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Intrasinus Administration of Topical Budesonide to Allergic Patients With Chronic Rhinosinusitis Following Surgery

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Objective: **Whether instillation into the maxillary sinus of topical budesonide affected the immune response and improved allergic patients with chronic rhinosinusitis that had persistence of symptoms despite appropriate surgical intervention was assessed.** ***Study Design:*** **Double-blind placebo-controlled.** ***Methods:*** **Twenty-six patients with allergy to house dust mites who had previously had surgery and who had persistent symptoms of disabling rhinorrhea or pressure-pain resistant to oral antibiotics and intranasal corticosteroids were recruited. During the double-blind study, patients instilled 256 μg budesonide daily or placebo through an intubation device (maxillary antrum sinusotomy tube) into one of the maxillary sinuses for 3 weeks before clinical assessment and a second biopsy.** ***Results:*** **We found an improvement in the symptom scores in 11 of the 13 patients who received budesonide; we also found a decrease in CD-3 (P = .02) and eosinophils (*P* = .002), and a decrease in the density of cells expressing interleukin-4 (*P* = .0001) and interleukin-5 messenger RNA (*P* = .006) after treatment.** ***Conclusion:*** **Topical budesonide delivered through a maxillary antrum sinusotomy tube can control chronic rhinosinusitis that persists after surgery.** ***Key Words:*** **Chronic rhinosinusitis, maxillary sinus, budesonide, type 2 T-helper-cell cytokines, allergy.**

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a disease of the nasal and paranasal sinuses characterized by the symptoms of facial pain, nasal obstruction, and rhinorrhea.[1] Surgery, involving the removal of ethmoidal tissue and middle meatus antrostomy,[2] is indicated when recurrent infection and clinical symptoms are not improved by medical therapy.[3] However, some patients with diffuse disease on computed tomography (CT) scan do not benefit from these surgical procedures and exhibit persistent mucosal disease, which leads to repetitive antibiotic treatment and even surgical revisions.[4]

The phenotypic qualities of CRS are considered a consequence of the inflammation that overwhelms the nasal and sinus mucosa. This inflammation occurs in both allergic and nonallergic patients, with the most notable increase being in the number of eosinophils, and in allergic individuals there is also an elevated number of T cells and the type 2 T-helper-cell (Th_2) cytokines, including interleukin-4 (IL-4) and interleukin-5 (IL-5).[5] Together, these two cytokines mediate the development of the allergic inflammatory response observed within respiratory mucosa. Interleukin-4 influences activated naive T cells to express predominantly Th_2 cytokines; it facilitates eosinophil infiltration by enhancing endothelial expression of vascular cells adhesion molecules (VCAM)-1,[6] the counter ligand for very late antigen (VLA)-4 used by eosinophils for endothelial transmigration[7]; and it induces B cells to isotype switching in favor of immunoglobulin E (IgE).[8] Interleukin-5 is the required cytokine for eosinophil differentiation[9] and also activates[10] and enhances the survival of these cells.[11,12]

Topical corticosteroid treatment is well documented as an effective method for reducing inflammation and improving the symptoms of allergic rhinitis[13] but is less successful in patients with CRS.[14] Indeed, we have previously demonstrated that intranasal administration of topical corticosteroids can reduce the number of eosinophils and T cells and the expression of Th_2 cytokines IL-4, IL-5, and interleukin-13 (IL-13) in patients with perennial rhinitis.[15]

There are patients with persistent CRS who do not respond to intranasal topical corticosteroids or antibiotic treatment and show little improvement after surgery.[16] We recently demonstrated that sinus mucosa readily exposed to environmental air, the ethmoidal sinus mucosa, was more inflamed than maxillary sinus mucosa.[17] As such, surgical intervention, which increases exposure of

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the maxillary sinus mucosa to environmental air, may serve to increase mucosal inflammation and the need for surgical revision.

Intubation and irrigation of the maxillary cavity have been used for some time,[18] and instillation of saline solution has been associated with increased levels of immunoglobulin A (IgA), immunoglobulin G (IgG), complement fractions 3 and 4 (C3 and C4), and a reduction in proteolytic activity.[19] In light of this, we proposed that intubation and instillation of topical corticosteroids directly into the maxillary sinus might be more beneficial because it allows for steroids to access the inflamed site. Indeed, we demonstrate in the current study that instillation of topical budesonide into the maxillary sinus of patients with persistent CRS was successful in reducing both the sinus inflammation and the clinical symptoms. Furthermore, some of these patients were symptom free for up to 12 months after treatment with significant reduction in medication needs for sinus and pulmonary disease. As such, our results indicate that this route of administration holds real potential as a method of treating patients with persistent CRS.

