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RESEARCH ARTICLE

Randomized prospective double-blind comparative clinical study of ebastine and its combined preparation of montelukast in persistent allergic rhinitis

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ABSTRACT

Background: Antiallergic drugs are widely prescribed in allergic rhinitis (AR). Antihistamines and antileukotrienes are effective only in providing symptomatic relief of allergic symptoms, often used as fixed dose combinations (FDC) of both. Controversial reports regarding their efficacy in AR, when used alone or in their combined preparations, prompted the present study. **Aims and Objectives:** The aim of this study was 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. **Materials and Methods:** Mild-to-moderate PAR patients divided into three groups to receive drugs ebastine, montelukast, and their combined preparation for 3 weeks. Their efficacy was measured by total five nasal symptoms scoring system, AM, and PM symptom scores. The treatment was withdrawn in the last week, to assess the persisting anti-allergic action of treatment drugs. **Results:** When compared to baseline values, all the treatment groups showed a significant decrease in the total mean score of allergic symptoms. Ebastine and its combination with montelukast significantly decreased both AM and PM mean scores, but montelukast did only for PM mean score. Among three compared groups, ebastine and its combined preparation with montelukast were found significant in reducing total and AM symptoms. **Conclusion:** All 3 groups showed anti-allergic effects in a variable manner. Montelukast controlled daytime symptoms better. Ebastine and its combination with montelukast controlled allergic symptoms to a similar extent.

KEY WORDS: Ebastine; Montelukast; Allergic Rhinitis; Total Five Nasal Symptoms Scoring

INTRODUCTION

Allergic rhinitis (AR) is one of the most common ENT disorder having worldwide distribution affecting between 10% and 30% of population.[1] Its prevalence is on rise, and in USA, 17.6 million adults and 6.6 million children were diagnosed with seasonal AR in the annual year of 2012 duration.[2,3] It impairs quality of life (QOL), affecting work productivity, and this may be similar to other disorders considered to be severe.[4] AR is often considered to be a trivial disorder, despite the fact that symptoms of it were present in 75% of children and 80% of asthmatic adults. It can affect the physical, psychological, and social aspects of patient's life, can also impact work productivity of patients, a majoreconomic burden to the society. This also has been associated with both increase in the risk of asthma development and its severity.[5]

A variety of drugs in different formulations are available to treat AR, and majority of them provide only symptomatic

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relief. Immunotherapy appears to be a specific therapy on its own and modifies the basic pathological mechanisms of AR, but identification of specific antigen/antigens for desensitization, long duration of treatment, and high relapse rate after completing the course are the limitations of it.

Among the drugs providing symptomatic relief of symptoms, antihistamines are the mainstay in the treatment of AR, which acts by blocking H_1 receptors mainly. Conventional antihistamines have been replaced by newer ones, having some useful extra actions beyond the antagonism of histamine. They are entering into clinical practice one after the other, and many more are in the pipeline. A search continues for the best drug for better control of symptoms, as the patients of AR are either not satisfied with present drugs or remain using them with their unacceptable side effects. It is well-known fact that antihistamines are effective in controlling the symptoms in the majority of patients of intermittent and persistent types of AR of varying severity, as long as they are administered. They decrease the subjective nasal symptoms such as sneezing, itching, congestion, and discharge and also extranasal symptoms such as eye redness, itching, and lacrimation and meanwhile improves the QOL. There are also objective evidence of betterment of disease by improving nasal peak flow,[6] decrease in nasal eosinophils, reduced serum soluble intracellular adhesion molecule,[7] and experimentally induced nasal congestion.[8] Montelukast, an antileukotriene drug, is also used extensively in AR treatment. It acts by blocking leukotrienes which are derived from arachidonic acid metabolism by the action of enzyme lipooxygenase, and they are also equally important as histamine in the pathogenesis of AR. Thus, montelukast also decreases nasal and extranasal symptoms and improves QOL equivalent to that of antihistamines.

