ORIGINAL ARTICLE

Treatment of Recurrent Chronic Hyperplastic Sinusitis With Nasal Polyposis

Desiderio Passàli, MD, PhD; Joel M. Bernstein, MD, PhD; Francesco Maria Passàli, MD; Valerio Damiani, MD; Giulio Cesare Passàli, MD; Luisa Bellussi, MD, ChD

Objective: To demonstrate the long-term efficacy of intranasal furosemide, an inhibitor of the sodium chloride cotransporter channel at the basolateral surface of the respiratory epithelial cell, vs no therapeutic intervention vs intranasal mometasone furoate, a corticosteroid, in preventing relapses of chronic hyperplastic sinusitis with nasal polyposis.

Design: Randomized prospective controlled study. Patients were examined every 6 months during follow-up (range, 1-9 years).

Patients: One hundred seventy patients with bilateral obstructive or minimally obstructive chronic hyperplastic sinusitis with nasal polyposis.

Intervention: All patients were surgically treated in the ENT Department, University of Siena Medical School. One month after surgery, group 1 patients (n=97) started treatment with intranasal furosemide, group 2 (n=40) received no therapeutic treatment, and group 3 (n=33) were treated with mometasone.

Main Outcome Measures: Clinical and instrumental evaluation of postoperative outcomes.

Results: Seventeen (17.5%) of 97 patients in group 1, 12 (30.0%) of 40 patients in group 2, and 8 (24.2%) of 33 patients in group 3 experienced nasal polyposis relapses. We noted a prevalence of early-stage relapse in patients treated with furosemide or mometasone, whereas patients who did not receive any treatment experienced more severe grades of chronic hyperplastic sinusitis with nasal polyposis ($P<.005$).

Conclusion: Use of intranasal furosemide represents a valid therapeutic treatment in the prevention of chronic hyperplastic sinusitis with nasal polyposis.

Arch Otolaryngol Head Neck Surg. 2003;129:656-659

THE TREATMENT of nasal polyposis, and the prevention of relapses of this common disorder, is a subject of much debate among clinicians and researchers. In allergy-related nasal polyposis, medical treatment is, in most cases, not sufficient, and surgical treatment for nasal polyposis is only partially successful.[1-3] Better knowledge on the cause and pathogenesis of nasal polyposis is mandatory in the treatment of nasal polyps.

The efficacy of systemic corticosteroids is well-known,[4] but these drugs are of limited use for pathologic conditions of the sinus, because of their serious adverse effects and their contraindications in such diseases as heart disease, hypertension, diabetes mellitus, obesity, and cataracts. The use of topical corticosteroids is considered by some to be the best treatment for the prevention of recurrence of nasal polyposis.[5,6] Systemic adverse effects are rare, and use of these topical drugs avoids dystrophy or atrophy of the nasal mucosa, although it is associated with some burning, epistaxis, and oral candidiasis.[7] Despite these local adverse effects, these drugs have been used in various clinical trials. Beclomethasone dipropionate was the first corticosteroid reported to be topically administered for nasal polyps, resulting in a 20% relapse among patients after a 2-year follow-up.[8] Later, flunisolide was used with good results, but this study[9] had only a 1-year follow-up. The efficacy of fluticasone propionate during postoperative follow-up requires further investigations.[10,11]

Although we consider these results important, the best therapeutic approach to relapse of nasal polyposis is to interfere with the early phase of nasal polyp development. A key element in this context is the edematous infiltrate. Manipulation of this target may be effective in preventing relapses after surgery.[12] According to

From the ENT Department, University of Siena Medical School, Siena, Italy (Drs D. Passàli, F. M. Passàli, Damiani, G. C. Passàli, and Bellussi); and Departments of Otolaryngology and Pediatrics, State University of New York at Buffalo (Dr Bernstein). *The authors have no relevant financial interest in this article.*

this hypothesis, the genesis of nasal polyposis is the result of alterations of sodium chloride net flux.

