

MOMETASONE FUROATE INTRA NASAL SPRAY FOR THE TREATMENT OF BILATERAL NASAL POLYPOSIS

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ABSTRACT

Objective: To know the safety and efficacy of Topical mometasone furoate nasal spray (NS) for the treatment of bilateral nasal polyposis..

Material and Methods: It was a randomized, double-blind, placebo controlled, parallel-group study, conducted in the department of Otorhinolaryngology (Rhinology division) of Khyber Teaching Hospital, Peshawar-Pakistan. A total of 310 subjects 18 years or older with bilateral nasal polyps. Interventions: (1) A 200- μ g dose of mometasone furoate NS in the morning and matching placebo in the evening; (2) 200- μ g doses of mometasone furoate NS in the morning and evening; or (3) matching placebo in the morning and evening. All 3 regimens were administered as a nasal spray for 4 months, from September 2018 to December 2018. Primary end points were change from baseline to last assessment in physician assessed bilateral polyp grade and change from baseline in subject-assessed congestion and/or obstruction score averaged over the first month of treatment. Analysis of variance was used for all efficacy end points except for change in bilateral polyp grade, for which baseline polyp grade was added as a covariate to the analysis of variance model to account for any between-group baseline differences in this variable.

Results: Mometasone furoate NS doses of 200 μ g administered once or twice daily produced greater reductions in bilateral polyp grade at the end point than placebo, with differences reaching statistical significance with twice daily dosing ($P=.04$). Over 1 month, both mometasone furoate NS regimens produced statistically superior improvements from baseline in congestion and/or obstruction score vs placebo ($P=.01$ for once-daily dosing; $P.001$ for twice daily dosing). The drug was well tolerated.

Conclusion: Mometasone furoate NS is an effective and well-tolerated treatment for bilateral nasal polyposis in adults, reducing nasal polyp size and symptoms of nasal congestion and/or obstruction.

Key Words: Intranasal, bilateral, nasal, polyposis, Topical, Steroids.

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INTRODUCTION

Nasal polyps are benign growths of the nasal mucosa associated with edema, fibrosis, reduced vascularization, a decreased number of glands and nerve endings, and damaged epithelium^{1,2}. The cause of nasal polyposis is not completely understood; however, it is frequently associated with asthma and intolerance to aspirin³. The condition is thought to be a result of

underlying mucosal disease and is characterized by eosinophil inflammation: approximately 65% to 90% of polyps are classified histologically as eosinophilic^{4,5}. The symptoms of nasal polyposis include nasal obstruction and discharge, and impairment of sense of smell⁶. The objectives for the management of the condition include elimination or reduction in the size of polyps followed by reestablishment of an open nasal airway and nasal breathing, improvement or restoration of sense of smell, and ultimately prevention of polyp recurrence^{7,8}. In nasal polyposis, topical nasal corticosteroids are considered the medical treatment of choice, and several different intranasal corticosteroids have been investigated with regard to both effect on symptoms and reduction in polyp size. These benefits may be attributed, at least in part, to the effect of topical corticosteroids on decreas-

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ing eosinophilic infiltration in the nasal mucosa⁹. The objective of the present large, appropriately powered study was to evaluate the efficacy and safety of 200- μ g doses of mometasone furoate nasal spray (NS) administered once daily (QD) in the morning or twice daily (BID) as monotherapy, compared with placebo, in the treatment of patients with nasal polyposis.

MATERIAL AND METHODS

This randomized, placebo-controlled, parallel-group, double blind, was conducted at department of Otorhinolaryngology (RhinoLOGY division) of Khyber Teaching Hospital, Peshawar-Pakistan. The study was carried out in accordance with the Declaration of Helsinki, the US code of Federal Regulations, and guidelines on Good Clinical Practice. The study protocol and statement of informed consent (obtained from all subjects prior to study entry) were reviewed and approved by an institutional review board and independent ethics committee. The total study period ran from September 2018 to December 2018. Subjects enrolled in the trial were at least 18 years old and had an endoscopically confirmed diagnosis of bilateral nasal polyps at the screening and baseline visits.

