Expanding the evidence base for the medical treatment of nasal polyposis

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Key words: *Nasal polyposis, intranasal, corticosteroids, polyp, topical, mometasone furoate nasal spray*

Abbreviation used
MFNS: Mometasone furoate nasal spray

Individuals with nasal polyposis continue to present a clinical challenge to the treating physician: we do not yet completely understand the underlying inflammatory and infectious pathways of the condition and the intricacies of the relationship with chronic rhinosinusitis, nor have we yet established the best means of producing long-lasting improvements in polyp size and associated symptoms.

Strategies for nasal polyposis management usually involve surgical treatment, medical treatment, or a combination of both, often depending on the preference and experience of the individual physician. To date, the evidence base has lacked adequately powered studies to direct either the specialist or the primary care practitioner to the most appropriate method of treatment.

Surgery is generally carried out endoscopically to relieve nasal blockage and to allow greater aeration of the sinus mucosa, thereby promoting recovery of the diseased tissue. Although the benefits of surgery include improvements in symptoms and health-related quality of life, incremental effects over medical therapy have not been well established.[1,2] Indeed, recurrence rates after endoscopic sinus surgery are as high as 60% after a median of 2 years,[3-5] with the likelihood of a successful outcome being influenced by a number of factors. These include aspirin sensitivity, asthma, or patient-specific anatomic obstructions, such as lateralization of the middle turbinate.[3,6] In addition, major adverse events of endoscopic sinus surgery, such as cerebrospinal fluid leakage or periorbital hematoma, occur in approximately 1% of patients, with minor events occurring in 5% to 6% of patients.[7]

Given the invasive nature of any form of surgery, in combination with its inherent risks and required recovery time, the recently published ''European position paper on rhinosinusitis and nasal polyps'' advocates medical treatment of mild-to-moderate nasal polyps with intranasal corticosteroids, reserving surgery for more severe forms of the disease.[7] Furthermore, because nasal polyposis is characterized by a mucosal pathology involving dense eosinophilic infiltration,[8] targeting the underlying inflammatory pathways with corticosteroids is a rational approach to treatment, irrespective of whether surgery is also considered.

The effects of intranasal corticosteroids on nasal polyp size and nasal symptoms were first formally investigated by Mygind et al[9] in the 1970s. Since then, at least 10 placebo-controlled clinical trials evaluating the efficacy and safety of intranasal corticosteroids in nasal polyposis have been published and are neatly summarized in the ''European position paper on rhinosinusitis and nasal polyps.''[7] Taken together, these trials indicate that nasal steroids are effective in treating polyposis; however, they are limited by small subject numbers or short duration of treatment. Only 4 trials enrolled more than 100 subjects, and these trials ranged in duration from 6 to 12 weeks.[10-13] The trial of longest duration (26 weeks) enrolled only 55 subjects, who were randomized to 1 of 3 treatment arms.[14]

Of interest in these trials is the variation in the effects of steroid treatment on symptoms, objective measures, and polyp size. The majority found a statistically significant improvement in total nasal symptoms and nasal blockage with topical steroid therapy; however, no significant effect on sense of smell was noted in several of the larger trials.[11-13] Although significant improvements in polyp size were reported in the trials with budesonide,[10,12,15] those carried out with fluticasone propionate (as nasal spray or nasal drops) failed to show a consistent effect on polyp size.[11,13,14,16] Peak nasal inspiratory flow rate, an objective measure of nasal blockage, generally improved, irrespective of whether significant changes in polyp size occurred. These findings are reflective of the observation that improvements in polyp size, objectively assessed nasal blockage, and nasal symptoms might be, at least partially, disparate processes.[1] Furthermore, the outcomes highlight the need to use multiple outcome measures when evaluating the effectiveness of nasal polyposis treatments.

Evidence-based medicine has been described as the integration of best research evidence with clinical expertise and patient values.[17] The cornerstone of evidence-based

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Disclosure of potential conflict of interest: M. Blaiss has consultant arrangements with Schering-Plough, HSK, and sanofi-aventis and is on the speakers' bureau for Schering-Plough, GSK, sanofi-aventis, and AstraZeneca.

Received for publication September 8, 2005; revised September 14, 2005; accepted for publication September 14, 2005.

Available online November 14, 2005.

