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Original Research

To compare the efficacy, safety, and cost-effectiveness of montelukast-levocetirizine and montelukast-fexofenadine in patients of allergic rhinitis

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ABSTRACT:
Aim: To compare the efficacy, safety, and cost-effectiveness of montelukast-levocetirizine and montelukast-fexofenadine in patients of allergic rhinitis. **Methods:** The Institutional Ethics Committee authorised a prospective, randomised, doubleblind, parallel, activecontrolled, comparative 4week experiment including 70 patients with AR. Patients from the ENT outpatient department between the ages of 18 and 65 who had moderatesevere intermittent or mild chronic AR according to the original Aria categorization were eligible. Patients with a total nasal symptom score (TNSS) of 5 or higher who had not been treated with antihistaminics in the preceding week were eligible for the trial. **Results:** When comparing baseline to fourth week TNSS in Group A, there was a statistically significant change (P< 0.0001). The baseline TNSS in Groups A and B was 11.15 and 10.68, respectively. This parameter was reduced for the first time in the second week and remained reduced until the fourth week. Group B had similar findings, however the drop in this parameter was greater than in Group A, as indicated in Table 2. From baseline to the fourth week, the mean change in TNSS score was 8 in Group A and 9.46 in Group B. The mean change in TNSS in Group B was statistically significant (P< 0.0033) when compared to Group A. When the differential eosinophil count was evaluated from baseline to the fourth week, no group demonstrated a significant difference. **Conclusion:** The mean change in TNSS was significantly greater in the montelukast fexofenadine group than in the montelukastlevocetirizine group. The costeffectiveness ratio was lower in the montelukastlevocetirizine group than in the montelukastfexofenadine group. Although the reduction in TNSS was greater in the montelukastfexofenadine group, the montelukastlevocetirizine combination is less expensive.
Key words: Allergic rhinitis, cost-effectiveness, fexofenadine, levocetirizine, montelukast

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INTRODUCTION

Allergic rhinitis (AR) is a worldwide health issue. It is the leading cause of death and disability globally. [1] According to estimates, AR affects 10% to 25% of the world's population. [2] The most common symptoms of AR include nasal congestion, rhinorrhea, itching, sneezing, and nonnasal symptoms including burning, itching, and watery eyes, as well as irritating ears and tongue. By interfering with cognitive and emotional functioning, these symptoms may have a significant impact on a patient's quality of life. [3] In the United States, the estimated yearly cost of AR varies from $1.4 billion to over $6 billion in direct costs. [4] Antiallergic treatment nowadays is focused on allergy avoidance, symptomatic medication, targeted immunotherapy, and education. [5] The cornerstones of AR therapy include oral/intranasal H1antihistaminics, decongestants, leukotriene receptor antagonists, and intranasal corticosteroids. Secondgeneration antihistamines have grown in popularity due to their equivalent effectiveness and decreased frequency of side effects when compared to firstgeneration competitors. [6,7] Levocetirizine, a powerful secondgeneration histamine (H1) receptor antagonist, is effective against persistent AR, improving quality of life while decreasing comorbidities and societal costs. [8] Fexofenadine is a secondgeneration H1 receptor antagonist that is selective, nonsedating, and has an extra effect on inflammatory mediators. [9] Montelukast is a highly selective leukotriene D4 type

I receptor antagonist. The leukotriene modifiers are antiinflammatory as well as bronchodilators. [10]
According to the literature review, adding an antihistamine to montelukast provides an extra advantage.[11] The combined medication of montelukast and antihistamine has boosting and complementary effects, successfully lowering symptoms.[12] The effects of simultaneous levocetirizine and montelukast medication on symptoms and quality of life in AR are superior than monotherapy with levocetirizine.[13] In the treatment of AR symptoms, fexofenadine combined with montelukast is more effective than an antihistaminic alone. There is research comparing contemporaneous levocetirizine and montelukast to monotherapy or placebo, as well as concomitant fexofenadine and montelukast to monotherapy or placebo. However, there is a scarcity of evidence comparing contemporaneous montelukastlevocetirizine with montelukastfexofenadine. As a result, we sought to examine the efficacy, safety, and costeffectiveness of different combinations in AR patients.