Nasal polyps were graded as 1, 2, or 3 (on a scale of 0 to 3) in each of the right and left nasal cavities. In addition, subjects had to have clinically significant nasal congestion or obstruction, with a morning score of 2 or higher (on a scale of 0 to 3) for each of the last 7 days of a 14-day run-in period. Subjects with asthma were required to have a documented forced expiratory volume in 1 second of at least 80% of the predicted value within the 6 months prior to screening and no asthma exacerbations within the 30 days prior to screening. Subjects treated with inhaled corticosteroids were required to be taking a moderate, stable dose of no more than 800 μ g/d of beclomethasone dipropionate or the equivalent for at least 1 month prior to screening and to remain with a stable dose throughout the study period. Subjects were excluded from the study if they had a history of seasonal allergic rhinitis within the past 2 years, sinus or nasal surgery within the past 6 months, 3 or more nasal surgical procedures, or any surgical procedure that prevented accurate grading of polyps according to the study protocol. In addition, subjects were excluded if they had any of the following conditions: fibrotic nasal polyposis (based on endoscopic examination); complete or nearly complete nasal obstruction; nasal septal deviation requiring corrective surgery or nasal septal perforation; acute sinusitis,

nasal infection, or upper respiratory tract infection at screening or in the 2 weeks prior to screening; ongoing rhinitis medicamentosa; Churg-Strauss syndrome or dyskinetic ciliary syndromes; cystic fibrosis; glaucoma or a history of posterior subcapsular cataracts; allergies to corticosteroids or aspirin; or any other clinically significant disease that could interfere with the evaluation of therapy. Use of concomitant medications that would interfere with study evaluations was not permitted, including nasal sodium cromoglycate; nasal atropine or ipratropium bromide; corticosteroids (except permitted oral inhaled corticosteroids for asthma or mild or medium-strength corticosteroids for dermatologic purposes); antihistamines; decongestants; topical, oral, or ocular anti-inflammatory drugs; or topical, nasal, or oral antifungals.

Use of acetaminophen (paracetamol) was encouraged for analgesic purposes, with nonsteroidal anti-inflammatory drug use limited to 5 consecutive days if alternative analgesia was required. Antibiotics were permitted for bacterial infection. Subjects who met eligibility criteria at the screening visit (day -14, visit 1) underwent a 14-day, single-blind, placebo run-in period to help exclude placebo responders and identify subjects with stable disease. Eligible subjects at baseline (day 1, visit 2) were then randomized to receive 1 of 3 regimens: 200- μ g mometasone furoate NS in the morning and matching placebo NS in the evening, 200- μ g mometasone furoate NS in the morning and evening, or matching placebo NS in the morning and evening. Randomization was performed in blocks of 3 using random numbers generated by SAS function UNIFORM (SAS Institute, Cary, NC) with seed based on clock time. Randomization was stratified by the presence or absence of concurrent asthma. Subjects who presented with concurrent asthma were assigned randomization numbers in ascending sequential order using the lowest numbers available at the study center.

Subjects without asthma were assigned randomization numbers in descending sequential order. Mometasone furoate NS was supplied as commercial Nasonex (Schering-Plough Corp, Kenilworth, NJ) in a metered-dose manual pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mometasone furoate calculated on the anhydrous basis. The aqueous medium contained glycerin, microcrystalline cellulose, carboxymethylcellulose sodium, sodium citrate, 0.25% w/w phenylethyl alcohol, citric acid, benzalkonium chloride,

and polysorbate 80. Treatment was administered for 4 months in a blinded manner, with study visits on day 8 (visit 3) and months 1, 2, 3, and 4 (visits 4 to 7). Treatment compliance was evaluated at visits 3 through 7 by weighing each study drug bottle without the subject's knowledge. Unused study drug was collected at each visit. The primary end points of the study were change from baseline to the end of the study (data from the last visit carried forward) in physician-evaluated bilateral polyp grade, calculated as the sum of grades in the left and right nasal cavities, and the change from baseline in subject-assessed congestion and/or obstruction averaged over the first month of treatment. Nasal endoscopy was performed by the physician at each visit, excluding visit 3, without using vasoconstrictors or decongestants. The size and extent of the polyps were graded on endoscopy as 0 (no polyps), 1 (polyps in the middle meatus, not reaching below the inferior border of the middle turbinate), 2 (polyps reaching below the inferior border of the middle concha, but not the inferior border of the inferior turbinate), or 3 (large polyps reaching below the lower inferior border of the inferior turbinate). Bilateral polyp grade was obtained as the sum of the individual grades for the left and right nasal cavities.