A result of the movement of these electrolytes is development of inflammatory cytokines, such as tumor necrosis factor α and interleukin 1, and chemokines responsible for eosinophilic migration, which results in the persistence of eosinophils in the lamina propria of the nasal polyp. The primary inflammatory mediator released by eosinophils is major basic protein. There is some evidence that major basic protein leads to an alteration of the flux of sodium chloride at the apical surface of the respiratory cell, resulting in increased net sodium absorption and the resultant increased water absorption in the cell and lamina propria. This leads to the inflammatory finding in nasal polyposis, namely, edema.[13]

Imbalance of ionic flow may also occur in the absence of inflammatory events, as demonstrated by investigations using ultrasonic nebulized distilled water on bronchial and nasal mucosa.[14] The hypotonic solution that leads to a flow of sodium may be followed by the entrance of calcium and the activation of various cellular functions associated with this cation. Considering this information together, the topical use of furosemide, a loop diuretic and inhibitor of the potassium and sodium chloride cotransporter channels, at the basolateral surface of the respiratory epithelial cell may result in a decrease in sodium absorption and an ultimate decrease in water absorption. Therefore, furosemide can cause a chemical gradient between the submucosa and the luminal surface of the respiratory epithelium and lead to an increased absorption of sodium and water. This would effectively dehydrate the surface of the respiratory epithelial cell. The efficacy of this drug, administered by nasal inhalation, has been previously demonstrated in the prevention of relapses of chronic hyperplastic sinusitis with nasal polyposis (CHS-NP) after surgery.[15,16]

The aims of the present study were to demonstrate the long-term efficacy of intranasal furosemide, a topical diuretic, and to compare its efficacy with that of mometasone furoate, an intranasal corticosteroid, vs placebo in preventing relapses of CHS-NP.

METHODS

One hundred seventy patients (95 men and 75 women; age range, 19-63 years; mean age, 37.3 years) were studied from January 7, 1991, to December 18, 2000. All patients had bilateral obstructive or subobstructive CHS-NP and had failed medical therapy, requiring a surgical approach to their nasal disease.

By using nasal endoscopy and acoustic rhinometry (AR), we preoperatively classified nasal polyps as follows: stage 1, polyps confined to the middle meatus, with AR values within the normal range (normal mean ± SD total nasal volumes, 24.5 ± 1.5 cm^3); stage 2, polyps prolapsing beyond the middle turbinate, with less than a 10% reduction of nasal volumes, as measured by AR; and stage 3, polyps leading to a complete or subcomplete obstruction of the nasal fossae, with greater than a 50% reduction of nasal volumes at AR. Suitable patients were considered for surgery when their polyps failed to be controlled by medical management and caused greater than a 50% reduction of the normal nasal volume in each nasal fossa (stage 3 polyposis).

All patients were surgically treated in the ENT Department, University of Siena Medical School. Patients did not differ regarding the type and extent of pathologic condition of the nose and sinuses, so that the severity of the disease before surgery was similar in the 3 groups. Endoscopic polypectomy plus anterior and anteroposterior ethmoidectomy was performed in 95 and 49 patients, respectively. The 3 groups of patients and their surgical procedures are summarized in **Table 1**. All patients provided informed written consent. In the immediate postoperative period, all patients received standard medical treatment, consisting of nasal lavage with isotonic sodium chloride solution and emollient oil.

Table 1. Surgical Procedures of Enrolled Patients

Group	No. of Patients	Procedure*		
		EPAE	EPAPE	EP
1	**97**	53	18	26
2	**40**	25	15	0
3	**33**	17	16	0
Total	**170**	**95**	**49**	**26**

Abbreviations: EP, endoscopic polpectomy; EPAE, endoscopic polypectomy plus anterior ethmoidectomy; and EPAPE, endoscopic polpectomy plus anteroposterior ethmoidectomy.
*Data are given as number of patients.

One month after surgery, all patients underwent a complete ear, nose, and throat examination, active anterior rhinomanometry (performed using a computerized Menfis Rhino System; Menfis Biomedica, Bologna, Italy), AR (performed with a Stimotron Rhinolack 1000 rhinometer, with an ophthalmologic cephalostat as a stand for the chin and forehead of the patient in repeated recording; Menfis Biomedica), and nasal endoscopy with a fiber-optic instrument (Olympus ENF type P2; Pentax Italia, Florence, Italy). All of these results were found to be within the normal range in all patients; moreover, residual polyposis was not present in any patient after surgery.

At the time of recruitment, the 170 patients were randomly divided into 3 groups. From January 7, 1991, to December 22, 1997, we assigned patients to furosemide treatment (group 1) or placebo (group 2). Subsequently, considering the positive results obtained with furosemide,[16] we decided to compare the efficacy of this drug with that of a topical corticosteroid (mometasone), currently the most accepted treatment for the prevention of postsurgical relapses of polyposis. For this reason, and with the aim of validating the use of this drug during a long follow-up, we continued to enroll patients into the furosemide group, ceased to enroll patients into group 2 (placebo), and began to enroll patients into the mometasone group (group 3).

