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Original Research Article

# Comparative Clinical Study of Ebastine and its Combined Preparation of Montelukast in Persistent Allergic Rhinitis: A Randomized Prospective Double-Blind Analysis

**Sanjeev Kumar[1], Vinay Kumar Sinha[2], Jeetendra Kumar[3]**

[1]Tutor, Department of Pharmacology, Jawaharlal Nehru Medical College and Hospital (JLNMCH), Bhagalpur, Bihar

[2]Tutor, Department of Pharmacology, Jawaharlal Nehru Medical College and Hospital (JLNMCH), Bhagalpur, Bihar

[3]Professor, Department of Pharmacology, Jawaharlal Nehru Medical College and Hospital (JLNMCH), Bhagalpur, Bihar

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**Corresponding Author:Dr. Vinay Kumar Sinha**

**Conflict of interest: Nil**

**Abstract:**

**Background:** Several physicians give antiallergic medications to treat allergic rhinitis (AR). Antihistamines and antileukotrienes, which are frequently used in fixed dose combinations (FDC) of both, are only beneficial in treating allergy symptoms symptomatically. The current investigation was motivated by contentious reports about their effectiveness in AR, either in isolation or in combination with other treatments. The purpose of this study was to assess the effects of montelukast, ebastine, and their FDC on the extranasal and nasal symptoms that patients with mild-to-moderate persistent AR (PAR) reported as subjective.

**Methods:** Patients with mild-to-moderate PAR were divided into three groups and given three weeks of treatment with ebastine, montelukast, and their combination preparation. AM and PM symptom scores, as well as the overall five nasal symptom grading system, were used to gauge their effectiveness. In order to evaluate the therapy medications' continued anti-allergic effects, the treatment was stopped over the last week.

**Results:** The overall mean score of allergy symptoms decreased significantly in all treatment groups as compared to baseline values. Both the AM and PM mean scores were significantly reduced by ebastine when combined with montelukast; montelukast only affected the PM mean score. The three groups that were analyzed showed a significant reduction in both AM and overall symptoms when ebastine and its combination preparation with montelukast were used.

**Conclusion:** The anti-allergic effects were variable among all three groups. Montelukast provided superior daytime symptom management. To a similar degree, ebastine and montelukast together managed allergy symptoms.

**Keywords:** Ebastine; Montelukast; Allergic Rhinitis; Total Five Nasal Symptoms Scoring.



## Introduction

Between 10% and 30% of people worldwide suffer with allergic rhinitis (AR), one of the most prevalent ENT disorders.[1] Due to its increasing prevalence, 17.6 million people and 6.6 million children in the USA received a diagnosis of seasonal AR during the course of the 2012 year.[2,3] It lowers quality of life (QOL), which has an impact on productivity at work. This may be comparable to other serious diseases.[4] Even though 75% of children and 80% of adults with asthma have symptoms, AR is frequently written off as a minor condition. It may have an impact on a patient's social, psychological, and physical well-being as well as their ability to function at work, which would be extremely costly for society. This also has been associated with both increase in the risk of asthma development and its severity.[5] There are numerous medications available for treating AR, most of which merely offer symptomatic relief. Immunotherapy appears to be a distinct therapy in and of itself, altering the fundamental pathogenic mechanisms of AR; nevertheless, its drawbacks include the need to identify particular antigens or combinations of antigens for desensitization, a lengthy course of treatment, and a high likelihood of relapse upon completion of the course. Antihistamines, which primarily function by inhibiting H1 receptors, are the cornerstone of medication used to treat AR symptoms. Newer antihistamines, which have certain beneficial side effects in addition to opposing histamine, have supplanted conventional antihistamines. One by one, they are starting to