MATERIAL AND METHODS

The Institutional Ethics Committee authorised a prospective, randomised, doubleblind, parallel, activecontrolled, comparative 4week experiment including 70 patients with AR.
Patients from the ENT outpatient department between the ages of 18 and 65 who had moderatesevere intermittent or mild chronic AR according to the original Aria categorization were eligible. Patients with a total nasal symptom score (TNSS) of 5 or higher who had not been treated with antihistaminics in the preceding week were eligible for the trial. The level of nasal symptoms (rhinorrhea, nasal itching, nasal blockage, and sneezing) is measured using a fourpoint Likert scale ranging from 0 to 3 (0 = no symptom, 1 = mild, 2 = moderate, and 3 = severe). [10] The TNSS was calculated by adding all four individual symptom ratings, with a potential total score ranging from 0 (no symptoms) to 12. (maximum symptom intensity). The trial comprised patients who signed written informed permission, followed the study protocol, were free of any clinically significant condition, and had normal electrocardiography (ECG). Children, pregnant women, nursing mothers, patients with asthma requiring chronic use of inhaled or systemic corticosteroids, a history of failure to improve symptoms with antihistaminic drug treatment in the past, a history of allergies to study medication or tolerance to antihistamines, and use of study drug in the previous 7 days were all excluded. Patients with major hematologic, cardiovascular, hepatic, renal, neurologic, psychiatric, or autoimmune disorders were also eliminated.
AR patients were randomly assigned into two groups of 35, A and B. The block randomization approach was utilised to achieve consistent allocation ratios for the study medicines, montelukastlevocetirizine and montelukastfexofenadine, with a block size of 4 in equal proportions (1:1). The medications were similar in form, size, weight, texture, and packaging for the double-blind trial. A statistician used a random number table to produce the randomised treatment allocation sequence. It was given to a third individual who was not directly participating in this research, along with similar plastic containers containing study medicines. This individual labelled the containers based on the random allocation order of patients receiving medication. The code for this random allocation sequence was kept in a sealed envelope and opened only after the research was completed during data analysis. The therapy was unknown to both the patients and the investigators. The drugs were given to the patients for one week at a time. Every week, patients were given a fresh supply of medication. Patients were instructed to bring any unused medicines or containers to their appointments until the trial was completed (4 weeks). The unused pill number was used to assess the patients' medical compliance. The returning medications were thrown away. At the conclusion of the trial, the drugs were decoded. Group A got a fixeddose combination of montelukast 10 mg and levocetirizine 5 mg once day. Group B was given a fixed dosage of montelukast 10 mg with fexofenadine 120 mg once day. Throughout the trial, the same dose was used. At the first session, the patients were handed an 8day symptom journal (screening visit). A few additional day diaries were sent in the event that the patient did not report on the designated day. The patients were expected to record TNSS parameters. During the research period, no concomitant condition was detected in these individuals. After the trial, the patients were turned over to their treating physician. The change in TNSS from baseline was used to assess efficacy. Improvements of two or more points were regarded notable. [10]
For cost-effectiveness analysis, only direct cost parameters were taken into consideration. Direct cost parameters were cost of medications used, medical procedures, and hospitalization charges, if any. Cost-effectiveness ratio of both treatment groups was calculated based on the following formula:
Cost-effectiveness ratio = cost/outcome
The efficacy of the outcome was assessed. The major efficacy metric was the TNSS. ECG, total leukocyte count, differential leukocyte count, liver function test, and kidney function test were done on each patient at the beginning and conclusion of the research. General clinical safety was assessed by close monitoring of patients for the management of any emergent adverse events, which were documented in the case report form. Patients who had an adverse medication response were carefully treated.

RESULTS

The protocol was followed by 65 of the seventy patients who were randomised and assigned to the therapy. Two patients in the montelukastlevocetirizine group, i.e., Group A, and three patients in the montelukastfexofenadine group, i.e., Group B, were lost to follow-up at the conclusion of the first week and were not included in the analysis. In terms of baseline demographic data, the two groups were similar [Table 1].

When comparing baseline to fourth week TNSS in Group A, there was a statistically significant change (P< 0.0001). The baseline TNSS in Groups A and B was 11.15 and 10.68, respectively. This parameter was reduced for the first time in the second week and remained reduced until the fourth week. Group B had similar findings, however the drop in this parameter was greater than in Group A, as indicated in Table 2. From baseline to the fourth week, the mean change in TNSS score was 8 in Group A and 9.46 in Group B. The mean change in TNSS in Group B was statistically significant (P< 0.0033) when compared to Group A. When the differential eosinophil count was evaluated from baseline to the fourth week, no group demonstrated a significant difference.

Table 1: Baseline demographic characteristics of allergic rhinitis patients

	Group A	Group B	*P*
Patient recruited	35	35	
Patient follow-up	33	32	
Male; female (%)	43.66; 56.34	46.55; 53.45	
Age (mean)	38	37	0.6269a
TNSS at baseline (SD)	11.15 (1.17)	10.68 (1.4)	0.2522b
TLC mean (SD)	8384.8 (12,224.52)	8368 (972)	0.7678b
Differential eosinophil Count	7.25 (0.69)	7.08 (0.64)	0.3828b

The cost-effectiveness ratio was used to assess cost-effectiveness. In terms of cost, the treatment method with the lowest cost-effectiveness ratio is deemed best. For a period of four weeks, the cost of therapy in Groups A and B was Rs.184.8 per patient and Rs.282.8 per patient, respectively. Group A has a lower cost-effectiveness ratio than Group B.