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J Allergy Clin Immunol 2005;116:1272-4.
0091-6749/$30.00
© 2005 American Academy of Allergy, Asthma and Immunology
doi:10.1016/j.jaci.2005.09.009

medicine is valid, impacting, and applicable evidence. Although it is evident that a number of studies have evaluated the effects of intranasal corticosteroids in nasal polyposis, the evidence base has lacked large-scale studies with sizable effects that could be translated into useful application in a clinical setting. However, in this month's issue of the *Journal of Allergy and Clinical Immunology,* Small et al[18] report the first of 2 large-scale, multicenter, randomized, double-blind, placebo-controlled clinical trials evaluating the efficacy and safety of the intranasal corticosteroid mometasone furoate in subjects with nasal polyposis. This is the largest controlled study of its kind to be carried out to date, involving 354 subjects with mild or moderate bilateral nasal polyps, and provides compelling evidence that this management strategy is valid for nasal polyposis. In this study subjects were randomized to 4 months of treatment with 200 μg of mometasone furoate nasal spray (MFNS) or placebo administered once or twice daily. The primary endpoints of the trial were (1) change from baseline to endpoint (at 4 months or using data from the last visit carried forward) in bilateral polyp grade and (2) change from baseline in nasal congestion/obstruction score averaged over the first month of treatment.

Over the 4-month treatment period, polyp grades were reduced by a mean of 27% ($P \leq .001$) and 22% ($P \leq .01$) with once- or twice-daily MFNS, respectively, compared with a 12% reduction with placebo. Similarly, congestion-obstruction score improved over 1 month by 21% ($P = .001$) and 26% ($P < .001$) with once- or twice-daily MFNS, respectively, compared with the 11% improvement seen with placebo. When these parameters were considered together by determining the proportion of subjects with both a 1-point or greater improvement in nasal polyp grade and a 0.5-point or greater improvement in congestion/obstruction score, 43% and 57% of once- and twice-daily MFNS recipients, respectively, were responders compared with 34% of placebo recipients.

The internal validity of this trial is high and, as such, provides a useful basis from which to evaluate the applicability of MFNS in clinical practice. The trial design was robust, and the outcome measures chosen were appropriate for assessing nasal polyposis from both an objective and a subjective standpoint. The subject population was relatively homogenous, and confounders were minimized. Furthermore, threats to external validity were minimized by stringent inclusion and exclusion criteria, relatively low subject dropout numbers, and an appropriate duration of therapy.

Nevertheless, questions remain. Are the results of this trial clinically significant? Will they have an effect on the way in which we treat patients presenting with mild or moderate nasal polyps? Indeed, when considered in the light of studies of fluticasone propionate nasal drops, the clinical significance of these findings is notable. It has been suggested that drop formulations of topical steroids are more appropriate than spray formulations for nasal polyposis because they reach the middle meatus more successfully.[19] Furthermore, recent guidelines advocate use of nasal spray formulations for mild disease and reservation of nasal drops for moderate disease.[7] Although the present trial cannot be directly compared with fluticasone propionate studies, it is interesting that no statistically significant difference in visual assessment of polyp size over 12 weeks of treatment was reported with 400 μg once daily fluticasone propionate drops compared with placebo in subjects with mild or moderate disease.[13] In another study, a 24% reduction in polyp size was observed with fluticasone propionate drops (400 μg once daily) after 12 weeks; however, this was not statistically significant relative to placebo.[11] Reductions in polyp size with MFNS in the study by Small et al[18] were statistically significant, however, and consistent with those seen in trials with the intranasal spray formulation of budesonide.[10,12,15]

Subject-evaluated improvements in symptoms also provide a useful guide to the clinical significance of treatment. In the trial by Small et al,[18] notable improvements in congestion/obstruction were observed and sustained over time. Of particular interest, however, is the improvement in sense of smell reported in this trial, particularly because such an effect has not been reported in other studies, even when a reduction in polyp size was observed.[11-13,15]

The publication of the findings of this trial by Small et al[18] lends a certain weight to the evidence base for intranasal corticosteroid use in nasal polyposis and further validates first-line use of medical therapy in this condition. The data strongly suggest that MFNS is an effective medical treatment for nasal polyposis in terms of reducing polyp size and improving symptoms. Furthermore, like other intranasal corticosteroids, clinical trials of MFNS in subjects with seasonal or perennial allergic rhinitis indicate a low risk/benefit ratio and low systemic bioavailability.[20-25] This is particularly important, given that intranasal corticosteroid use in nasal polyposis is likely to be chronic.

We look forward to the generation of further outcomes data with MFNS to enable an assessment of the effect of this agent on the need for surgery, health-related quality of life, and productivity in subjects with nasal polyposis. This, combined with our growing knowledge of the underlying inflammatory pathways, might promote the development of and elucidate the potential role for other intranasal corticosteroids.

Editorial assistance was provided by Thomson Gardiner-Caldwell London, supported by the Schering-Plough Research Institute, Kenilworth, NJ.

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