work in clinical settings, and there are still a ton more on the way. Patients with AR are either dissatisfied with current medications or continue to take them despite their intolerable side effects, thus the hunt for the best medication to better control symptoms is still ongoing. Antihistamines are known to be helpful in reducing symptoms in most individuals with intermittent and persistent kinds of AR, regardless of severity, if they are taken as prescribed. In addition to improving QOL, they lessen extranasal symptoms such eye redness, itching, and lacrimation as well as subjective nasal symptoms like sneezing, itching, congestion, and discharge. Objective evidence of improved nasal peak flow, decreased nasal eosinophils, decreased serum soluble intracellular adhesion molecule, and experimentally generated nasal congestion have all been linked to improved illness outcomes.[7],[8] Another medication that is frequently used to treat AR is montelukast, an antileukotriene. It works by inhibiting leukotrienes, which are produced by the lipooxygenase enzyme during the breakdown of arachidonic acid. Histamine and leukotrienes are both crucial to the pathophysiology of AR. Consequently, montelukast enhances QOL comparable to antihistamines while reducing nasal and extranasal discomfort.

From a theoretical perspective, concurrent administration of antihistamines and montelukast in AR should result in better, more efficacious treatment of symptoms. The subjective and objective parameters of AR were greatly improved when different antihistamines were delivered in conjunction with montelukast, as demonstrated by numerous clinical [9–11] and experimental trials. This was in contrast to when antihistamines and montelukast were administered separately.

Contrary to this conclusion, numerous comparative studies conducted on patients with AR have found that certain antihistamines, such as fexofenadine, loratadine,[12] and desloratidine,[7,13] are just as effective when taken alone as when combined with montelukast. As a result, the various fixed-dose combinations (FDC) of antihistamines and montelukast that are currently on the market are not warranted.

The review of the literature also showed how little research has been done on the comparison of various antihistamines in AR, such as second-generation medication ebastine, and montelukast. The current investigation was motivated by the aforementioned contentious reports regarding the interactions between other antihistamines and montelukast, as well as the dearth of comparable data regarding ebastine. Thus, the aims and objectives of the present study were to compare the anti-allergic effect of ebastine, montelukast, and their FDC on the subjective nasal and extranasal symptoms in mild-to-moderate persistent AR (PAR) patients.

## Material and Methods

In patients with mild-to-moderate PAR, a randomized prospective double-blind comparison study was conducted. From January to June of 2023, it was held in the Department of Pharmacology at Jawaharlal Nehru Medical College and Hospital in Bhagalpur, Bihar, in cooperation with the Department of ENT. According to AR, PAR is a kind in which allergic reactions last more than 28 days or more than five days per week. After being screened for PAR, subjects received a diagnosis and were informed about the study's objectives, potential risks, benefits, and safety precautions in the local language. Their questions were successfully addressed, and the specifics of the investigation were clarified. Following their informed consent, the inclusion and exclusion criteria were established for the study.

Patients with a diagnosis of persistent mild-to-moderate AR in either sex between the ages of 18 and 65 who are literate, understand how to accurately and promptly record any adverse effects that may occur, without bias, in the dairy provided, and who consent to medication treatment and planned follow-up were included in this study.

Patients with a history of significant systemic disorders, chronic smokers, chronic alcoholics, drug addicts, psychiatry patients, deviated nasal septum, nasal polyps, atrophic rhinitis, and any nasal mass were excluded from this study. Additionally, patients with associated bronchial asthma, atopic dermatitis, severe PAR, immunotherapy/herbal therapy, and corticosteroid therapy were also not allowed to participate.

Using a sample size calculator, the sample size was calculated with the power of the study set at 90%, the level of significance set at 0.05%, and the confidence interval at 10%. The sample size for each group of three subjects was around 35. Prior to beginning the experiment, randomly assigned volunteers were denied access to medicines and underwent baseline examinations including an electrocardiogram (ECG), liver function test (LFT), respiratory function test (RFT), and complete blood count (CBC). For the purpose of controlling severe symptoms in sneezers and nasal blockers, respectively, short-acting medications such as chlorpheniramine maleate 25 mg and oxymetazoline nasal drops 0.05% were given. The enrolled subjects were randomly divided into three groups and were received following oral treatment for 3 weeks, once daily post cibum at 8:00 PM.

Group A: Ebastine 10 mg,

Group B: Montelukast 10 mg,

Group C: Ebastine 10 mg + Montelukast 10 mg.

Both the patients and the investigators received double-blinded drug treatment. Every prescription was packaged on a tiny blue paper and put inside a large blue envelope with a code. A third party not directly engaged in the study administered the drug to the individuals once a week, and decoding was carried out following data analysis.