At the end of follow-up, group 1 consisted of 97 patients (54 men and 43 women); group 2, 40 patients (18 men and 22 women); and group 3, 33 patients (23 men and 10 women).

Each patient assigned to group 1 started treatment with furosemide diluted in physiological solution (2 mL furosemide and 2 mL isotonic sodium chloride solution) administered as nasal puffs (2 puffs per day per nostril, each puff corresponding to 50 µg) for 30 days. This therapy was administered for 1 month and then interrupted for 1 month, etc, for the first 2 years (total treatment, 6 mo/y). During the third, fourth, and fifth years of treatment, patients followed this regimen for 1 month and then interrupted treatment for 2 months (total treatment, 4 mo/y). After 5 years of treatment, furosemide was administered for 1 month twice a year. Group 2 received no specific treatment. Patients assigned to group 3 started treatment with mometasone administered as nasal puffs (2 puffs per day per nostril, each puff corresponding to 100 µg) for 30 days. As suggested by others[7] and with the aim of preventing adverse

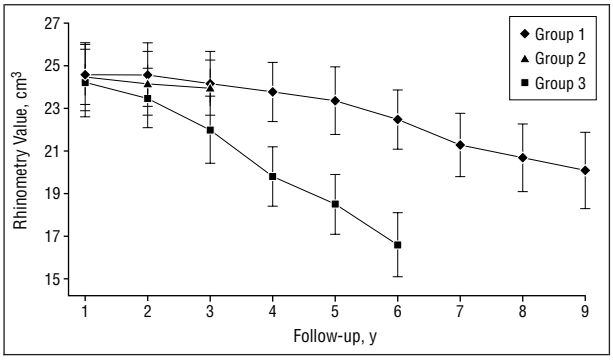

Figure 1. Acoustic rhinometry results during follow-up. Data are expressed as mean±SD.

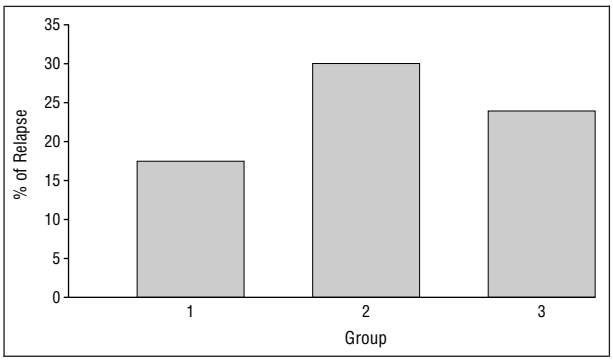

Figure 2. Percentages of nasal polyposis relapse.

Table 2. Nasal Polyposis Relapses

Group	No. of Patients	Stage*				All Stages
		0	1	2	3	
1	97	0	10	5	2	**17**
2	40	0	0	4	8	**12**
3	33	0	5	2	1	**8**
Total	**170**	**0**	**15**	**11**	**11**	**37**

*Data are given as number of patients.

effects of a continuous prolonged corticosteroid treatment, mometasone was administered according to a therapeutic protocol similar to that described for furosemide, requiring administration of the drug to be followed by washout.

During follow-up, no other treatments were administered to the patients enrolled in the study. Patients were examined every 6 months (group 1 follow-up range, 1-9 years; group 2, 1-6 years; and group 3, 1-3 years). Control subjects received the same examinations performed 1 month after surgery as did the other 2 groups (complete ear, nose, and throat examination, active anterior rhinomanometry, AR, and nasal endoscopy).

Relapsing nasal polyposis was staged as follows: stage 0, no polyp seen; stage 1, polyp or polyps confined to the middle meatus, with AR values within the normal range (normal mean±SD total nasal volumes, 24.5±1.5 cm^3); stage 2, polyps prolapsing beyond the middle turbinate, with less than a 10% reduction of nasal volumes, as measured by AR; and stage 3, subobstructive forms requiring another operation (>50% reduction of nasal volumes).

To exclude confounding by systemic effects of furosemide, blood pressure was monitored daily during 5 months of the first year of treatment, and blood cell counts and renal function were tested every 6 months after surgery. We subjected the measured data to statistical analyses using χ^2 and *t* tests.

RESULTS

Group 1 and group 3 patients tolerated the therapy with furosemide and mometasone well; no patient abandoned therapeutic protocols. In these 2 groups, we did not note any cutaneous, pancreatic, or hematic adverse effects. **Figure 1** summarizes the nasal volumes, as measured by AR, in the 3 groups during follow-up.