Congestion and/or obstruction scores ranged from 0 (none) to 3 (severe). Subjects were instructed to evaluate their congestion and/or obstruction symptoms once a day in the morning before dosing, from screening until the end of treatment. Symptom evaluation reflected severity at the time of dosing (that is, instantaneous). Secondary end points included changes from baseline for the following variables: symptoms of loss of smell, anterior rhinorrhea, and postnasal drip scores averaged over the first month of treatment and peak nasal inspiratory flow (PNIF) over months 1, 2, 3, and 4. Subjects scored their symptoms on a scale from 0 (none) to 3 (severe) each morning before dosing. Following this symptom assessment, they measured their PNIF each morning using a PNIF meter (Clement Clarke International Ltd, Harlow, England). In addition, the proportion of subjects demonstrating an improvement (defined as a reduction in bilateral polyp grade of 1 from baseline and a reduction in congestion and/or obstruction score of 0.5 from baseline) was recorded at the end point. The investigator also evaluated symptom at therapeutic response at the end point using a scale of 0 (complete relief) to 4 (no relief). Safety variables included adverse event recording, laboratory tests, vital

signs, and physical examination. Details of all reported adverse events were recorded throughout the study, with severity graded as mild, moderate, severe, or life-threatening, and the relationship to treatment determined by the investigator. Vital signs were measured at all visits.

Summaries of data were based on all randomized subjects (intention-to-treat principle). An analysis of variance was used to analyze responses for the efficacy end points, with stratification for sources of variability (treatment and asthma status). Baseline bilateral polyp grade was added as a covariate to the analysis of variance model for analysis of the change from baseline in bilateral polyp grade (analysis of covariance) to account for any between-treatment baseline differences in this variable. Comparisons between treatment groups were based on differences in mean estimates from the analysis of variance or analysis of covariance models. All tests were carried out at the unadjusted significance level of $\alpha = .05$. It was determined that a total sample size of 100 subjects per treatment group would provide 90% simultaneous power at a 2-sided alpha level of .05 to detect a difference of at least 1.0 point in the change in bilateral polyp grade from baseline to the end point (assuming a standard deviation [SD] of 1.44) and of at least 0.37 points in the change in average congestion and/or obstruction score from baseline over the first month of treatment (assuming an SD of 0.8). With 100 subjects per treatment group, a difference of 0.66 in bilateral polyp grade would be detectable with 90% individual power.

RESULTS

A total of 310 subjects were randomized to treatment. The 3 treatment groups were well matched with regard to baseline demographic and disease characteristics. Small differences in baseline bilateral polyp grade were observed between treatment groups. Approximately 65% of subjects had a baseline bilateral polyp grade of 4 or more, and 85% to 88% of subjects had a moderate to severe baseline congestion/obstruction score. More than 85% of subjects completed the 4-month treatment period, with more than twice as many placebo recipients as active drug recipients discontinuing during the treatment phase (18% vs 8%). Approximately 90% of subjects were considered to be compliant with the dosing regimen (defined as using 59% to 138% of prescribed doses, according to medication bottle weight).

Treatment with 200 µg of mometasone furoate NS QD or BID produced a greater change from baseline to the end point in bilateral polyp grade than did placebo; this difference reached statistical significance with the BID dose ($P = .04$). The BID dose was significantly superior to placebo in change from baseline in congestion/obstruction score over the primary time interval of 1 month ($P.001$) and during the entire 4 months of treatment ($P.001$). The QD dose also resulted in statistically significant changes in congestion/obstruction score compared with placebo at 1 month ($P = .01$), 2 months ($P = .02$), and 4 months ($P = .02$). Effects of treatment were observed as early as week 1 with BID dosing ($P.001$ vs placebo) and week 2 with QD dosing ($P = .01$ vs placebo), with scores continuing to decrease over the course of the study. These results demonstrated a continued effect of treatment over time in both active treatment groups and in the placebo group, with the relative difference between both active treatments and placebo remaining relatively constant. For the secondary end point of change from baseline in loss of smell averaged over the first month of treatment, the 200-µg BID dose of mometasone furoate NS demonstrated a statistically significant improvement over placebo ($P = .05$). Furthermore, the BID dose maintained a numerically greater decrease from baseline in this symptom than placebo throughout the study. In addition, the BID dose resulted in statistically significant improvements over placebo for anterior rhinorrhea ($P.001$) and postnasal drip ($P.001$) at month 1, with improvements maintained at month 4. Statistically significant improvements relative to placebo were also seen for anterior rhinorrhea at all study time points after month 1 ($P.004$) and for postnasal drip at all time points except month 3 ($P.03$).