The total five nasal symptom scoring (T5NSS) approach, which has been used in previous studies [14,15], was modified appropriately to evaluate the subjective symptoms of PAR. Patients were asked to record their symptoms twice a day for four weeks. The five parameters of this scoring system were sneezing, rhinorrhea, itching, congestion, and eye symptoms (itching, lacrimation, and congestion). The parameters were scored on a severity scale that ranged from 0 to 3, with 0 representing none, 1 representing mild, 2 representing moderate, and 3 representing severe. The maximum possible score was 15. At the first visit on day 1, after stopping their anti-allergic medication for the previous three days, the patients were instructed to rate the intensity of their allergy symptoms in the dairy that was given to them and a baseline score was taken. They were instructed to note their symptoms score twice a day, at 8 a.m. and 8 p.m., without fail, as well as any negative effects that they experienced. The prescriptions were valid for one week. After a week, the second visit was compensated for both making sure the patient complied with instructions and for accurate, correct, and consistent diary entries. Data from the first week were gathered, and prescriptions for the second week were distributed. At the third appointment, which took place two weeks later, data were gathered, medication was discontinued, and participants were advised to keep documenting in dairy without taking any medication. On the fourth appointment, dairy was collected, current readings were recorded, and tests including the CBC, LFT, RFT, and ECG were redone.

## Results

Three headings were created from the data collected from the subjects' dairy: total nasal, AM, and PM symptom scores. In terms of scores, mean± standard error mean was used. Within each group, the corresponding baseline scores were compared, as were the weekly scores between each group. ANOVA was used to determine statistical significance at $P < 0.05$, and the Tukey HSD post-hoc test was used after.

**Table 1: Anti-allergic effects of various drug treatments**

| Group | Week 1 | | Week 2 | | Week 3 | | Week 4 | |
|---|---|---|---|---|---|---|---|---|
| | Total score | | Total score | | Total score | | Total score | |
| | AM score | PM score | AM score | PM score | AM score | PM score | AM score | PM score |
| Group 1 Ebastine | 146.86±1.5<br>69.23±0.8* | 77.46±1.1 | 131.98±1.2*<br>58.70±0.9* | 73.32±1.0 | 110.62±0.8*<br>50.18±0.8* | 59.88±0.9 | 142.53±1.6<br>69.91±1.1 | 72.62±1.4 |
| Group 2 Montelukast | 149.92±1.6<br>79.28±1.5 | 70.64±1.3* | 138.62±0.9<br>76.93±1.2 | 61.69±1.1* | 113.31±1.1<br>64.51±1.0 | 48.80±0.6 | 145.66±1.3<br>73.79±1.3 | 71.87±1.1 |
| Group 3 Ebastine + Montelukast | 151.05±1.7<br>71.62±0.9* | 79.43±1.5 | 134.27±1.0<br>65.67±1.2* | 68.60±1.4* | 114.19±0.9<br>56.45±1.0* | 57.74±0.9 | 146.09±1.4<br>71.92±1.3 | 74.17±1.5 |
| F value | 1.83 | | 10.17 | | 3.90 | | 1.71 | |
| P value | P<0.165 | | P<0.0001 | | P<0.023 | | P<0.184 | |

*P<0.05

When compared to the baseline T5NSS mean score of 157.89 ± 1.6, ebastine significantly ($P \leq 0.05$) decreased the mean T5NSS score at 1, 2, 3, and 4 weeks, with values of 146.86 ± 1.5, 131.98 ± 1.2, 110.62 ± 0.8, and 142.53 ± 1.6, respectively, in Group A (Table 1).

Comparing the group's AM and PM symptom scores to the baseline mean scores of 75.58 ± 1.0 and 82.31 ± 1.2, respectively, revealed a significant change ($P < 0.05$) in all four weeks. When compared to the baseline mean value of 161.72 ± 1.5, montelukast significantly ($P < 0.05$) lowered T5NSS in Group B (Table 1), with mean values of 149.92 ± 1.6, 138.62 ± 0.9, 113.31 ± 1.1, and 145.66 ± 1.3 in 1, 2, 3, and 4 weeks, respectively. With the exception of the third week, when significance was determined to be $P < 0.05$, montelukast did not significantly lower mean values from the baseline mean AM score of 75.45 ± 1.4.