In all 3 patient groups, surgery restored nasal patency to the normal range during the first year of follow-up. Subsequently, in the untreated group, at the end of their 6-year follow-up, we noted a significant worsening of nasal volumes, falling to a mean±SD of 16.6±1.3 cm^3 ($P=.02$). In contrast, use of furosemide and mometasone maintained nasal patency in the physiological range during the first 3 years of follow-up; moreover, in the furosemide group, we noted normal patency after 9 years of follow-up.

Seventeen (17.5%) of 97 patients in group 1, 12 (30.0%) of 40 patients in group 2, and 8 (24.2%) of 33 patients in group 3 experienced nasal polyposis relapses (**Figure 2**). **Table 2** summarizes the distribution of these relapsing cases of CHS-NP according to severity stages. We noted a prevalence of early-stage relapse in patients treated with furosemide or mometasone, whereas patients who did not receive any treatment experienced more severe grades of CHS-NP ($P<.005$). We did not note any significant adverse effects among the groups treated with furosemide or mometasone.

COMMENT

Although CHS-NP affects only 1% to 4% of the adult population, it represents an important clinical problem for physicians in general and for ear, nose, and throat specialists in particular. There is a high incidence of postsurgical recurrences.[17,18] Difficulties in treating and preventing relapses of CHS-NP result from the lack of information regarding the multiple factors in its pathogenesis. Data from our laboratory and others[12,13] support the concept that an important element in the genesis of nasal polyps and their relapse is the development of edema secondary to increased plasma and water absorption into the lamina propria of the nasal polyp tissue. For this reason, we used furosemide, a diuretic that inhibits sodium reabsorption. In the present study, 17.5% (17/97) of patients treated with furosemide had relapses, compared with 24.2% (8/33) in the mometasone group and 30.0% (12/40) in the untreated group. These values, although not statistically different ($P=.10$), show that after 9 years of follow-up the percentage of recurrence in the furosemide-treated group was similar to that in the mometasone-treated group and in the untreated group, obtained after 3 and 6 years of follow-up, respectively. Further studies are needed, but our

data seem to show a potential long-term protective effect of furosemide against the development of recurrences.

Moreover, if we consider the severity of relapsing polyposis, 2 (11. 8%) of 17 patients treated with furosemide had stage 3 polyposis, whereas significantly more (8 [66.7%] of 12) in group 2 had stage 3 polyposis ($P<.005$). Finally, group 3, treated with corticosteroids, had a 12.5% (1/8) recurrence rate for stage 3 polyposis, which is similar to that of the furosemide group and markedly better than that of the untreated group ($P<.005$).

The demonstrated long-term efficacy of nasal topical treatment with furosemide suggests complex events involving water absorption in the development of nasal polyposis. It appears that an increase in the net flux of sodium chloride leads to an increased absorption of water across the apical surface of the respiratory epithelium, leading to edema and therefore growth of the nasal polyp. Furthermore, the imbalance of sodium chloride transmembrane net flux probably leads to a dysregulation of calcium homeostasis, with its concomitant effect on interstitial and intracellular second-membrane messengers. The depletion of calcium would result in a destabilization of the cells populating the nasal mucosa of patients prone to having polyps.

The molecular biological events that occur in the development of nasal polyps have been recently reviewed.[13] Various cytokines are upregulated in the lamina propria of the nasal polyp, which leads to the upregulation of cytokines and adhesion molecules that eventually are responsible for the influx of eosinophils. The influx of eosinophils is probably the major histopathological event that takes place in the development of nasal polyps. Finally, the release of major basic protein from the eosinophils has an effect on the epithelial architecture and on the sodium chloride flux into and out of the apical epithelial cells of the tissue.

In the present study, we measured the effect of furosemide, a potassium and sodium chloride cotransport inhibitor of the resting membrane potential of the respiratory epithelial cell, on the rate and extent of recurrence of nasal polyposis in patients undergoing polypectomy for CHS-NP. Our long-term follow-up study supports the use of furosemide as a valid therapeutic approach to the prevention of CHS-NP and as an alternative to the use of topical corticosteroids, which have some clinical adverse effects on the nasal mucosa.

Accepted for publication October 18, 2002.

Corresponding author and reprints: Desiderio Passàli, MD, PhD, ENT Department, University of Siena Medical School, V. le Bracci, 53100 Siena, Italy (e-mail: Passali@unisi.it).

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