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Original Research Article

Efficacy and safety of ebastine 10 mg and phenylephrine 10 mg fixed-dose combination in Indian patients with allergic rhinitis: A phase 4 multicentre study

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ABSTRACT

Background and Objective : There is a lack of comprehensive studies examining the efficacy and safety of the fixed-dose combination (FDC) of ebastine 10 mg and phenylephrine 10 mg in allergic rhinitis (AR), especially in Indian settings. So, this study aimed to fill the existing research gap by evaluating the efficacy and safety of the FDC ebastine 10 mg and phenylephrine 10 mg in Indian patients with moderate/severe persistent AR.

Materials and Methods : An open-label, non-randomized, single-group, multicentric, phase 4 clinical study included adult patients visiting the outpatient departments of 4 sites across India. All the selected subjects received the FDC once daily in the evening for 5 days. Safety and efficacy of the FDC were evaluated by comparing the Individual Symptoms Score (ISS), Total symptom Score (TSS), and analysing adverse event profiles reported by patients, assessed by the investigator, from baseline to 6 days. The study also assessed the impact of this condition on patients' quality of life using the rhino-conjunctivitis quality of life scale (RQLS).

Results: The study included 145 participants with a mean age of 37.17 ± 12.65 years and male-to-female ratio of 1:1.26. Comparison of baseline symptoms with day 6 revealed statistically significant and clinically meaningful improvements in Individual Symptoms Score (ISS). The mean difference in Total Symptom Score (TSS) from baseline to day 6 also showed a substantial improvement of 3.52 ± 1.54 (95% CI: 3.27-3.78; P <0.001). Rhino-conjunctivitis quality of life scale (RQLS) also demonstrated statistically significant improvement from day 1 to day 6 (t = 24.44, P <0.001). Adverse events were effectively managed with the use of readily available over-the-counter medications like antipyretics, analgesics, and/or antacid.

Conclusion: The study validated the efficacy and safety of the FDC ebastine 10 mg and phenylephrine 10 mg, in managing AR with good safety profile. The findings underscore the importance of this combination as a viable therapeutic option, with significant improvements in symptom scores and quality of life observed within a short duration.

1. Introduction

The prevalence of allergic diseases is rising globally, affecting about 10-25% of the population and ranking

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among the top ten reasons for visits to primary care.[1] Allergic rhinitis (AR), a widespread condition, impacts 400 million individuals across the globe.[2] The burden of AR, characterized by nasal congestion, rhinorrhea, sneezing, postnasal drip, and nasal pruritis, is substantial, both in terms of individual suffering and societal impact. AR affects a significant percentage of adults worldwide, ranging from 18 to 40%. In India, the condition is more prevalent, affecting 20 to 30% of its population.[1] The direct medical cost associated with AR is a staggering 3.4 billion dollars, with almost 50% of the cost attributed to prescription medication.[3]

Histamine, which acts mainly through the H1 receptor, is a critical mediator of allergy symptoms in the treatment of AR. During the early stage of the immune response, it is released as a preformed mediator from activated mast cells.[4] H1-antihistamines, which stabilize the receptor in its inactive form, are the preferred treatment for allergic conditions and are included in international AR management guidelines. However, as a standalone therapy, antihistamines may not comprehensively alleviate all AR symptoms. Therefore, they are often combined with other decongestants like ebastine and phenylephrine.[5]

Ebastine, a second-generation H1-antihistamine, has been available worldwide for almost three decades. It is non-sedating and increases the threshold quantity of allergens involved in the allergic response. This can result in an anti-allergic effect that lasts for more than 48 hours.[4,6] On the other hand, phenylephrine is a decongestant and a selective $\alpha 1$ agonist. It induces vasoconstriction by stimulating the post-synaptic α receptors. When combined with ebastine, it is more effective in treating AR and decongestant symptoms without causing sedation compared to other antihistamine drugs.[7] Studies have reported that the bioavailability of phenylephrine monotherapy is poor due to extensive first-pass metabolism in the gut and liver, and it can be enhanced when used in combination therapy.[8]

The primary objective of the study was to evaluate the safety and efficacy of the fixed-dose combination (FDC) of ebastine 10 mg and phenylephrine 10 mg by comparing the Individual Symptoms Score (ISS), Total Symptom Score (TSS), and analyzing adverse event profiles reported by patients with AR, assessed by the investigator, from baseline to 6 days. The secondary objective was to assess the impact of this condition on patients' quality of life using the rhino-conjunctivitis quality of life scale (RQLS).