From a theoretical point of view, when antihistamines and montelukast are concomitantly administered in AR, this combination would work better with greater efficacy, achieving good symptom control. Various clinical[9-11] and experimental studies have shown, when different antihistamines were administered with montelukast, the subjective and objective parameters of AR were significantly improved than the individual administration of antihistamines and montelukast.

To contradict this finding, many comparative studies in AR patients have concluded that individual antihistamines such as fexofenadine, loratadine,[12] and desloratidine[7,13] are as effective as their combinations with montelukast, thus not justifying the various fixed-dose combinations (FDC) of antihistamines with montelukast available in market. Literature survey also revealed that comparative studies of other antihistamines in AR such as ebastine, a second-generation drug, with its combination with montelukast are very much scanty. These above controversial reports about the interaction of various antihistamines with montelukast and paucity of similar information about ebastine prompted the present study. 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.

MATERIALS AND METHODS

It was a randomized prospective double-blind comparative study in patients diagnosed mild-to-moderate PAR. It was conducted in a polyclinic in a district place of Southern India for about 6 months from June 2015 to December 2015. Study was approved by Institutional Ethics Committee (No. AIMS/IEC/308/2015-16). AR defines PAR as a type, where allergic symptoms occur for more than 5 days/week or more than 28 days. Subjects were screened for PAR, and once diagnosed, they were explained in the local language about the study purpose, its benefits and possible risk involved, and safety measures taken during the study. Their queries were satisfactorily answered while explaining the study details. After getting informed consent from them, the study was started with the following inclusion and exclusion criteria.

Inclusion Criteria

- Subjects of 18-65 age group of either sex having diagnosed persistent mild-to-moderate AR.
- Subjects giving informed consent.
- Literate patients who understand, to record AR symptoms and any adverse effects occurred, correctly and promptly without any bias, in the dairy provided.
- Subjects agreeing for drug treatment and for scheduled follow-up.

Exclusion Criteria

- Patients of intermittent AR, severe PAR, non-AR, associated bronchial asthma, and atopic dermatitis patients.
- Patients with deviated nasal septum, nasal polyps, atrophic rhinitis, and any nasal mass.
- Patients who are allergic and intolerant to medications used in the study.
- Patients who are on immunotherapy/herbal therapy or corticosteroid therapy either presently or in the recent past.
- Chronic smokers, chronic alcoholics, drug addicts and psychiatry patients, pregnant and lactating mothers.
- Patients with a history of any significant systemic disorders.

The sample size was determined using sample size calculator, keeping the power of study at 90%, level of significance at 0.05%, and confident interval at 10%, and the sample size

came around 35 subjects of each group of three. At baseline, randomly divided subjects were subjected to investigations such as complete blood count (CBC), liver function test (LFT), respiratory function test (RFT), and electrocardiogram (ECG) and were refrained from any drugs before starting the experiment. Short-acting drugs such as chlorpheniramine maleate 25 mg and oxymetazoline nasal drops 0.05% were administered sos to control severe symptoms in sneezers and nasal blockers, respectively. 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.

Drug treatment was double-blinded for both investigators and patients. Each medication was wrapped in a small blue paper and was placed in a big blue-coded envelope. The medication was given to subjects on a weekly basis by a third person who was not directly involved in the study, and decoding was done after the data analysis.

Subjective symptoms of PAR were assessed using total five nasal symptom scoring (T_5NSS) system, adopted in earlier studies,[14,15] with suitable modification. This scoring system had 5 parameters, namely, sneezing, rhinorrhea, itching, congestion, and eye symptoms (itching, lacrimation, and congestion), and they were scored on a severity scale which measured from 0 to 3, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe, with a maximum possible score of 15, and patients were requested to record their symptoms twice daily for 4 weeks.