On the other hand, compared to the baseline value of 86.2 ± 1.8, the mean PM score was shown to have statistical significance ($P < 0.05$) in all 4

weeks. The T5NSS values of 151.05 ± 1.7, 134.27 ± 1.0, 114.19 ± 0.9, and 146.0.9 ± 1.4, respectively, for the combination of ebastine and montelukast in Group C (Table 1) were statistically significant when compared to the baseline T5NSS value of 165.61 ± 1.9.When compared to the baseline mean AM (78.49 ± 1.1) and PM (87.12 ± 1.8) scores, this group showed significant control ($P < 0.05$) of both AM and PM mean nasal symptom scores in all 4 weeks, in contrast to the montelukast and ebastine groups. Upon comparing individual groups, our investigation showed inconsistent findings. Among the three groups, the combination group consisting of ebastine and montelukast, as well as the ebastine group, showed a substantial decrease in AM score in weeks 1, 2, and 3 ($P < 0.01$). (Figure 1)

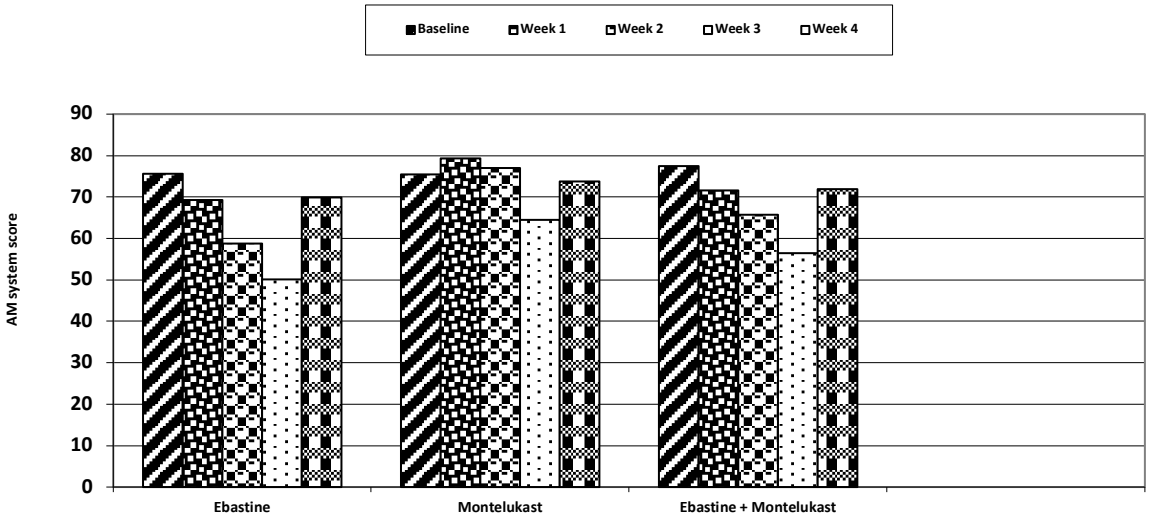


**Figure 1: Anti-allergic effects of various drug treatments on AM symptom score (*P≤0.05)**

Comparing the PM scores of the three groups at one, two, and three weeks revealed that montelukast considerably outperformed the ebastine group and its combination group with montelukast in lowering PM scores ($P < 0.000$). (Figure 2)