PATIENTS AND METHODS

Patients

The current study was undertaken after approval by the Ethics Committee of Notre Dame Hospital (Montreal, Quebec, Canada). Patients were enrolled and followed for 1 year between November 1995 and April 1998. Written, informed consent was obtained in 29 nonsmoking patients with CRS, which was defined as a clinical syndrome of rhinorrhea, congestion, and facial pressure-pain lasting for more than 6 months and resistant to medical therapy, including antibiotics, topical steroids, or oral prednisone. In all patients, persistent CRS was confirmed by nasosinusal endoscopy examination that showed diffuse bilateral thickening or erythema in both the ethmoid and maxillary sinuses with obvious signs of inflammation (Fig. 1). The presence of atopy was determined clinically by positive reaction on skin test (wheal $\geq$3 mm) to house dust mite, as well as a panel of 11 other common aeroallergens. Peripheral eosinophil counts with complete blood cell counts were performed in all patients, and the presence of specific IgE was determined by RAST testing in patients with negative or small skin reactions. Nasal steroids were withheld for 14 days and systemic steroids were witheld for 2 months withheld before the study. Patients with nasal polyposis or immunodeficiency and individuals who required further sinus surgery were excluded from the study.

Intubation of Maxillary Sinus

Only one of the maxillary sinuses was intubated. The most affected maxillary sinus identified during endoscopy was selected for intubation. The maxillary antrum sinusotomy tube (MAST) (Fig. 2) is a flexible tube that is used to provide access to the maxillary sinus cavity and has an anchoring member at its distal end. The curve of this distal end and the flanges conform to the lateral wall of the nose and keep the flexible tube under the inferior turbinate, leaving the airway passage free of obstruction. When the proximal end is cut at the level of the nostril, it does not show outside the nose, yet is still accessible to the patient for self-irrigation (Fig. 3). Every MAST was installed with the patient under local anesthesia using 4% topical lidocaine and adrenalin for 10 minutes before injecting 1 to 2 mL of 1% lidocaine (1:100,000) at the anterior part of the inferior turbinate and under the inferior turbinate on the lateral wall of the nose, to provide anesthesia up to the level of its posterior attachment. A Karl Storz canula with a distal lip was directed under the inferior turbinate with endoscopic guidance and rotated to get to the posterosuperior area of the inferior meatus because penetration is easier at that level. The endoscope was removed, and a trocar or a specially designed trephine was used to penetrate the maxillary antrum. Once the canula was in place with the aid of endoscopy and tissue resection if needed, the MAST was pushed through, into the cavity, and the canula removed. In effect, this technique is a sinus lavage procedure in which the tube is left in place.

Study Design and Tissue Collection

The maxillary sinus was intubated, and the patient received a 3-week course of steroid or placebo treatment in which 256 μg topical budesonide (five sprays of Rhinocort [Astra-Zeneca Canada, Inc., Mississauga, Ontario, Canada], 100 μg/spray) in a 3-mL syringe injected through a 19-gauge needle) or matched placebo was instilled directly into the maxillary sinus using the MAST. Follow-up visits were scheduled at 2 and 3 weeks. Biopsy specimens were obtained from the most affected maxillary sinus at the time of intubation and after the 3-week treatment period. The Karl Storz flexible optical biopsy and grasping forceps with a 2.7-mm oblique telescope was used to gain access to the maxillary sinus cavity either through the opened middle meatus or through the canula passing under the inferior meatus into the sinus cavity. Each tissue sample was bisected with a No. 11 blade and processed for in situ hybridization or immunocytochemical study. Patients with pollen sensitivity underwent intubation at a time outside the respective pollen season.

Assessment of Clinical Response

Categorization of the patients into responders and nonresponders to maxillary sinus irrigation and steroid administration was performed using a total score based on questionnaires and endoscopic evaluation. Patients were assessed before as well as 3 weeks and 6 to 12 months after intubation. The questionnaire assessed all of the patient's symptoms without focusing on the side that was treated. The questionnaire focused on three major symptoms: facial pressure or pain, nasal congestion, and obstruction and rhinorrhea, as assessed by the patient using an ordinal scaled visual analogue score of 0 to 10 (0 = no symptoms and 10 = severe symptoms). At the 3-week visit videoendoscopy was performed, providing an objective evaluation of the nasal, ethmoidal, and maxillary sinus cavity. The endoscopic appearances were quantified on a three-point basis for the presence of discharge (0 = none, 1 = clear and thin, and 2 = thick and purulent) and mucosal status (0 = normoplasia, 1 = light hyperplasia with no erythema, and 2 = hyperplasia or obvious erythema). A total score was calculated for each visual analogue scale and the endoscopic assessment. The patients were considered to have responded to intubation when they reported a digital analogue score of less than 2.5 for all the symptom scores or an average decrease of at least 50% from the initial score and when the endoscopic score was 0 or 1 at 3 weeks after the intubation. The follow-up period consisted of a visit at 3 to 6 months and at 1 year.

