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Montelukast As An Adjunct To Treatment of Chronic Rhinosinusitis With Polyposis: A Prospective Randomized Controlled Trial

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Abstract

In a prospective, randomized controlled trial, forty consecutive adult patients with bilateral nasal polyps were randomized into two groups. Twenty subjects in Group A were treated with oral prednisolone for 14 days and budenoside nasal spray for 8 weeks while the twenty subjects in Group B received a similar treatment with additional oral montelukast for 8 weeks. Subjects completed a modified nasal ICSD symptom score at the start of treatment and at 8 and 12 weeks after beginning the treatment. Symptom scores improved in both the groups after treatment. Subjects in Group B reported a statistically significant improvement in sense of smell ($p = 0.0002$), sneezing ($p = 0.008$) and overall score ($p = 0.0006$) at 8 weeks than controls. Four weeks after the completion of treatment, a statistically significant improvement was seen in the sense of smell ($p = 0.0006$), headache ($p = 0.03$) and overall score ($p = 0.003$) in patients in Group B when compared to Group A. Montelukast therapy may have clinical benefit as an adjunct to oral and inhaled steroid in chronic nasal polyposis.

Key Words

Montelukast, Chronic Rhinosinusitis, Polyposis, Steroid

Introduction

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is one of the most difficult forms of CRS to treat and exhibits frequent recurrence regardless of therapeutic modality (1). Current consensus guidelines support long-term medical treatment with intranasal corticosteroid (INCS) sprays, supplemented with short, infrequent courses of oral corticosteroids. Several reviews have systematically examined local corticosteroid use in patients with CRSwNP, showing improvements in symptom scores and polyp size via meta-analysis (2,3). Similarly, high-level evidence supports the use of oral corticosteroids in CRSwNP patients to improve symptoms and polyp size (4); however, the effects are short lived, and long-term use is limited because of the risk of severe side effects. Despite the routine use of corticosteroid medications, a large percentage of patients with CRSwNP will continue to have ongoing symptoms requiring additional treatment, usually in the form of surgery, which provides immediate improvement but is not curative. In recent years, there has been increasing interest in the potential role of leukotrienes, potent biological mediators produced by eosinophils, mast cells, monocytes and basophils. They are derivatives of arachidonic acid via the 5-lipoxygenase pathway. There is convincing evidence for the role of leukotrienes in the pathogenesis of asthma, by causing bronchoconstriction, airway hyperresponsiveness, and airway inflammation (5). A number of drugs that selectively modify the leukotriene pathway (or antileukotrienes) have been developed (6). These use one of the two main strategies: either inhibition of the production of leukotrienes by 5-lipoxygenase (zileuton), or by antagonism of the action of the leukotriene at the

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cysLt1 receptor (montelukast, zafirlukast, panlukast).Antileukotrienes in both groups have been shown to cause clinical improvement in mild-to-moderate chronic stable asthma (7-10). Leukotrienes have also been implicated in the pathology of allergic rhinitis, with measurable increases in LTC4 and LTD4 in nasal secretions of patients after nasal challenge as well as during natural allergen exposure (11).It has been hypothesized that the LTC4 concentration in polyp tissue may have a prognostic value, as high levels of LTC4 were found to correlate with early recurrence of polyps (within 18 months) (12). The aim of this study is to examine the potential benefits offered by the leukotriene receptor antagonist - montelukast as an adjunct to oral prednisolone in patients with chronic nasal polyps.