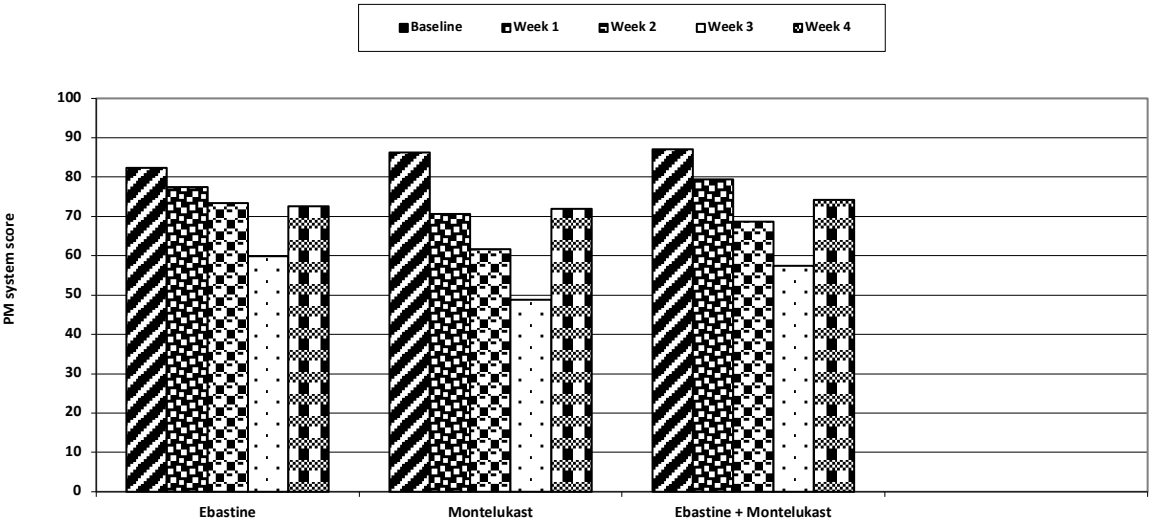


**Figure 2: Anti-allergic effects of various drug treatments on PM symptom score (*P≤0.05)**

Comparing the T5NSS mean values (Figure 3) revealed statistical significance in the second week of therapy with ebastine ($P < 0.01$), in the third week with only ebastine ($P < 0.05$), and in the second week with both ebastine and montelukast combined ($P < 0.01$). The results for weeks one and two revealed no change. Nevertheless, no medication was observed to have a significant effect on the T5NSS, AM, or PM symptom scores in the fourth week.

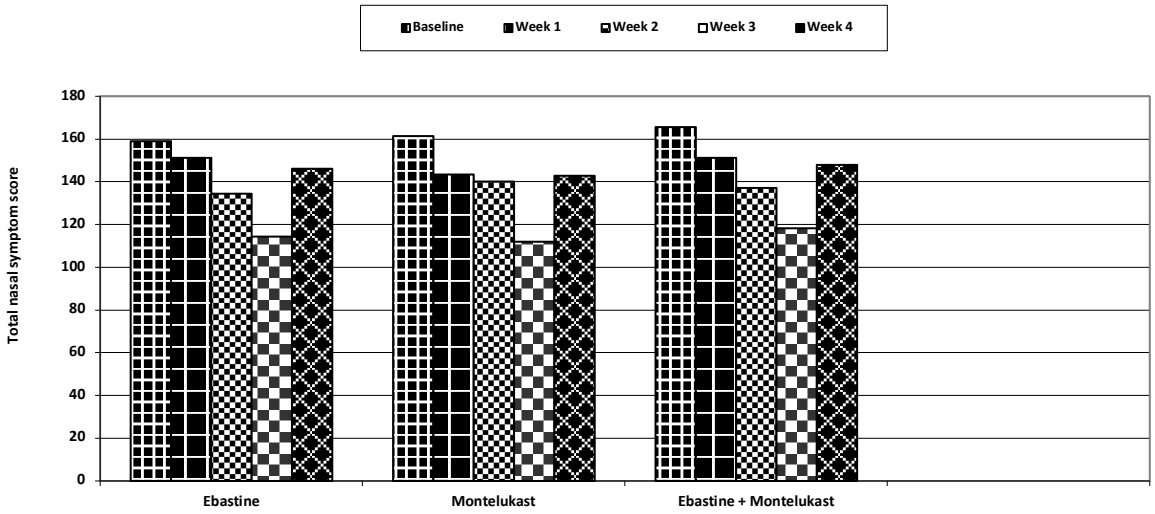


**Figure 3: Anti-allergic effects of various drug treatments on total nasal symptoms score (*P ≤ 0.05)**

## Discussion

As previously mentioned, the study compared the effectiveness of ebastine, montelukast, and their combination on nasal and extranasal symptoms of mild to moderate PAR. It was based on the few available reports on ebastine as well as a number of contentious reports on the anti-allergic efficacy of various antihistamines when combined with montelukast. In our study, we discovered that ebastine significantly reduced all five nasal symptoms, nocturnal symptoms, and daytime symptoms over the course of four weeks when compared to baseline values. In contrast to the earlier study, the montelukast group demonstrated a significant reduction in daytime symptoms and total symptoms as evidenced by a decrease in T5NSS and PM symptoms but failed to demonstrate a significant control of nighttime symptoms.[16]