The 1st visit on day 1, with the past 3-day anti-allergic medication off, subjects were educated to record their allergic symptomology according to its severity in the dairy provided to them and baseline scoring was recorded. They were directed to record their symptoms score every day twice at 8 am and 8 pm without fail and also to record any adverse effects occurred to them. Medications were issued for 1 week. The 2nd visit was paid after a week for ensuring patient compliance and also for proper, consistent, and accurate recordings in the dairy. The 1st week data were collected, and medications were issued for the 2nd week. In the 3rd visit, 2 weeks later, data were collected, medication was stopped, and subjects were informed to continue their recording in dairy without taking medications. The 4th visit was made to collect dairy with up-to-date readings entered, and investigations such as CBC, LFT, RFT, and ECG were repeated.

RESULTS

The data obtained from subjects dairy were tabulated under three headings, i.e., total nasal, AM, and PM symptom scores. Scores were expressed as mean ± standard error mean The comparison was made with the respective baseline scores within the groups and with the respective weekly scores in between the groups. Statistical significance at $P < 0.05$ was calculated using ANOVA test followed by Tukey HSD *post-hoc* test (statistical calculator on statpages.org).

In Group A (Table 1), ebastine showed a significant ($P \leq 0.05$) decrease in mean T_5NSS score at 1, 2, 3, and 4 weeks with the values of 146.86 ± 1.5, 131.98 ± 1.2, 110.62 ± 0.8, and 142.53 ± 1.6, respectively, when compared to baseline T_5NSS mean score of 157.89 ± 1.6. The AM and PM symptom scores of the group were also decreased with significant difference ($P<0.05$) in all 4 weeks, when compared to baseline mean AM and PM symptom scores of 75.58 ± 1.0 and 82.31 ± 1.2, respectively. In Group B (Table 1), montelukast significantly ($P < 0.05$) reduced T_5NSS 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, when compared to that of baseline mean value 161.72 ± 1.5. The baseline mean AM score was 75.45 ± 1.4, montelukast failed to show any significant decrease in mean values in all 4 weeks except the 3rd week, where significance was shown to be $P < 0.05$. In contrast, the mean PM score

Table 1: Anti-allergic effects of various drug treatments

Groups	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		131.98±1.2*		110.62±0.8*		142.53±1.6	
	69.23±0.8*	77.46±1.1	58.70±0.9*	73.32±1.0	50.18±0.8*	59.88±0.9	69.91±1.1	72.62±1.4
Group 2 Montelukast	149.92±1.6		138.62±0.9		113.31±1.1		145.66±1.3	
	79.28±1.5	70.64±1.3*	76.93±1.2	61.69±1.1*	64.51±1.0	48.80±0.6	73.79±1.3	71.87±1.1
Group 3 Ebastine + Montelukast	151.05±1.7		134.27±1.0		114.19±0.9		146.09±1.4	
	71.62±0.9*	79.43±1.5	65.67±1.2*	68.60±1.4*	56.45±1.0*	57.74±0.9	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	

*$P<0.05$

was shown to have statistical significance ($P < 0.05$) in all 4 weeks, when compared to that of baseline value (86.2 ± 1.8). In Group C (Table 1), the combination of ebastine and montelukast had T_5NSS of 151.05 ± 1.7, 134.27 ± 1.0, 114.19 ± 0.9, and 146.0.9 ± 1.4, respectively, in 1, 2, 3, and 4 weeks, and they were statistically significant, when compared to that of baseline T_5NSS value of 165.61 ± 1.9. Unlike montelukast group and like ebastine group, this group had significant control ($P < 0.05$) of both AM and PM mean nasal symptom score in all 4 weeks when compared to that of baseline mean AM (78.49 ± 1.1) and PM (87.12 ± 1.8) scores.

When individual groups were put into comparison, our study depicted variable results. In weeks 1, 2, and 3, among 3 groups, ebastine group and combination group (ebastine and montelukast) were found to be significant in decreasing AM score ($P < 0.01$) (Figure 1). When PM scores were compared among 3 groups, in 1, 2, and 3 weeks, it was montelukast,found significantly better in reducing PM score ($P < 0.000$), when compared to ebastine group and its combined group with montelukast (Figure 2). As far as T_5NSS mean values were compared (Figure 3), statistical significance was seen with ebastine ($P < 0.01$) and combined ebastine and montelukast ($P < 0.01$) in the 2nd week and only with ebastine ($P < 0.05$) in the 3rd week of treatment. Week 1 and 2 results showed insignificant change. However, in the 4th week, none of the drugs was found significant in T_5NSS, AM, and PM symptoms scores.

