DOI: 10.7860/JCDR/2021/48303.15183

Original Article

Pharmacology Section

Efficacy of Oral Bilastine in Comparison with Levocetirizine in Allergic Rhinitis- A Randomised Clinical Study

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ABSTRACT

Introduction: Allergic rhinitis is a heterogeneous disorder characterised by major symptoms like sneezing, itching, nasal congestion and rhinorrhea. Because of bothersome side effects of first-generation antihistaminic drugs, second generation antihistaminic drugs have been used since few years. Recent studies have showed that novel drug Bilastine has been approved as an effective treatment in Allergic rhinitis.

Aim: To evaluate Total Nasal Symptom Scores (TNSS), Serum Immunoglobulin E (IgE), Serum Absolute Eosinophil Count (AEC) in patients with allergic rhinitis, pre and post-treatment with Bilastine and Levocetirizine.

Materials and Methods: A randomised, open-labelled, study was conducted between January 2020 to March 2020. Hundred patients with allergic rhinitis were enrolled into the study. They were randomised into two groups of which group A received tablet Bilastine 20 mg once daily for two weeks and group B received tablet Levocetirizine 5 mg once daily for two weeks. The results of TNSS, IgE, AEC and pre and post-treatment values were compared in both the treatment groups. Unpaired t-test was used as the test of significance between the two treatment groups.

Results: The prevalence of allergic rhinitis in the study was 49% in males and 51% in females. The mean difference in pre and post-treatment in TNSS (group A=1.627, group B=1.143), serum IgE (A=33.118, B=49.653), serum AEC (A=28.00, B=27.245) showed no statistically significant difference between two groups (p-value >0.05).

Conclusion: Bilastine and levocetirizine are equally efficacious. Though there is clinical significance in treatment of allergic rhinitis between the groups, there is no statistical significance which would prove Bilastine is clinically superior to Levocetirizine for the allergic rhinitis treatment.

Keywords: Serum absolute eosinophil count, Serum immunoglobulin E, Total nasal symptom score

INTRODUCTION

The prevalence of the allergic diseases is increasing globally, including the Asia Pacific region as per current evidence [1]. Estimates suggest that 20% to 30% of the world's population suffer from some form of allergic condition [1]. Allergic diseases may include asthma, rhinitis, anaphylaxis, food allergy, eczema, urticaria and angioedema [1]. Around 40% of patients with allergic rhinitis which is type I hypersensitivity reaction, suffer from asthma also and up to 80-90% of patients with asthma also have allergic rhinitis [1]. Prevalence is increasing 1% per year in Africa, Asia-pacific, India, Latin America and Europe [2]. Although the reasons of the worldwide "allergy epidemic" are not known, the increase in allergy prevalence is mainly centered in middle to low-income countries [2]. Allergic rhinitis should be evaluated properly in asthmatics; since allergic disease is a chronic lifelong disease, the socio-economic burden will increase [3]. Few researches done by the standardised International Study of Asthma and Allergies in Childhood (ISAAC) showed that the allergic rhinitis in children had a significant,1.92-fold, increase (from 14.6% to 28.1%) [4]. A research done in China showed a marked increase in the prevalence rates of allergic diseases in China [5].

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines is the most commonly used guidelines for the treatment of Allergic Rhinitis. According to ARIA Guidelines, the first line pharmacological treatment for allergic rhinitis is second generation oral H1 antihistamines. Also, these guidelines recommend that these antihistamines should not cause sedation and should not interact with the cytochrome P450 enzymes [6]. Most of the ARIA recommendations on pharmacological therapy of allergic rhinitis are conditional. The severity of allergic rhinitis can be assessed by Total Nasal Symptom Score (TNSS), Serum IgE (Immunoglobulin E) levels and Serum AEC (Absolute Eosinophil count) levels [7].