Immunocytochemistry

The cellular infiltrate was quantitated by performing alkaline phosphatase–antialkaline phosphatase immunocytochemistry on sections of biopsy tissue obtained from the maxillary sinus, as previously described.[20] Mouse anti-human monoclonal antibody directed against CD4 and major basic protein (MBP) (kind gift from Redwan Moqbel, PhD, University of Alberta, Edmonton, Alberta, Canada) to detect T cells and eosinophils, respectively.

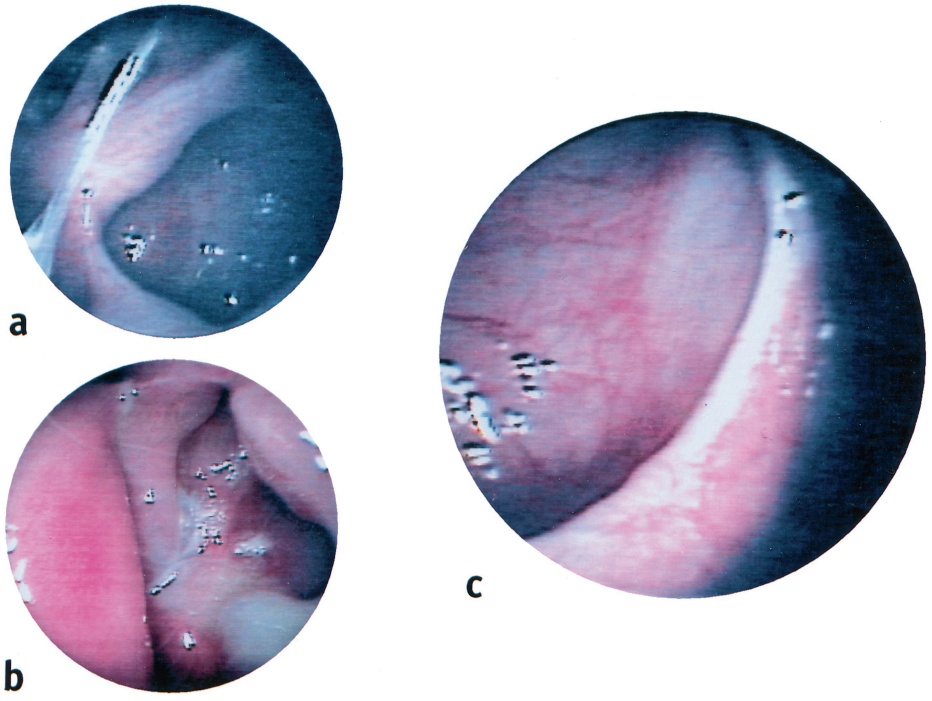

Fig. 1. Endoscopic images from a 2.7-mm, 30°, wide-angle telescope of the mucosa of the right-side maxillary sinus. (**A**) Erythema and hypertrophy of the mucosa; (**B**) hypertrophy and swelling of the mucosa; and (**C**) normal mucosa are evident.

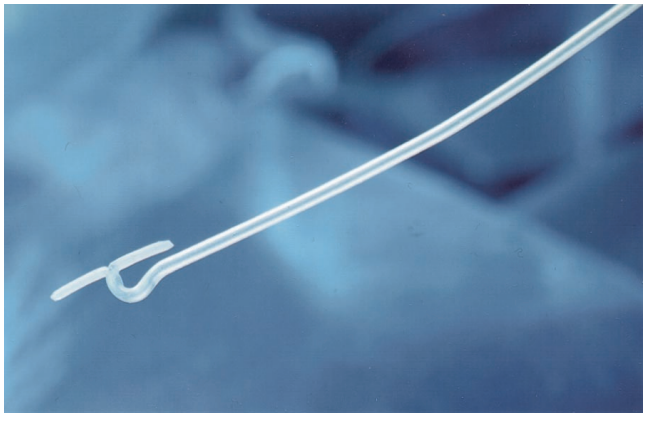

Fig. 2. The maxillary antrum sinusotomy tube (Hood Laboratories, Pembroke, MA).

