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.

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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 22, 1997. 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 ± 4.5 cm³); 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.

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 cefalostat 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, 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 30 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). 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). 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 and with the aim of preventing adverse

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Procedure*</th>
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<tbody>
<tr>
<td>1</td>
<td>97</td>
<td>EPAE</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>EPAE</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>EPAE</td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
<td>95</td>
</tr>
</tbody>
</table>

Abbreviations: EP, endoscopic polypectomy; EPAE, endoscopic polypectomy plus anterior ethmoidectomy; and EPAPE, endoscopic polypectomy plus anteroposterior ethmoidectomy.

*Data are given as number of patients.

REFERENCE

1. Weisbach H, Bell RW. Furosemide, a loop diuretic, and to compare its efficacy with that of mometasone furoate, an intranasal corticosteroid, vs placebo in preventing relapses of CHS-NP. JAMA. 1989;262(21):3021-3026.

2. Weisbach H, Bell RW. Furosemide, a loop diuretic, and to compare its efficacy with that of mometasone furoate, an intranasal corticosteroid, vs placebo in preventing relapses of CHS-NP. JAMA. 1989;262(21):3021-3026.

3. Weisbach H, Bell RW. Furosemide, a loop diuretic, and to compare its efficacy with that of mometasone furoate, an intranasal corticosteroid, vs placebo in preventing relapses of CHS-NP. JAMA. 1989;262(21):3021-3026.
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 \( \chi^2 \) 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 polyp 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

![Figure 1](https://example.com/figure1.png)

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

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Percentages of nasal polyposis relapse.

**Table 2. Nasal Polyposis Relapses**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Stage*</th>
<th>All Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97</td>
<td>0</td>
<td>10 5 2 17</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>0</td>
<td>0 4 8 12</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>0</td>
<td>5 2 1 8</td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
<td>0</td>
<td>15 11 11 37</td>
</tr>
</tbody>
</table>

*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).
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 < 0.005). 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 < 0.005).

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. 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.

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

REFERENCES