2. Materials and Methods

We conducted an open-label, non-randomized, single-group, multicentric, phase 4 clinical study and included adult patients visiting the outpatient departments of four sites across India. Ethical approval was obtained prior to the study, and it was registered with the Clinical Trial Registry of India (CTRI/2018/08/015262).

2.1. Inclusion criteria

1. Males and females aged 18-65 years (inclusive).
2. Diagnosis of mild and moderate-severe intermittent allergic rhinitis ($\leq$ 4 days per week AND $\leq$ 4 weeks).
3. Able to provide informed consent to participate in the study.
4. Ability to understand study procedures and comply with them for the entire study duration, including the ability to record symptom scores in a diary (literate patients).
5. Total Symptom Score (TSS) baseline score of at least 5 on both screening and randomization days (based on investigator assessment).
6. Treatment-naive for the current episode of allergic rhinitis (if the patient has already consumed any medication for the current episode, a wash-out of about 6-7 days should be given before administering the study medication).

2.2. Exclusion criteria

1. Asthma patients.
2. Subjects with a current history of frequent, clinically significant sinusitis, or chronic purulent postnasal drip.
3. Subjects dependent on nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids, as determined by the investigator.
4. Any illness requiring steroid use by any route.
5. Urticaria, vasomotor rhinitis, rhinitis medicamentosa.
6. Subjects with clinically significant nasal structural abnormalities, including large nasal polyps or marked septum deviation, that significantly interfere with nasal airflow.
7. Pregnancy or lactation.
8. Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
9. Use of any other investigational drug in the last 90 days.
10. Subjects known to have an idiosyncratic reaction to any of the ingredients in the FDC.

Subjects meeting the criteria were included for a 6-day study period and were followed up till day 14. A sample size of 135 subjects was deemed sufficient to detect a difference of 20% in the TSS scale from baseline to the end of treatment, assuming a power of 80% and a 5% level of significance. Considering a dropout rate of 10%, the net sample size for the study was determined to be 150 subjects.

The screening evaluations conducted on visit 1 (day 1) included physical examination, vital signs, assessment of TSS medical/medication history, ENT examination, ECG, lab investigations (hematology, serum chemistry, liver function test (LFT), renal function tests (RFT), lipid profile) and urine pregnancy test for female subjects >18 years).

Subjects who had clinically significant abnormal variations in the baseline hematological, serum biochemical, any ECG findings or who did not give consent were termed screen failures. All female subjects of childbearing potential underwent a urine pregnancy test and only subjects who had a negative test result were enrolled in the study. All the selected subjects received ebastine 10 mg + phenylephrine 10 mg FDC once daily in the evening for 5 days.

The ISS, TSS (the sum of the total nasal symptom score and total ocular symptom score), and RQLS assessments were conducted on the day 6. The TSS consists of 5 AR symptoms rated by the investigator on a 0 to 3-point scale, where 0 represents absence of symptoms and 3 indicates severe symptoms. RQLS was employed to assess the quality of life of the subjects. The RQLS utilizes a 0 to 9 scale, where 0 signifies that the subject is not troubled and 9 indicates that the activity is not done. For this assessment, selected subjects were allowed to choose three activities of their preference from a list of 29 daily activities provided in the subject diary. Notably, the RQLS assessments were conducted on both day 1 and day 6 of the study.

Adverse effects of the drug were assessed by monitoring adverse events, vital signs, physical examination, and significant changes in laboratory parameters. Safety endpoints were evaluated by comparing the laboratory investigations and ECG records taken during visit 1 (baseline) and visit 2 (day 6) of the treatment period. All subjects were followed up telephonically on day 14 to inquire about the current status and recording the adverse events, if any.

3. Results

3.1. Patient selection

As per the subject-selection criteria, 162 individuals within the age range of ≥18 years and ≤65 years, irrespective of gender, were screened for clinical diagnosis of moderate/severe persistent AR (≥4 days per week AND ≥4 weeks). No stratification based on any factors was considered during the screening process. A total of 6 screen failures were reported, and 11 subjects were lost to follow-up between visit 1 and visit 2. The study successfully enrolled 145 subjects, who were followed up until day 14.