The combination of ebastine and montelukast group significantly reduced all five nasal symptoms as well as AM and PM symptoms, indicating that they were more effective throughout the course of the four weeks in managing overall, daytime, and nighttime symptoms. Therefore, it was discovered that ebastine by itself was similar to ebastine plus montelukast. As compared to the first three weeks, none of the three groups showed any discernible improvement in the fourth week's management of PAR symptoms. As a result, it was discovered that their effectiveness diminished when the pharmacological treatment was stopped. Thus, they demonstrate that they are not the moderators of the fundamental pathology of AR, but rather suppliers of short-term symptomatic alleviation.

When ebastine, montelukast, and their combinations were compared for their anti-allergic effects, the results showed that they were equally effective in the first and fourth weeks; however, in the second week, the combination of ebastine and montelukast was found to be significant, and in the third week, only ebastine was significant in controlling T5NSS values. In terms of daytime symptoms, montelukast was found to be significantly better in controlling PM symptom scores than ebastine and the combination of ebastine and montelukast groups in the first, second, and third weeks. It was discovered that ebastine and ebastine and montelukast combination groups performed better than montelukast in reducing nocturnal allergy symptoms.

Total nasal symptoms were managed by ebastine, daytime symptoms were managed by montelukast, and nighttime symptoms were managed by ebastine in conjunction with montelukast. It would be assumed that ebastine was more effective than other groups at controlling both nighttime and overall nasal symptoms. It also reduced symptoms during the day, though not as much as montelukast. Given that the combination did not outperform ebastine alone, it is reasonable to question the rationale of preparing ebastine and montelukast combined.

The findings of our investigation thus corroborate those of previous past investigations[6,7,17] that assessed the anti-allergic impact of several antihistamines and their combination with montelukast in AR. Individual antihistamines outperformed their combinations with montelukast in these[12,13] studies, which also measured objective indicators of anti-allergy, such as domiciliary nasal peak flow, nasal eosinophilia, and serum soluble intracellular adhesion molecule.

However, conflicting research has demonstrated that, in addition to controlling subjective symptom scores[18,19], the combination of various antihistamines with montelukast also significantly increased objective evidence of anti-allergic effects

in AR compared to single antihistamines.[8–11][21] None of the supporting or non-supportive studies examined ebastine, though. The anti-allergic effect[21] was observed the day after the first dose of treatment, but the effect became significant on the second day for groups receiving ebastine in combination with montelukast, and on the third day for montelukast, and it persisted for the duration of treatment.

The fourth week of treatment was discontinued, but the three groups' symptom scores were kept up to date. By the conclusion of the fourth week, every group had demonstrated a considerable anti-allergic response that was well-lasting and could be attributed to the drug's pharmacokinetic and pharmacodynamic qualities. This assessment of the anti-allergic impact that persisted was a novel finding in a number of trials with AR patients. A larger sample size, assessment of certain objective data, and quality of life in allergy sufferers could have given the study greater weight.

This study was designed in response to the contentious reports of several anti-histaminics, montelukast, and scant ebastine investigations. The results showed that ebastine, montelukast, and their combination were useful in managing symptoms of AR. During the day, montelukast was useful in managing symptoms. In our investigation, ebastine and its combo with montelukast showed comparable efficacy in managing overall, AM, and PM symptoms.

## Conclusion

Antihistamines have shown throughout time to be highly successful symptom relievers in AR. There are a number of more recent antihistaminics on the market, both by themselves and in conjunction with montelukast. Our research suggests using a single antihistamine instead of combining it with montelukast to manage AR symptoms during the day and at night, which will save money and reduce the need for an extra medication.

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