Material and Methods

The present study was conducted in the Department of Otorhinolaryngology and Head & Neck surgery at SMGS Hospital, Govt. Medical College, Jammu for a period of 1 year during which 40 adult patients in age group of 24-58 yrs, with bilateral nasal polyps that extended beyond the middle meatus, confirmed by nasal endoscopy were enrolled. Subjects with unilateral pathology, ones with any contraindication to steroid intake, any previous nasal surgery or any history of sensitivity to any of protocol drugs were not included in the study. All subjects underwent complete ENT examination including CT scan of nose and paranasal sinuses and nasal endoscopy. Written consent was given by each patient, after they were explained the purpose and requirements of the study by one of the authors. The subjects recruited for the study were randomized into two treatment groups, group A and B. Subjects in group A were treated with a two week reducing doses of oral steroid and an eight week course of steroid nasal spray while subjects in group B received two week reducing doses of oral steroid and an eight week course of oral montelukast and nasal steroid spray.Subjects completed validated questionnaire related to nasal symptoms (International Classification of Sinus Disease) before commencement of treatment and at 8 weeks and 12 weeks from baseline. The ICSD records patients symptoms of facial pain and pressure; headache; nasal blockage or congestion; nasal discharge; disturbance of smell and overall discomfort on a 0 to 10 ordinal scale. In addition, subjects scored their sneezing, a symptom not addressed by the ICSD score. The baseline characteristics of the two groups and the differences in the modified ICSD questionnaire scores between the two groups for each domain were analyzed statistically. A p value of less than 0.05 was considered statistically significant.

Results

The 40 patients in the present study were divided into group A and group B, of 20 patients each, after randomization. The mean age of patients in group A and B was 44.05 years and 42.1 years respectively. Baseline characteristics of the patients in both the groups were studied as shown in *table 1*. The treatment protocol followed in both the groups i.e. A and B is as shown in the *table 2*. The mean ICSD questionnaire score (baseline, at 8weeks and 12 weeks) of patients in Group A and B is shown in *table 3*. Based on the ICSD questionnaire score, statistical analysis was carried out, and it was found that the post-treatment scores in group B when compared to group A, were statistically significant for sense of smell (p=0.0002), sneezing (p=0.008) and overall score (p=0.0006) at 8 weeks. A statistically significant difference in favour of group B, for the sense of smell (p=0.0006) and overall score (p=0.003) continued when the score at 12 weeks were compared. In addition to these two scores there was also a statistically significant improvement in the symptom score of headache in favour of group B at 12 weeks. No statistically significant difference was seen in the treatment score of both the groups for nasal discharge, facial pain and nasal blockage both at 8 and 12 weeks. (*Table 4*)

Discussion

In the present study, when compared with subjects treated with steroid alone (Group A), subjects treated in addition with montelukast (Group B) showed a significant reduction in symptom scores at eight weeks with respect to sense of smell, overall score and sneezing. In a similar study done by Stewart *et al*.(13) subjects treated with montelukast showed a significant reduction in symptom scores at eight weeks with respect to headache, facial pain, and sneezing. However, montelukast therapy did not have a significant effect on the symptom score of nasal blockage, headache, facial pain and nasal discharge, in the present study but in the study by Stewart *et al*. (13) montelukast therapy did not have a significant effect on the overall symptom score or on symptoms of nasal blockage, hyposmia, or nasal discharge. In the present study, at 12 weeks there was improvement in symptom

Table 1. Showing the Baseline Characteristics of Patients in Group A and Group B

	Group A	Group B	Total
Age			
Mean	44.05 years	42.1 years	
Range	26-58	24-56	24-58
Gender			
Male	12(60%)	14(70%)	26(65%)
Female	8(40%)	6(30%)	14(35%)
Nasal septum on anterior rhinoscopy			
No septal deformity	14(70%)	16(80%)	30(75%)
Septal deformity but no obstruction	3(15%)	3(15%)	6(15%)
Septal deformity with obstruction	3(15%)	1(5%)	4(10%)
Asthma	6(30%)	8(40%)	14(35%)
Sensitivity to aspirin	2(10%)	1(5%)	3(7.5%)
Currently smoke	3(15%)	1(5%)	4(10%)
Exposed daily to smoke	2(10%)	3(15%)	5(12.5%)
Exposed to chemicals/fumes	1(5%)	2(10%)	3(7.5%)