Both primary antibodies, as well as the secondary rabbit anti-mouse antibody and tertiary rat anti-rabbit antibody conjugated to alkaline phosphatase antibody, were diluted in a commercially available diluting buffer. Sections were incubated with the primary antibody at 4°C overnight and then with the secondary and tertiary antibodies for 30 minutes each. The reaction was visualized with Fast Red TR (Sigma Chemical Company, St. Louis, MO) and alkaline phosphatase substrate. Using this method, positive cells stain red.

In Situ Hybridization

Radiolabeled complementary RNA probes for IL-4 and IL-5 messenger RNA (mRNA) were generated by in vitro transcription in the presence of ^{35}S-conjugated UTP and T7 or SP6 RNA polymerases for sense and antisense probes. Tissue sections were made permeable with 0.3% Triton X-100 and a 1-μg/mL solution of proteinase K at 37°C and were fixed in 4% paraformaldehyde. A wash in 50% formamide in 2× standard saline citrate (SSC) at

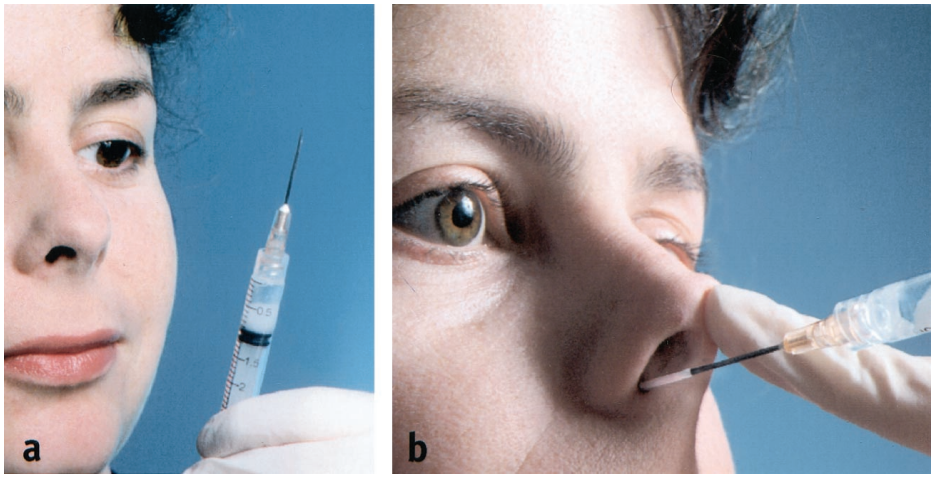

Fig. 3. The tube is accessible at the nostril level for self-irrigation when the patient sits in front of a mirror.

42°C was performed to equalize the tissues and increase adherence to the slide. Sections were incubated overnight at 42°C with 1×10^6 counts per minute per section of riboprobe. Washing after hybridization was performed in decreasing concentrations of SSC ($4 \times$ SSC $- 0.1 \times$ SSC) at 42°C. Excess probe was destroyed by incubating with a 20-μg/mL RNAse A solution at 42°C. Sections were then dehydrated by washing in increasing concentrations of ethanol. For autoradiography, slides were dipped in Amersham LM-2 emulsion (Oakville, Ontario, Canada), stored at 4°C for a period of 12 days, developed in Kodak D-19 (Eastman Kodak, Toronto, Ontario, Canada), and counterstained with Mayer's hematoxylin. Positive signal was identified as a discrete collection of silver grains overlying the cell. Negative control experiments using sense probes or RNAse A pretreatment, or both, was performed to confirm probe specificity.

Quantification

Slides were counted in a blinded fashion using an Olympus light microscope (Carson Group Inc., Markam, Ontario, Canada) at 200× magnification. The graticule was placed under the basement membrane, and the number of positive cells were counted and reported as the mean of the counts for at least six (range 6–8) grids of 0.2 mm^2 each. The within-observer coefficient of variation for repeated counts of immunostaining was 8%, and for hybridized sections, less than 5%. Data are expressed as the median (range) and analyzed using Wilcoxon's signed-rank test. *P* values of less than .05 were considered significant. Correlational analysis was applied using Pearson's correlation coefficient (SyStat, version 7.1, SyStat Inc., Evanston, IL).