DISCUSSION

As already stated, the study was conducted to compare the efficacy of ebastine, montelukast, and their combination on nasal and extranasal symptoms of mild to moderate PAR and it was based on the sparse reports about ebastine and also on various controversial reports regarding the anti-allergic efficacy of different antihistamines with montelukast. In our study, we found ebastine, when compared to baseline values, it significantly decreased in total 5 nasal symptoms, nocturnal symptoms, and daytime symptoms in all 4 weeks, montelukast group showed significant decrease in total symptoms and daytime symptoms, as indicated by a decrease in T_5NSS and PM symptoms but failed to show significant control of nighttime symptoms, contrast to the study reported earlier.[16] The combination of ebastine and montelukast group significantly controlled total 5 nasal symptoms and also AM and PM symptoms, suggesting their better efficacy in controlling total, day and night symptoms in all 4 weeks. Thus, ebastine alone was found equivalent to its combination with montelukast. All 3 groups failed to show significant control of symptoms of PAR in the the 4th week, when compared to that of first 3 weeks. Hence, their efficacy was found to get decreased with the stoppage of drug treatment. Thus, proving themselves to be temporary symptomatic relief providers rather than the modifiers of basic pathology of AR.

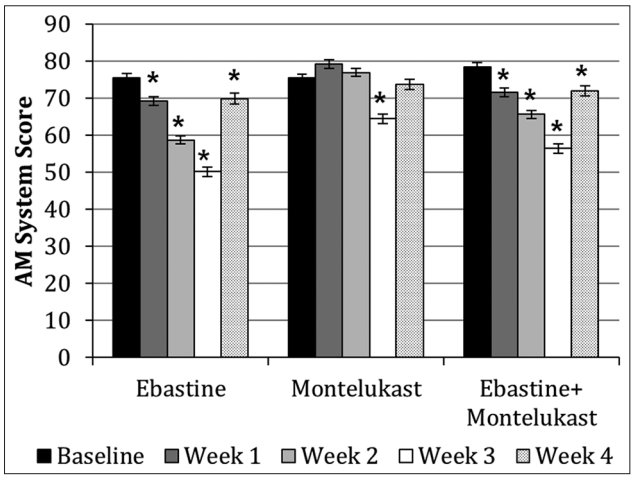

Figure 1: Anti-allergic effects of various drug treatments on AM symptom score (*P≤0.05)

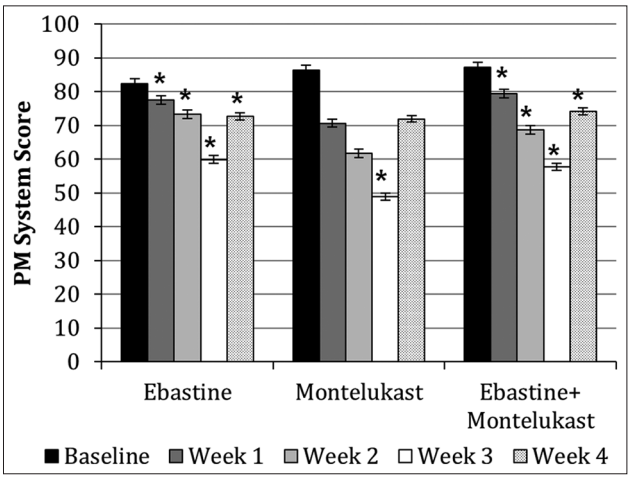

Figure 2: Anti-allergic effects of various drug treatments on PM symptom score (*$P \leq 0.05$)