Treatment with the QD dose also resulted in statistically significant improvements in anterior rhinorrhea over placebo at month 1 ($P = .02$) and at all subsequent study time points except month 3. Over the 4-month study period, the BID dose of mometasone furoate NS was statistically superior to the QD dose for anterior rhinorrhea at week 3, week 4, and month 1 of the study ($P.02$) and for postnasal drip at week 2, week 3, and month 1 ($P.03$). Significant improvements in PNIF were measured in subjects receiving the BID dose at all time intervals ($P.001$) and in those receiving the QD dose at week 2 and all subsequent time intervals ($P.004$) compared with placebo (Figure 4). Subjects receiving the BID dose had greater improvements in PNIF than those receiving the QD dose at all time intervals, with

the exception of week 2 ($P.04$). A significantly greater proportion of subjects receiving the BID dose (49%) met improvement criteria compared with those receiving either the QD dose (34%; $P = .03$) or placebo (25%; $P.001$). Consistent with this finding, both active treatment groups were associated with significantly greater improvement in therapeutic response score (as assessed by investigators) at the end point compared with placebo ($P.001$ for both groups).

Treatment with mometasone furoate NS was well tolerated and showed no unusual or unexpected events. Most adverse events were of mild or moderate intensity. The overall incidence of treatment-emergent adverse events was similar among the 3 treatment groups: 53%, 56%, and 51% in the QD, BID, and placebo groups, respectively. The most frequent treatment-emergent adverse events were upper respiratory tract infection, headache, and epistaxis (defined to include a wide range of bleeding episodes, from frank bleeding to bloody nasal discharge and flecks of blood in the mucus), with epistaxis being reported more frequently in the BID group (15% of subjects) than in the other groups (6% of QD subjects and 5% of placebo subjects). The incidences of upper respiratory tract infection and headache were similar in all treatment groups. No deaths or life-threatening adverse events were reported. Serious adverse events were reported in 6 subjects, but these were considered to be unrelated to the study drug. Only 1 subject discontinued treatment because of an adverse event (a placebo recipient who experienced a severe loss of taste). Seven subjects interrupted randomized treatment because of an adverse event (1 QD subject, 3 BID subjects, and 3 placebo subjects). No clinically meaningful changes in laboratory parameters, vital signs, or limited physical examinations were noted in any treatment group.

DISCUSSION

The inflammatory processes underlying nasal polyposis are dominated by eosinophilic infiltration into the nasal mucosa and inhibition of eosinophil apoptosis. This dysregulation of eosinophil function may be, at least in part, mediated through expression of inflammatory cytokines by T cells. In vitro studies indicate that corticosteroids may attenuate eosinophilic inflammation by inducing apoptosis¹⁰⁻¹². Indeed, a series of small clinical trials has suggested that intranasal corticosteroids may reduce nasal polyp size and improve associated symptoms in subjects with nasal polyposis¹³, although this finding has yet to be validated in large, robust trials.

The present study was 1 of 2 similar trials designed to assess the efficacy and safety of 200- μ g. Change in mean individual symptom scores (loss of smell, anterior rhinorrhea, and postnasal drip) at month 1 (A) and month 4 (B) of the study period. Least square means and P values obtained from analysis of variance with treatment, baseline asthma status, and treatment center effects added as covariates.

All mometasone furoate was administered as 200- μ g doses of nasal spray. QD indicates once daily; BID, twice daily. Asterisk indicates P.05 vs placebo; dagger, P.01 vs placebo; double dagger, Change from baseline in mean peak nasal inspiratory flow (PNIF) during the treatment period. Least square means and P values obtained from analysis of variance with treatment, baseline asthma status, and treatment center effects added as covariates. All mometasone furoate was administered as 200- μ g doses of nasal spray. QD indicates once daily; BID, twice daily. Asterisk indicates P.05 vs placebo; dagger, P.01 vs placebo; double dagger, P.001 vs placebo; section mark, P.05 vs QD dose; and parallel mark, P.01 vs QD dose. Mometasone furoate is a potent, topically active, synthetic corticosteroid with anti-inflammatory activity. The NS formulation of mometasone furoate is used therapeutically and prophylactically in seasonal allergic rhinitis and therapeutically in perennial allergic rhinitis¹⁴⁻¹⁷. The present study was conducted over a 4-month treatment period, chosen to allow for optimal assessment of treatment effect. It is recognized that, owing to the chronic inflammatory nature of the condition, change in polyp size is likely to be slow, a hypothesis supported by several small studies of the use of intranasal corticosteroids in nasal polyposis¹⁸⁻²¹. A parallel mometasone furoate NS study, conducted at sites in the United States and South America, is reported elsewhere²². The primary end points in this study were change in bilateral polyp grade over the 4-month treatment period and change in congestion/obstruction score over the first month of treatment. It was important that the study was sufficiently powered to detect appropriate differences in both of these parameters, given that they appear to be disparate processes. Indeed, it has been shown that, although endoscopic nasal surgery reduces nasal polyp size, it has limited effect on perceived nasal obstruction and other symptoms, 4 presumably owing to the underlying inflammatory disease that contributes to symptoms. After 4 months of treatment, both QD and BID doses produced numerically greater reductions in bilateral