RESULTS

Patients

Twenty-four of the 29 patients who were recruited completed the study. These patients had perennial rhinitis and persistent CRS but without nasal polyposis. Of the 29 patients, 18 were women and 11 were men with a mean age of 46 ± 10.7 years (mean ± standard deviation). There were only three smokers with 10, 15, and 19 pack/year histories of smoking; two were responders to intubation, and one was a nonresponder. A typical example of a CT scan obtained before therapy is shown in Figure 4.

Adverse Effects

In general, the instillation of budesonide did not generate any irritation of the sinus cavity. In three patients the tube fell out after manipulation during the self-administered irrigation and was replaced the next day. There were three cases of epistaxis; one required complete packing of the nostril, and local application of Surgicel (Ethicon, Inc., Johnson & Johnson, Somerville, NJ) was sufficient for the other two cases. One of the two diabetic patients had to increase insulin intake during treatment to control glycemia. Five patients could not complete the study. There was one case of *Staphylococcus aureus* infection with pus surrounding the tube after 1 week of the study. Two patients had an asthma attack during intubation requiring steroid treatment, but one was reintroduced later into the study, after a sufficient washout period. For three other cases, either the first or the second biopsy was insufficient for analysis.

Clinical Response to Treatment

At the evaluation before intubation, patients selected for the placebo and the steroid groups experienced a similar degree of discomfort, which was assessed by general score, pain, rhinorrhea, and congestion (Fig. 5). The effect of budesonide compared with placebo treatment was assessed using visual analogue scores, which demonstrated that 11 of 13 patients receiving budesonide improved by more than 50% for a period of 2 to 12 months (Fig. 6). In the placebo group, 4 of 13 patients improved by more than 50%, but the reduction of symptoms was significantly less important than with budesonide and the duration of improvement was less than 2 months, mainly during the

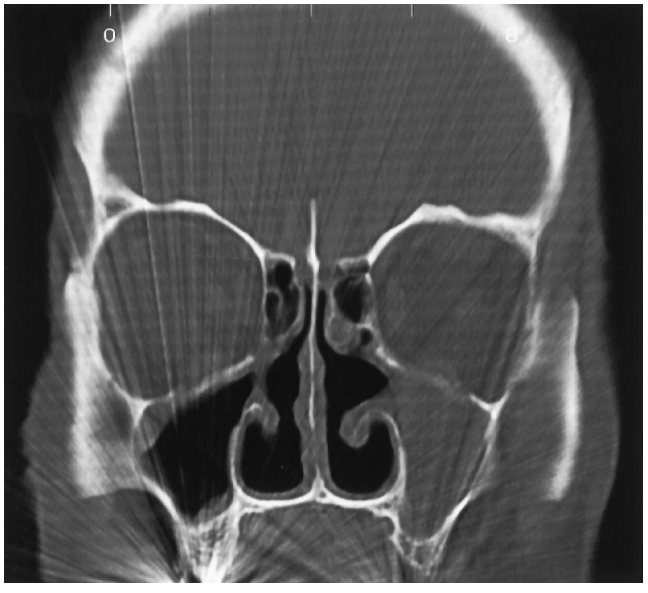

Fig. 4. Computed tomography scan of a patient with persistent chronic sinusitis after ethmoidectomy and middle meatus antrostomy. Scan confirms the patency of the antrostomy and the persistence of mucosal hypertrophy.

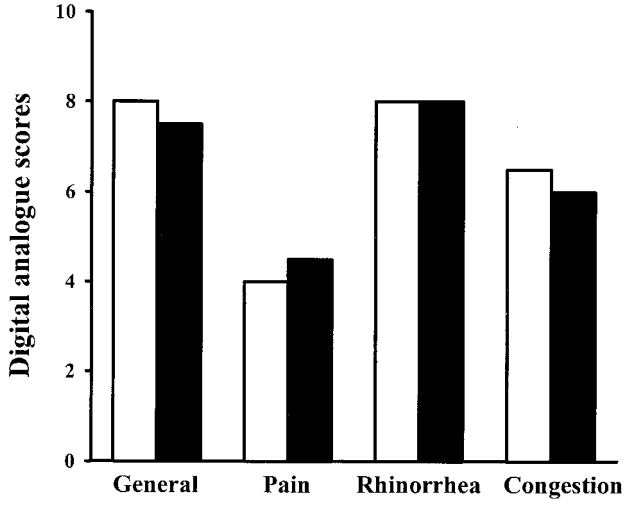

Fig. 5. Relative level of symptomatology on a scale of 1 to 10; general discomfort and specific symptoms show that the two groups were comparable before irrigation. Rhinorrhea was the most inconvenient symptom for the patients.