The overall incidence of side effects was 15% in Group A and 22% in Group B, respectively. In both groups, no major adverse events were documented. The side effects documented in both groups did not need a dosage decrease or any additional medication to manage. Fisher's exact test was used to assess the incidence of adverse effects between two groups, and the results were insignificant.

Table 2: Total nasal symptom score at baseline and at 2 weeks and 4 weeks after the initiation of treatment in Group A and Group B patients with allergic rhinitis

Parameter	Baseline	2 weeks	4 weeks	*P** (4 weeks to baseline)
TNSS				
Group A (*n*=33)	11.15 (1.17)	5 (0.70)	3.15 (1.58)*	0.0001
Group B (*n*=32)	10.68 (1.4)	4.28 (0.68)	1.21 (0.65)*	0.0001

DISCUSSION

This is the first double blind trial to examine the efficacy, safety, and cost effectiveness of montelukastlevocetirizine and montelukastfexofenadine combos. We found just one randomised, open labelled, prospective, comparative, multicentric trial assessing solely the effectiveness and safety of the fixed dosage combination of montelukastlevocetirizine and montelukastfexofenadine. Furthermore, patients in India have limited access to expensive drugs. As a result, we thought it would be beneficial to undertake this double blind trial in an Indian setting to compare the efficacy, safety, and cost effectiveness of various fixed dosage combinations. In terms of demographic factors, the baseline data demonstrate no substantial variation between the research groups. This demonstrates the similarity of the study patients in the two groups. The effectiveness of medications was evaluated by TNSS, and the difference was substantial in both groups at the fourth week. The mean change in TNSS was significantly greater in the montelukastfexofenadine group than in the montelukastlevocetirizine group. This shift might be attributed to fexofenadine's extra antiinflammatory action and montelukast's bronchodilator effect. There have been studies that demonstrate that combining levocetirizine and montelukast improves nasal symptoms statistically more than monotherapy. [12,14] Another research found a substantial improvement in the quality of life of AR patients with a combination of montelukast and levocetirizine. [15] Some trials found that levocetirizine and montelukast alone were successful in controlling nasal symptoms and inflammatory markers, but the combination therapy provided even greater symptom management. [8] According to one research, montelukastfexofenadine substantially improved AR symptom management when compared to those taking antihistaminic alone or with placebo. [16]

However, owing to a lack of data on the comparability of study combinations, we were unable to compare our findings. The difference in differential eosinophil count was not statistically significant in either group. The change in ECG and adverse medication response were used to determine safety. The incidence of adverse effects was not statistically significant in either group. The adverse effects documented in both groups did not need a dosage decrease or any treatment. Only the direct cost of the pharmacological therapy was considered when comparing the costeffectiveness of the two treatments. Throughout the therapy of AR, the costeffectiveness ratio was lower in the montelukastlevocetirizine group than in the montelukastfexofenadine group. In pharmacoeconomic analysis, the treatment option with the lowest costeffectiveness ratio is deemed best. The cost of montelukastlevocetirizine was Rs. 6.6 per day, but the cost of montelukastfexofenadine was Rs. 10.07. Although the efficacy measured by TNSS was higher in the montelukastfexofenadine group than in the montelukastlevocetirizine group throughout the research, the montelukastlevocetirizine combination was more costeffective than montelukastfexofenadine for the treatment of AR. A research found that levocetirizine is a costeffective choice that improves quality of life clinically when compared to other secondgeneration antihistamines and leukotriene antagonists. [4,17] However, following a thorough search, we were unable to locate any research similar to our discovery, since there had previously been no costeffective studies conducted between montelukastfexofenadine combination and montelukastlevocetirizine in AR patients. As a result, this research is unusual in that it compares two commercially available fixeddose combinations on the market. Despite the fact that the current research was doubleblind, had a small sample size, and was brief in length, the importance of its findings cannot be overstated. However, bigger sample sizes and longer followup periods in studies comparing montelukastfexofenadine combination and montelukastlevocetirizine combination may give more important findings.

CONCLUSION

The mean change in TNSS in the montelukast fexofenadine group was substantially bigger than in the montelukastlevocetirizine group. The cost-effectiveness ratio for montelukastlevocetirizine was lower than for montelukastfexofenadine. Although the montelukastfexofenadine group had a higher decrease in TNSS, the montelukastlevocetirizine combination was less costly.

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