polyp grade compared with placebo. These differences reached statistical significance for the BID dose when analyzed using an analysis of covariance model. This model allowed for between-group differences in baseline polyp grade thus enhancing the precision of the measurement and has been used in other studies of intranasal corticosteroids for nasal polyposis²³⁻²⁷.

For the primary end point of change in congestion/obstruction score, both BID and QD doses produced statistically significantly superior improvements compared with placebo after 1 month and over the 4-month treatment period. Furthermore, the BID dose was significantly superior to the QD dose for this end point throughout the study from week 2 onward. These findings were supported by the objective measurements of PNIF recorded on a daily basis. Improvements in other symptoms such as sense of smell, postnasal drip, and anterior rhinorrhea were also observed with mometasone furoate NS. The clinical significance of mometasone furoate NS is evident when the relative changes in polyp size and congestion/obstruction scores from baseline are examined. Considering that the mean baseline polyp grade was approximately 4, the 1-point change from baseline in polyp grade with the BID dose represents approximately 25% improvement. Likewise, the 0.5-point improvement in congestion/obstruction score from baseline with active treatment represents approximately a 22% improvement from the mean baseline score of 2.3. The 2 doses selected for use in the study were based on the approved dose for the treatment of allergic rhinitis (200 μ g QD). However, to account for possible hindrance of study drug distribution due to the mechanical obstruction of the polyps and because the condition itself may be less responsive to treatment than allergic rhinitis, a second dose (200 μ g BID) was also investigated. The superior clinical efficacy of this BID dose seen for the primary end points is also supported by the significantly greater proportion of subjects who were classed as "improved" in the BID group compared with QD and placebo groups. In this study, statistically significant improvements in polyp size and congestion/obstruction score were observed; thus, the proportion of subjects with improvement analysis is an appropriate means to further assess the clinical benefits of mometasone furoate NS in the treatment of polyposis. Indeed, approximately half of the subjects treated with the BID dose experienced a clinically meaningful change in both polyp size (1 point) and congestion/obstruction score (0.5 points). This represents almost

twice the proportion of subjects considered improved compared with those who used placebo.

As the definition of response is based on individual subject changes, these results further support the notion that BID treatment with 200 μ g of mometasone furoate NS provides clinically meaningful benefits to patients with nasal polyposis. It is also interesting to observe the large placebo effect seen in this study, possibly attributable to the nonactive aqueous solution in the NS. Such an effect has been observed in other studies of intranasal corticosteroids in nasal polyposis^{28,29} and highlights the importance of including a placebo group in such studies to ensure that a true measure of treatment benefit can be attained. Reported compliance with the dosing regimen in this study was high (approximately 90%); however, it should be noted that bottle weight as a means of measuring compliance is limited by variability in individual bottle weights and by the potential for nonadherent subjects to actuate the device to improve reported compliance. Both doses of mometasone furoate NS were well tolerated. The most frequently reported adverse events were epistaxis (which included a wide range of bleeding episodes, from frank bleeding to flecks of blood in the mucus) and headache, a finding that is consistent with data from clinical trials in the treatment of allergic rhinitis³⁰. There is often concern within the medical community with regard to long-term use of corticosteroids, particularly in terms of impact on bone density, hypothalamic pituitary-adrenal axis suppression, and the development of cataracts or glaucoma. Although the effects of mometasone furoate NS on bone density have not been formally studied, systemic absorption of mometasone furoate NS is negligible and is unlikely to have an effect on this marker: even at 20 times the recommended daily allergic rhinitis dose, mometasone furoate NS has no adverse effect on urinary-free cortisol and plasma cortisol levels or on suppression of the hypothalamic pituitary-adrenal axis. Furthermore, reports of glaucoma or cataracts with intranasal corticosteroid use are few³¹

CONCLUSION

Mometasone furoate Nasal topical steroid is an effective and well-tolerated treatment for patients with bilateral nasal polyposis.

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Mometasone Furoate Intra Nasal Spray for the Treatment of Bilateral Nasal Polyposis

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Khan AR: Main Idea, Overall supervision.

Arif MAU: Data Collection, Follow up, Bibliography.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.