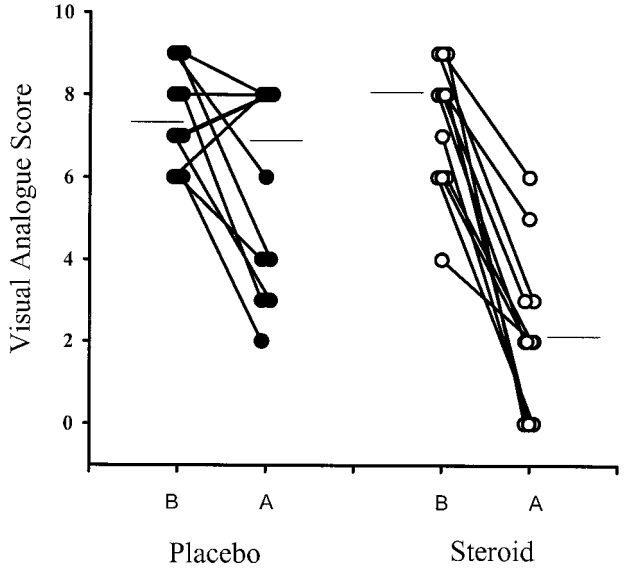

Fig. 6. Results of the summation of symptom scores after placebo and steroid therapy. The regression of symptoms was significantly more important in the budesonide group.

intubation period. The post-treatment endoscopy confirmed that the appearance of the untreated side had not improved. There was also a tendency to see a highlighting of the mucosa during endoscopy confirming the presence of an active inflammatory reaction with hypertrophy or erythema of the mucosa lining the sinuses.

Assessment of Cell Density and Profile of Cytokine Messenger RNA

The similarities between the two patient groups were confirmed by the demonstration of no statistical difference in the numbers of T cells and eosinophils within sections of maxillary sinus mucosa obtained from the placebo (28 [17–41] and 11.5 [5–18], respectively) and steroid (32 [21–42] and 16 [7–21], respectively [$P > .05$]) groups (Fig. 7) before treatment. After 3 weeks, the number of T cells was significantly reduced within sections of maxillary sinus mucosa obtained from patients receiving budesonide compared with pretreatment tissue (29 [16–35], $P < .05$), but not within sections obtained from patients who received placebo treatment (30 [25–37], $P > .05$). Similarly, there were also significantly fewer eosinophils in the tissues of steroid-treated patients (5 [3–11], $P < .05$) than in the tissues of placebo-treated patients (12.5 [4–24], $P > .05$). There were also cells expressing mRNA coding for IL-4 and IL-5 at baseline in similar numbers within the steroid-treated (6.0 [2–9] and 11 [5–18]) and placebo-treated (4.5 [2–11] and 10.75 [5–18], $P > .05$) groups (Fig. 8). However, within sections of sinus mucosa obtained after the steroid treatment there were significantly fewer cells expressing IL-4 (3.0 [0–7]) and IL-5 (4 [0–10]) mRNA compared with pretreatment values ($P < .05$). This reduction was not observed within tissue obtained from patients who were given a matched placebo (6.5 [3–11] and 11.0 [5–25], $P > .05$).