3.2. Demographic and baseline characteristics

The study included 145 participants with a mean age of 37.17 ± 12.65 years and male-to-female ratio of 1:1.26. Other baseline and demographic characteristics are listed in Table 1. The baseline scores for individual symptoms, as assessed by the investigator at visit 1 for all 145 enrolled subjects, were as follows: nasal congestion (1.49 ± 0.81), rhinorrhoea (1.76 ± 0.73), nasal itching (1.10 ± 0.75), sneezing (1.82 ± 0.69), and ocular pruritis (0.71 ± 0.74).

Table 1: Baseline demographic parameters of enrolled subjects (n =145)

Demographic characteristics	Mean ± SD
Age (years)	37.17 ± 12.657
Male	87
Female	69
Height (cms)	161.23 ± 8.934
Weight (kg)	62.61 ± 11.022
Blood Pressure (mm Hg)	SBP: 119.24 ±7.99 DBP: 78.62 ± 5.37
Pulse rate	77.88 ± 8.25
Respiratory rate	17.68 ± 1.88
Temperature °F	98.42 ± 0.27

3.3. Efficacy results and tabulations of individual patient data

Statistically significant and clinically meaningful improvements in ISS were noted upon comparison of the baseline symptoms with day 6 (Table 2, Figure 1). The change in the mean difference in the TSS from baseline to day 6 was 3.52 ± 1.54 (95% CI: 3.27-3.78; P <0.001), signifying a statistically significant improvement (Figure 2). RQLS also exhibited a significant improvement from day 1 to day 6 (t = 24.44, P <0.001, Figure 3). All the adverse events were fully resolved with the administration of over-the-counter medications such as antipyretics, analgesics and/or antacids. The most frequently reported adverse event was fever, noted by 5 subjects (3.2%). Body ache was reported by three subjects (1.95%), and hyperacidity was reported by an equal number of subjects. Furthermore, one subject each reported experiencing headache, nausea, and vomiting (0.65%).

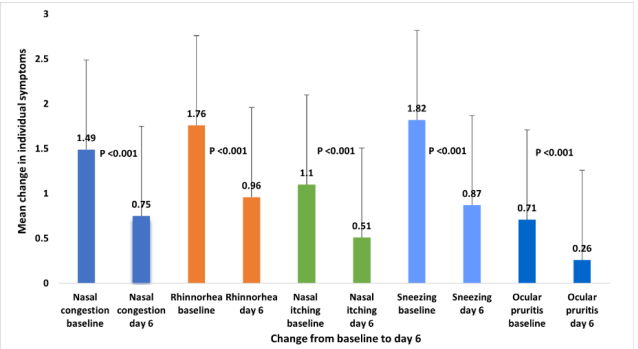

Figure 1: Comparison of mean change in individual symptoms between baseline and day 6

On physical examination, patients classically had pale nasal mucosa with swollen, oedematous turbinate's and clear nasal secretions (rhinorrhea). Some subjects reported headache as well as ocular itching. Safety evaluation included assessment of physical examination, periodic

Table 2: Comparison of ISS between baseline and day 6

Individual Symptom Score		Mean	SD	Std. Error (Mean)	95% CI (Mean) LB	95% CI (Mean) UB	t - value	P-value
Nasal congestion	Baseline (day 1)	1.49	0.81	0.07	1.353	1.618	14.600	<0.001
	Day -6	0.75	0.59	0.05	0.650	0.843		
Rhinorrhoea	Baseline (day 1)	1.76	0.73	0.06	1.640	1.881	18.013	<0.001
	Day -6	0.96	0.78	0.07	0.837	1.092		
Nasal itching	Baseline (day 1)	1.10	0.75	0.06	0.976	1.221	9.583	<0.001
	Day -6	0.51	0.58	0.05	0.419	0.610		
Sneezing	Baseline (day 1)	1.82	0.69	0.06	1.711	1.937	17.273	<0.001
	Day -6	0.87	0.67	0.06	0.763	0.984		
Ocular pruritis	Baseline (day 1)	0.71	0.74	0.06	0.590	0.833	7.901	<0.001
	Day -6	0.26	0.49	0.04	0.181	0.341		