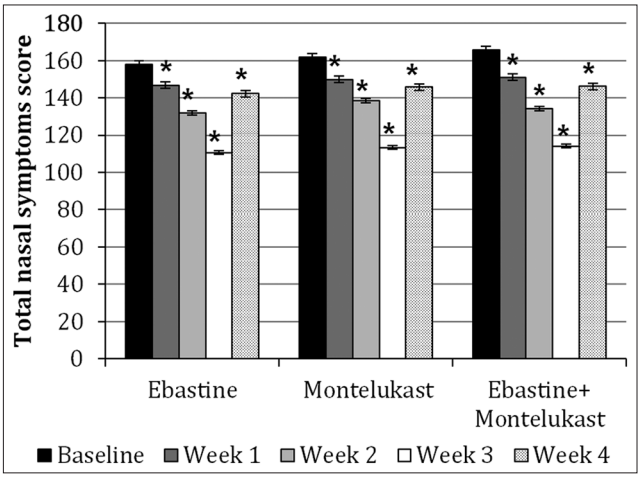

Figure 3: Anti-allergic effects of various drug treatments on total nasal symptoms score (*$P \leq 0.05$)

When their anti-allergic actions were compared to one another, ebastine, montelukast, and their combinations were found having similar efficacy in 1st and 4th weeks, whereas in the 2nd week, ebastine and ebastine montelukast combination

were found to be significant, and in a 3rd week, only ebastine was found to be significant in controlling T_5NSS values. As far as daytime symptoms were concerned, it was montelukast, had significant PM symptom scores, and thus showed to be effective in controlling daytime symptoms, when compared ebastine and the combination of ebastine and montelukast groups in 1st, 2nd, and 3rd weeks. In controlling nocturnal allergic symptoms, it was found ebastine and ebastine and montelukast combination groups to have better scores over montelukast. Ebastine controlled total nasal symptoms, montelukast controlled daytime symptoms, and ebastine and its combination with montelukast controlled nocturnal symptoms. It would be inferred that ebastine controlled total nasal symptoms, and night symptoms better than other groups. Daytime symptoms were also controlled (not to the extent of montelukast) by it. Thus, questioning the rationality of combined preparation of ebastine and montelukast as the combination did not score over ebastine alone.

Our study results, thus, support other earlier studies[6,7,17] which evaluated the anti-allergic effect of various antihistamines and their combination with montelukast in AR. In these[12,13] studies, along with subjective symptoms, objective evidence of anti-allergy such as domiciliary nasal peak flow, nasal eosinophilia, and serum soluble intracellular adhesion molecule were also measured, and individual antihistamines had upper hand over their combinations with montelukast. In contrast, other contradictory studies have shown that the combination of different antihistamines with montelukast had controlled not only subjective symptom scores[18,19] but also produced significant objective proof of anti-allergic actions, more than individual antihistamines, in AR.[21] and[8-11] However, ebastine was not studied in any of those supporting and non-supporting studies.

The anti-allergic effect[21] was seen on the next day of 1st dose of treatment, but significance was found on the 2nd day for ebastine and its combination with montelukast groups, and 3rd day for montelukast and effect continued as long as treatment continued. During 4th week, treatment was stopped with continuing the scoring of symptoms in all 3 groups. All the groups showed significant anti-allergic effect at the end of the 4th week, showing good persisting effect which could be explained by the pharmacokinetic and pharmacodynamic properties of a drug. This assessment of persisting anti-allergic effect was a unique feature and hard to find in various studies involving AR patients. Large number of subjects, evaluation of some objective evidence, and QOL in allergic patients could have put more weightage on the study. Based on the controversial reports of various anti-histaminics and montelukast and sparse ebastine studies, this study was planned and found that ebastine, montelukast and their combination were effective in controlling symptoms of AR. Montelukast was effective in controlling daytime symptoms. Ebastine and its combination with montelukast had similar efficacy in controlling total, AM, and PM symtoms in our study.

CONCLUSION

Time has proved antihistamines are very effective symtomatic releif providers in AR. Various newer antihistaminics alone and their combination with montelukast are available in the market. Our study supports the usage of individual antihistamine rather than its combination with montelukast in controlling day and night time symptoms of AR, thus decreasing the burden of an additional drug and cost.

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