore be performed if treatment with nasal corticosteroids after FESS is to be justified.

Acknowledgements

We would like to thank GlaxoSmithKline, R&D, UK for their personal and financial support for this study.

References

- 1 Kaliner MA, Osguthorpe DJ, Fireman P et al. Sinusitis: bench to bedside: current findings, future directions. *J Allergy Clin Immunol* 1997; 99:S829–48.
- 2 Kennedy DW. Prognostic factors, outcomes and staging in ethmoid sinus surgery. *Laryngoscope* 1992; 102:1–18.
- 3 Benninger MS, Anon J, Mabry RL. The medical management of rhinosinusitis. *Otolaryngol Head Neck Surgery* 1997; 117:S41–9.
- 4 Slavin RG. Sinusitis in adults and its relation to allergic rhinitis, asthma and nasal polyps. *J Allergy Clin Immunol* 1988; 82:950–56.
- 5 Gwaltney JM, Jones JG, Kennedy DW. Medical management of sinusitis: educational goals and management guidelines. The International Conference on sinus Disease. *Ann Otol Rhinol Laryngol (Suppl.)* 1995; 167:22–30.
- 6 Meltzer EO, Orgel HA, Backhaus JW et al. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. *J Allergy Clin Immunol* 1993; 92:812–23.
- 7 Sykes DA, Wilson R, Chan KL, Mackay IS, Cole PJ. Relative importance of antibiotic and improved clearance in topical treatment of chronic mucopurulent rhinosinusitis: a controlled study. *Lancet* 1986; 2:359–60.
- 8 Meltzer EO, Charous BL, Busse WW et al. Added relief in the treatment of recurrent sinusitis with adjunctive mometasone furoate nasal spray. The Nasonex Sinusitis Group. *J Allergy Clin Immunol* 2000; 106:630–7.
- 9 Holmberg K, Karlsson G. Nasal polyps: medical or surgical management. *Clin Exp Allergy* 1996; 26 (Suppl. 3):23–30.
- 10 Stammberger H. Surgical treatment of nasal polyps: past, present and future. *Allergy* 1999; 54:7–11.
- 11 Virolainen E, Puhakka H. The effect of intranasal beclomethasone dipropionate on the recurrence of nasal polyps after ethmoidectomy. *Rhinology* 1980; 18:9–18.
- 12 Dingsor G, Kramer J, Olsholt R, Soderstrom T. Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy. *Rhinology* 1985; 23:49–59.
- 13 Drettner B, Ebbesen A, Nilsson M. Prophylactic treatment with flunisolide after polypectomy. *Rhinology* 1982; 20:149–58.

- 14 Hartwig S, Linden M, Laurent C, Vargo AK, Lindqvist N. Budesonide nasal spray as prophylactic treatment after polypectomy. (a double blind clinical trial). *J Laryngol Otol Oncol* 1998; 102:148–51.
- 15 Karlsson G, Rundcrantz H. A randomized trial of intranasal beclomethasone dipropionate after polypectomy. *Rhinology* 1982; 20:144–8.
- 16 Lund VJ, MacKay IS. Staging in rhinosinusitis. *Rhinology* 1993; 31:183–4.
- 17 Stammberger H, Posawetz W. Functional endoscopic sinus surgery. Concept, indications and results of the Messerklinger technique. *Eur Arch Otorhinolaryngol* 1990; 247: 63–76.
- 18 Danielsen A, Olofsen J. Endoscopic endonasal sinus surgery: a long term follow-up study. *Acta Otolaryngol (Stockh)* 1996; 116:611–9.
- 19 Kerrebijn JD, Drost HE, Spoelstra HA et al. If functional sinus surgery fails: a radical approach to sinus surgery. *Otolaryngol Head Neck Surg* 1996; 114:745–7.
- 20 Wreesmann V, Fokkens WF, Knecht PP. Refractory chronic sinusitis: evaluation of symptom improvement after Denker's procedure. *Otolaryngol Head Neck Surg* 2001; 125:495–500.