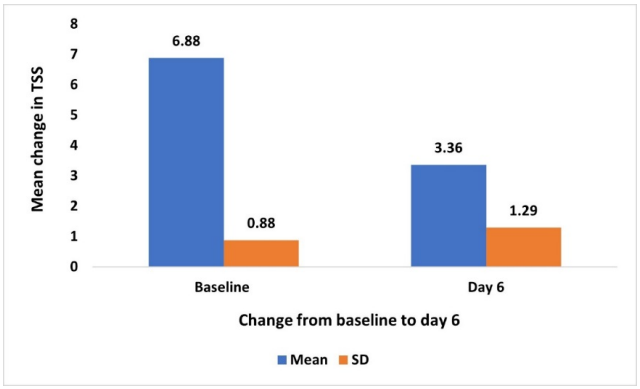

Figure 2: Comparison of mean change in TSS between baseline and day 6

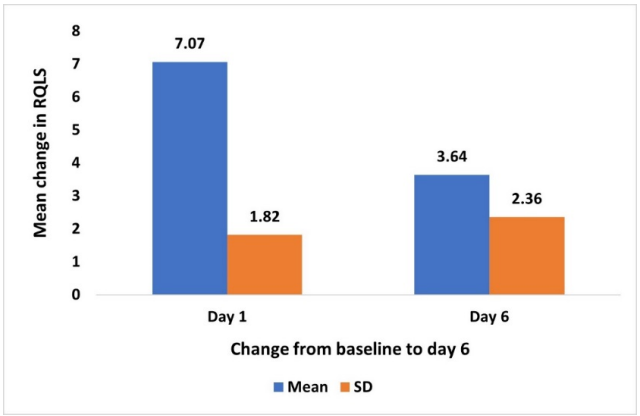

Figure 3: Comparison of mean change in RQLS between baseline and day 6

monitoring of vital signs (heart rate, respiratory rate, blood pressure and temperature), clinical, laboratory investigations (including haematology, serum chemistry, LFT, urine-analysis) and 12-lead ECG recording. ECG reports in both the visits did not show any abnormality. The safety parameters including findings in vital signs, laboratory parameters, physical examination findings were summarized and compared.

There were no adverse events reported in the follow-up visit [Telephonic visit, visit 3, day 14]. In this study, all adverse events were unrelated to the investigational product and were mild in nature. All events resolved with administration of antipyretics/ analgesics/ antacids. All events resolved completely without any sequale. There was no report of new unknown adverse events were reported. No serious adverse events reported in the study. The most common adverse event was fever with 5 subjects (3.2%) reporting it. Body ache was reported in three subjects (1.95%). Three subjects (1.95%) reported hyperacidity and one subject each reported headache, nausea, vomiting (0.65%).

4. Discussion

Combining a nasal decongestant with an antihistamine is a standard of care to improve allergy symptom control. This combination approach addresses a broader spectrum of symptoms, as antihistamines primarily target histamine-related symptoms such as sneezing and itching, while nasal decongestants specifically alleviate congestion by reducing swelling of nasal tissues.[9] However, the literature review reveals a paucity of studies exploring the efficacy and safety of the FDC of ebastine (10 mg) and phenylephrine (10 mg). The present study addresses a notable research gap and adds valuable evidence to the existing literature on the combined use of a decongestant with an antihistamine.

The significant decrease (P <0.001) noted in the current study in terms of ISS, including nasal congestion, rhinorrhea, nasal itching, sneezing, and ocular pruritus, as well as the TSS, as assessed by the investigator, validates the efficacy of the combination therapy with ebastine (10 mg) and phenylephrine (10 mg). In a meta-analysis, Ratner et al. demonstrated that ebastine exhibited good efficacy and induced a significant decrease from baseline in the mean AR symptom score compared to loratadine.[10] A double-blind multicentre study conducted by Murris-Espin et al. concluded that the individual and total baseline symptom scores of ebastine 10 mg are comparable to