Levocetirizine (R-cetirizine) is the pharmacologically active enantiomer of cetirizine. It is a potent histamine H1 receptor antagonist [8]. The are no cardiotoxic effects and few mild adverse events are associated with the drug like fatigue, headache, dizziness, and dry mouth. The drug cannot effectively cross the blood-brain barrier and shows low cerebral receptor binding. In patients with allergic rhinitis, levocetirizine at a dose of 5 mg daily significantly decreases sneezing, rhinorrhea, itching nose, itching eyes and nasal congestion [8]. In the study done by Devada Singh-Franco, Levocetirizine 5 mg/day was effective in reducing symptoms of perennial allergic rhinitis, seasonal allergic rhinitis, and improving quality of life, with an acceptable tolerability profile [9]. Side effects of levocetirizine reported are [10]:

1. Skin/allergy: hypersensitivity and acute allergic reaction (anaphylaxis), fixed drug eruption, skin eruptions with superficial pustules {acute generalised exanthemata's pustulosis (AGEP)}.
2. Neurologic effects such as convulsion, numbness and tingling, dizziness, aggression and agitation, hallucinations, depression, movement disorders, sudden muscle contractions, extrapyramidal symptoms.
3. Ocular side effects such as visual disturbances, blurred vision, cardiovascular effects such as irregular heartbeat and musculoskeletal effects such as muscle pain and joint pain.

Bilastine, a novel second-generation H1-antihistamine, was approved for the symptomatic management of allergic rhinitis in adults and children over 12 years of age in February 2019 by Central Drugs Standard Control Organisation (CDSCO). It was first approved in the European Union in 2010. Bilastine was initially used for allergic rhino conjunctivitis and urticaria [11]. Bilastine acts rapidly and for a longer duration of 12 to 15 hours. Pharmacokinetic study on Bilastine showed receptor antagonism for a longer duration with 60 to 70% antagonism which is evident 24 hours after the dosing of Bilastine [12]. Around

95% of the drug is excreted unchanged in faeces (67%) and urine (33%). Bilastine has a mean elimination half-life of approximately 12-14.5 hours [12]. Dosage adjustments is not required in renal or hepatic dysfunctions or in elderly patients [13]. Bilastine has limited potential for drug-drug interactions [13]. It is a substrate for P-glycoprotein, so can not pass across the blood-brain barrier, limiting the likelihood of Central Nervous System (CNS) effects [13]. A dose ranging study by García Gea C et al., with various doses of Bilastine as 20 mg, 40 mg, 80 mg showed nil significant anticholinergic effects [14]. The pharmacokinetic study by Roupe K et al., showed Bilastine up to 100 mg/day did not have any cardiovascular adverse effects [15]. No effect on QT interval by bilastine when co administered with ketoconazole was observed in a drug interaction study done by Sologuren A et al., [16]. Animal research studies on rat and mice did not show significant carcinogenic effects [17]. Antihistamine bilastine, contributes to improve the Quality of Life in allergic rhinitis patients [18].

There are researches comparing the efficacy of cetirizine 10 mg and bilastine 20 mg [19,20] as well as desloratadine 5 mg and bilastine 20 mg [21]. There are no studies comparing the efficacy of levocetirizine 5 mg and bilastine 20 mg. The aim of this study was to evaluate TNSS, serum IgE, serum AEC in patients of allergic rhinitis, pre and post-treatment with bilastine 20 mg and levocetirizine 5 mg. The primary objective of the research was to evaluate the TNSS at baseline and after two weeks of treatment in both groups. The secondary objectives were to compare the baseline values of serum IgE levels, serum AEC with follow-up values after two weeks of treatment in both groups.

MATERIALS AND METHODS

A randomised, open-label study was conducted in the Allergy Clinic of Government E.N.T. Hospital, Koti, Hyderabad, India from January 2020 to March 2020. Institutional Ethics Committee Approval (Reg No: ECR/300/Inst/AP/2013/RR-19, Ref No. EC/OMC/Research/2020/15) was taken prior to the research. Patients presenting with signs and symptoms of allergic rhinitis diagnosed by otorhinolaryngologist were selected for the study.