Table 2. Showing Distribution of Treatment Protocols

	Group A	Group B
Treatment protocols	**Oral steroid**:prednisolone 35 mg reducing by 5 mg every second day over 14 days+ **Nasal steroid**: budesonide nasal spray 2 metered doses to each nostril for 8 weeks	**Montelukast:** 10 mg for 8 weeks+ **Oral steroid:** prednisolone 35 mg reducing by 5 mg every second day over 14 days+ **Nasal steroid:** budesonide nasal spray 2 metered doses to each nostril for 8 weeks

Table 3. Showing Results of ICSD Questionnaire of Group A and Group B (mean values)

	Nasal blockage			Headache			Facial pain			Alteration in sense of smell			Nasal discharge			Sneezing			Overall		
	B	W8	W 12	B	W 8	W 12	B	W 8	W 12	B	W 8	W 12	B	W 8	W 12	B	W 8	W 12	B	W 8	W 12
A	7.4	3.8	4.7	4.7	3.2	3.7	3.8	2.7	3	7	4.9	5.7	6.4	3.4	3.9	4.3	2.2	2.5	7.5	5.2	5.8
B	7.5	4	4.6	5	2.8	3.3	4.4	2.4	3	7.8	4.2	4.6	6.8	3.2	4.1	4	1.6	2.5	7.9	4.1	4.8

Table 4. Statistical Analysis (p value) of Symptom Score Between group A&B at 8 &12 wks after Beginning the Treatment

	Facial pain	Sneezing	Sense of smell	Headache	Nasal blockage	Nasal discharge	Overall score
8 weeks	0.455	0.008	0.0002	0.25	0.659	0.535	0.0006
12 weeks	0.8	0.37	0.0006	0.03	0.282	0.52	0.0034

score in both the groups even after discontinuation of treatment but statistically significant difference between the 2 groups was seen in symptom score of sense of smell, headache and overall score. In the study by Stewart *et al*, (13) the effects were not maintained at the 12th week time-point.

In a prospective, randomized controlled study, Schaper *et al.*(14) described their work evaluating the effects of treatment with montelukast in patients with both CRSwNP and asthma. They treated 24 patients in a blinded, placebo-controlled fashion using 10 mg montelukast daily for 6 weeks, with a 4-week placebo phase randomly assigned

before or after treatment. Outcomes were measured in various fashions and compared to placebo, including the use of non-standardized, non-validated symptom and 4-point rhinoscopy scores, measurement of various inflammatory mediators in nasal lavage fluid, eosinophil counts in nasal smears and peripheral blood smears, rhinomanometry and olfactometry. Significant improvements were noted in all measured outcomes following montelukast treatment, including significant decrease in mean concentration of CysLTs, substance-P, eosinophil cationic protein, and neurokinin A in nasal lavage fluid, as well as significant decrease in peripheral blood and nasal smear eosinophil counts. Vuralkan *et al.*(15) compared the efficacy of montelukast versus mometasone furoate nasal spray for treatment of CRSwNP following Endoscopic Sinus Surgery(ESS). There was a significantly higher rate of polyp recurrence in the montelukast treatment group (48%) compared to the mometasone group (20%). Eosinophil counts were not significantly improved following either treatment, and higher eosinophil counts were noted to be a risk factor for polyp recurrence.

Pauli *et al.* (16) did a placebo controlled randomized controlled trial on patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) using montelukast and found significant improvements in nasal symptoms, nonnasal symptoms, headaches, and practical problems. Significant decrease in local extracellular protein (ECP) and polyposis was also seen.

A study by Kieff and Busaba (17) showed that patients with perennial allergic rhinitis appeared to derive more benefit from montelukast therapy than nonallergic patients, with respect to reduction in symptom scores and polyp eosinophilia. The findings of the present study suggested that the use of montelukast may be of clinical benefit as an adjunct to oral and inhaled steroid therapy in patients with bilateral nasal polyposis.

Conclusion

Leukotriene Antagonists (LTAs) like Montelukast may provide additional benefit to oral and Intranasal Corticosteroids (INCS) treatment in subjects with chronic nasal polyps. Antileukotrienes may also have a role in the long-term maintenance therapy for bilateral nasal polyposis; however, larger randomized controlled studies are required to evaluate the effects of more prolonged therapy.

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