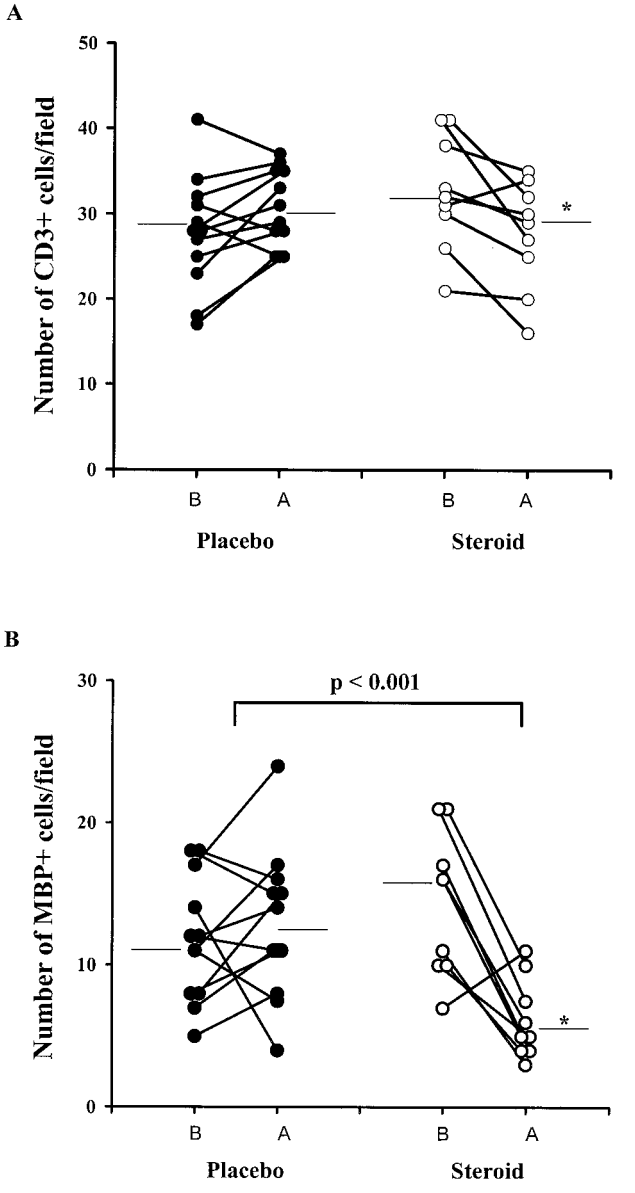

Fig. 7. T cells (**A**) and eosinophils (**B**) within sections of sinus mucosal tissue obtained before (B) and after (A) 3 weeks of intrasinus administration of 256 μg/mL budesonide or matched placebo.

DISCUSSION

This study assessed the efficacy of a new delivery system for topical corticosteroids to the maxillary sinus in patients with CRS. Our results demonstrate that a 21-day treatment in which 256 μg budesonide was instilled directly into the maxillary sinus reduced eosinophilia and reduction of the number of cells expressing mRNA for the Th_2 cytokines IL-4 and IL-5, and is associated with prolonged improvement in clinical symptoms.

Maxillary sinus intubation was introduced in North America as a therapeutic approach by Jasbi and Ritter[18] and has been mainly used for sinusitis in children. This approach for chronic maxillary sinusitis in children used a T-shaped tube with a relatively big lumen and a "T" shape

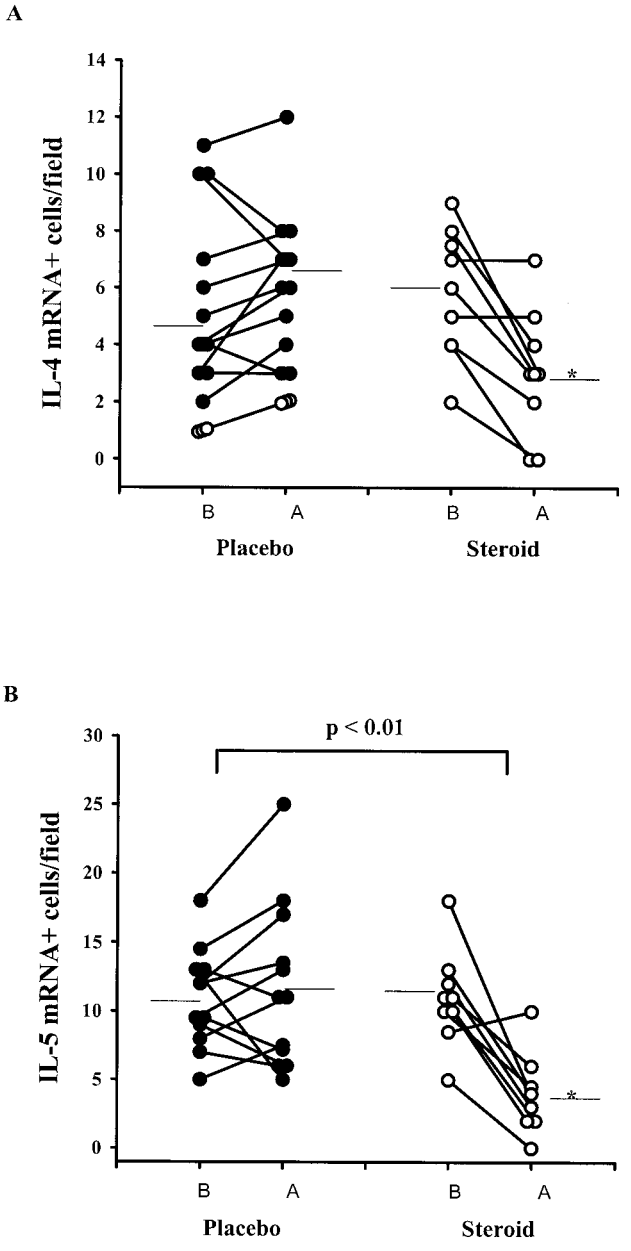

Fig. 8. Number of cells expressing messenger RNA coding for interleukin-4 (**A**) and interleukin-5 (**B**) within sections of sinus mucosal tissue obtained instead of (**B**) and instead of (**A**) intrasinus administration of 256 μg/mL budesonide or matched placebo.