After explaining about the study procedures, written informed consent was obtained from all study participants of age more than 18 years in a prescribed format, in regional language. If the participant was illiterate, left thumb impression was taken. The tablets for the research were purchased from G.P. Medical stores, Musheerabad, Secunderabad, Telangana.

Inclusion criteria: Patients of age group 18 to 55 years of either sex diagnosed to have allergic rhinitis, who were willing to give informed consent for the research study and those who were not on any antihistaminic drugs for last one month were included in the study.

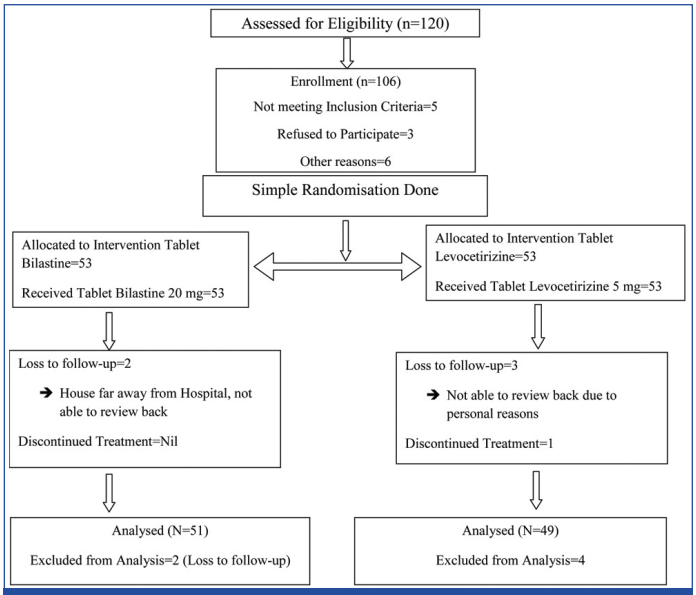
Exclusion criteria: Patients having other systemic diseases (renal, hepatic, cardiac failures etc.), psychiatric illness, diabetes, hypertension, immunocompromised patients. HIV/AIDS, patients with known history of allergy to study medications; patients on concomitant medications like Macrolides (Erythromycin) and Antifungals (Ketoconazole), pregnancy and lactating women or inadequate contraception in women of child bearing potential were excluded.

The sample size was calculated as 87 based on another study [20]. Considering drop outs and loss to follow-up 100 patients were enrolled for the study.

Overall 120 patients were screened. Out of 120 patients with allergic rhinitis, 106 patients who satisfied the inclusion criteria were enrolled into the study after getting informed consent. The subjects were randomised by simple randomisation in 1:1 allocation into Group A and Group B as per the treatment plan. During the study, five participants were lost to follow-up and one discontinued the treatment (total 6 patients- 2 from bilastine group and 4 from levocetirizine group) [Table/Fig-1].

Group A- Received Tablet Bilastine 20 mg once daily for two weeks.

Group B- Received Tablet Levocetirizine 5 mg once daily for two weeks.



[Table/Fig-1]: CONSORT Flowchart.

All participants were advised to take the drug every day at bedtime two hours after food. The participants were instructed to report immediately if they develop any adverse effects such as nausea, vomiting, drowsiness. Pre and Post-treatment TNSS, Serum IgE, AEC levels were observed. The TNSS was assessed based on the signs and symptoms like nasal congestion, rhinorrhea, nasal itching, and sneezing by interviewing the patients as shown in [Table/Fig-2].