Table 3: Distribution of safety evaluation parameters

Vital Signs		Mean	SD	Std. Error Means	95% CI Mean	
					LB	UB
DBP	Baseline (day 1)	78.62	5.37	0.45	77.738	79.510
	Day-6	78.99	4.76	0.40	78.207	9.778
SBP	Baseline (day 1)	119.24	7.99	0.67	117.922	120.605
	Day-6	199.61	6.03	0.51	118.615	120.605
Pulse rate	Baseline (day 1)	77.88	8.25	0.70	76.506	79.249
	Day-6	78.76	5.26	0.45	77.882	79.629
Respiratory	Baseline (day 1)	17.68	1.88	0.16	17.370	17.992
	Day-6	17.68	1.83	0.15	17.378	17.983
Temperature	Baseline (day 1)	98.42	0.27	0.02	98.372	98.463
	Day-6	98.44	0.23	0.02	98.406	98.482

that of cetirizine in reducing perennial AR symptoms.[10,11] Sastre evaluated 30 years of real-world data and clinical experience of ebastine in the management of AR. The study has concluded that ebastine, at recommended doses, is generally well-tolerated and ranks among the antihistamines with the lowest risk of adverse cognitive/psychomotor effects. Sastre has also highlighted the modulating effects of ebastine on the allergic inflammatory process apart from its antihistamine effects.[6] A meta-analyses of 7 crossover studies and the reanalysis of a parallel-group study corroborated the effectiveness of phenylephrine 10 mg as a decongestant in adults with acute nasal congestion related to the common cold.[12]

The significant improvement observed in the RQLS from day 1 to day 6 in the present study suggests a positive impact of the treatment on the subjects' overall quality of life. In addition, the manageable nature of the reported adverse events adds to the overall favourable safety and tolerability profile of the FDC. Although there are no sufficient data validating the safety of the FDC combination ebastine (10 mg) and phenylephrine (10 mg), there are studies reporting their safety as individual therapies. Gelotte and Zimmerman found that single oral doses of phenylephrine HCl at 10, 20, and 30 mg were well-tolerated with no serious adverse events. The researchers also noted that the treatment was not associated with clinically significant occurrences of pulse or blood pressure beyond the reference limits.[13] Hurst and Spencer reported that the efficacy of ebastine was comparable to other second-generation antihistamines and the treatment was not associated with any serious adverse cardiac effects.[14]

The synergistic effects of antihistamine and decongestant FDC offer a targeted approach to symptom management, addressing both histamine-mediated symptoms and congestion simultaneously. In addition, the FDC enhances patient compliance by simplifying the medication regimen. Stroms et al. revealed that combination therapy of antihistamine and decongestant was more effective that of monotherapy in relieving the symptoms of AR. The combination was better than its components in reducing nasal stuffiness and nasal discharge at day 4 evaluations.[9]

Overall, there was a significant decrease ($p<0.001$) for all the individual symptom scores viz. nasal congestion, rhinorrhea, nasal itching, sneezing, ocular pruritis as well as the total symptom scores as assessed by the investigator proving the efficacy of Ebastine (10 mg) and Phenylephrine (10 mg). There was significant improvement in quality of life (RQLS) from baseline to day 6 after administration of Ebastine (10 mg) and Phenylephrine (10 mg). No statistical difference between baseline and visit 2 (day 6) for safety parameters viz., adverse events, ECG, lab investigations after administration of Ebastine (10 mg) and Phenylephrine (10 mg). There were no adverse events reported in the follow-up visit. In this study, all adverse events were unrelated to the investigational product and were mild in nature. All events resolved with administration of antipyretics/ analgesics/ antacids. All events resolved completely without any sequale. There was no report of new unknown adverse events were reported. No serious adverse events reported in the study.

The present study holds significant relevance as there are no literature studies evaluating the FDC of ebastine and phenylephrine in the Indian population. One of the major strengths of the study is the robust enrolment of a diverse and clinically defined study population. Additionally, the study has gathered comprehensive baseline characteristics, including demographic information and baseline symptom scores. However, limitations include a relatively small sample size, potential bias from subjects lost to follow-up, a short study duration, potential reporting bias in adverse events, absence of a placebo control, and limited diversity in reported adverse events.

5. Conclusion

The FDC combination of ebastine (10 mg) and phenylephrine (10 mg) was safe and effective with favourable clinical outcomes and good safety profile in the management of AR.

6. Source of Funding

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7. Conflict of Interest

Dr Manjula S and Dr Krishna Kumar M are employees of Micro Labs Limited, Bangalore.

8. Acknowledgement

None.

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