that aligns the straight part of the tube toward the midline of the nose and as such has a tendency to irritate the nasal septum. In the present study, we designed a smaller tube that travels along the lateral wall of the nose as a delivery system, not for ventilation or drainage. The stability and tolerance of the tube were adequate because the tube fell out only when the manipulations for irrigation were excessive (3/24 cases) and no bleeding or irritation occurred during the days after the insertion. This is most likely attributable to the specific design of the tube, which keeps it under the inferior turbinate and away from the airway passage and nasal septum.

The increased requirement for insulin in one case suggests a systemic absorption of budesonide when it is delivered onto the inflamed mucosa of the sinus cavity. Further studies on bioavailability should address this question to determine the exact percentage of absorption. The use of irrigation was supported by clinical experience at Notre Dame Hospital since the 1960s, mainly for frontal sinus empyema, and from the Swedish literature. Although good results could be achieved in acute and subacute sinusitis, our experience with CRS has been that only temporary relief could be achieved from saline irrigation. Because of the similarities in Th_2 cytokine expression seen in allergic rhinitis and CRS,[5] we expected a reduction in the synthesis of IL-4 and IL-5 mRNA by intrasinus steroid application. At the onset of the current study we did not expect a clinical response from therapy because of unilateral application and the importance of mucosal abnormalities that were seen during endoscopic examination. The treatment duration of 21 days was determined mainly because of our knowledge of the clinical behavior of topical corticosteroids in allergic rhinitis[13] and the limited time period of 31 days for the use of the intubation device in Canada.

Corticosteroids act through the inhibition of mRNA synthesis[21] and have been shown to effectively inhibit the production of a number of proallergic mediators, including leukotrienes, histamine and cytokines like IL-4 and IL-13, that regulate IgE production,[22] and IL-5, which modulates eosinophil differentiation and survival within the tissues.[8] Because of the reciprocal relationship between the expression of Th_2 and Th_1 cytokines, steroid treatment has been associated with an increase in the expression of Th_1 cytokines.[23] We have previously shown that the relative level of Th_2 cytokine expression within the nasal and sinus mucosa of individuals with allergic rhinitis and sinusitis is associated with an elevated number of lymphocytes and eosinophils.[17] In the present study, we show that corticosteroids delivered into the maxillary sinus cavity of patients with persistent allergic CRS could reduce the inflammatory process. This supports the assumption that CRS is not simply an infectious disease but a complex inflammatory process. The effect on regression of mucosal hypertrophy in cases of persistent sinusitis even after surgery support the hypothesis that some patients with CRS could benefit from a mucosal therapy instead of surgery.

The possibility of a systemic, instead of topical, effect is not supported by our results. The endoscopic evaluation was unchanged on the untreated side with obvious changes of hypertrophy regression or disappearance of erythema on the budesonide-treated side. At present, we cannot explain why topical treatment influenced all the sinuses on one side in some cases. There did not appear to be an influence on the infundibulum and the drainage of the maxillary sinus because the ethmoid labyrinth was already disrupted at that level. There could possibly be an influence on the ipsilateral fifth nerve, which would be consistent with a previous study that examined neurokinins, pain, and inflammation.[24] In our experience, patients treated with oral prednisone need a longer period of treatment for the same condition, sometimes as long as 6

months. The influence of systemic corticosteroids on homeostasis of the sinuses supports the use of a topical preparation in this condition.

It has not yet been shown whether opening the sinus cavities to the environment, a consequence of ethmoidectomy and meatotomy, may negatively influence the outcome of CRS in patients with IgE-mediated allergy. Indeed, this surgical approach may not be the best treatment for CRS in patients with perennial allergy. The recurrence of symptoms in approximately half of the patients after 6 months to 1 year probably represents the time needed for the return of the vicious circle of inflammation associated with Th_2 cytokine expression within the sinus mucosa.

We have shown that a 21-day treatment of the sinus cavity with budesonide instilled through a MAST tube can control the clinical symptoms and the inflammatory process involved in persistent sinusitis for up to 12 months after treatment.

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