Symptoms	Pre treatment	Post treatment
1. Nasal congestion	**On day 1**	**On day 15**
None	0	0
Mild (symptom clearly present, but easily tolerated)	1	1
Moderate (symptom bothersome, but tolerable)	2	2
Severe (symptom difficult to tolerate, Interferes with activities)	3	3
2. Rhinorrhea	**On day 1**	**On day 15**
None	0	0
Mild (symptom clearly present, but easily tolerated)	1	1
Moderate (symptom bothersome, but tolerable)	2	2
Severe (symptom difficult to tolerate, Interferes with activities)	3	3
3. Nasal itching	**On day 1**	**On day 15**
None	0	0
Mild (symptom clearly present, but easily tolerated)	1	1
Moderate (symptom bothersome, but tolerable)	2	2
Severe (symptom difficult to tolerate, Interferes with activities)	3	3
4. Sneezing	**On day 1**	**On day 15**
None	0	0
Mild (symptom clearly present, but easily tolerated)	1	1
Moderate (symptom bothersome, but tolerable)	2	2
Severe (symptom difficult to tolerate, Interferes with activities)	3	3

[Table/Fig-2]: TNSS-Symptoms assessment pre and post-treatment [7].

The nasal symptoms were graded according to severity at baseline and after two weeks of treatment and improvement in symptoms were compared. Serum IgE and AEC levels were done in laboratory by Enzyme Linked Immunosorbent Assay (ELISA).

The TNSS was graded depending upon the summation of severity of the symptoms mentioned in [Table/Fig-2] and graded as mild when the score was less than 6; moderate and severe when the score was 6-9 and 10-12, respectively.

STATISTICAL ANALYSIS

The observations and results were tabulated accordingly, and data was analysed using the Software Package for the Social Sciences (SPSS) version 16.0. The Chi-square test was used for evaluating the proportion of gender and age distribution. Unpaired t-test was used to evaluate the statistical significance in between two groups. A p-value of <0.05 was considered significant.

RESULTS

At the end of the study, group A included 51 patients and Group B included 49 patients after dropouts. Age distribution of all the participants included in the study is shown in [Table/Fig-3]. Out of 100 participants, 49 patients were male and 51 patients were female [Table/Fig-4]. The mean difference in TNSS in Group A was 1.627 and in Group B was 1.143 (p-value 0.183) .The mean difference in serum IgE levels in Group A was 33.118 and in Group B was 49.653 (p-value 0.525). The mean difference in serum AEC levels in Group A was 28.00 and in Group B was 27.245 (p-value 0.868). There was no statistically significant difference in TNSS, serum IgE and serum AEC levels between the two groups [Table/Fig-5].

Age (Years)	Bilastine N (%)	Levocetirizine N (%)
18-25	15 (29.4)	10 (20.4)
26-35	16 (31.2)	13 (26.5)
36-45	14 (27.4)	15 (30.6)
46-55	6 (12)	11 (22.5)
Total	51 (100)	49 (100)
p-value (Chi square)	0.002*	

[Table/Fig-3]: Age distribution.
*Statistically significant

Gender	Bilastine n (%)	Levocetirizine n (%)
Male (49)	25 (49)	24 (49)
Female (51)	26 (51)	25 (51)
Total	51 (100)	49 (100)
p-value (Chi square)	0.001*	

[Table/Fig-4]: Gender Distribution. *Statistically significant

Parameters			Group A	Group B	p-value (Unpaired t Test)
TNSS	Pre TNSS	Mean (SD)	6.98 (1.594)	6.06 (1.573)	0.183#
	Post TNSS	Mean (SD)	5.35 (1.707)	4.92 (1.525)	
Serum IgE	Pre IgE	Mean (SD)	237.94 (81.121)	243.29 (93.008)	0.525#
	Post IgE	Mean (SD)	204.82 (85.678)	193.63 (89.839)	
Serum AEC	Pre AEC	Mean (SD)	392.31 (174.39)	397.31 (186.61)	0.868#
	Post AEC	Mean (SD)	364.31 (165.02)	370 (176.33)	

[Table/Fig-5]: TNSS, Serum IgE, Serum AEC in both treatment groups.
#Statistical Insignificant

DISCUSSION

The results demonstrated that the efficacy of once-daily Bilastine 20 mg was similar to that of once-daily Levocetirizine 5 mg. There was no statistical significance between the treatments arms even though there was clinical significance, as Bilastine provided rapid and sustained relief of symptoms.

A study done by Kuna P et al., compared the efficacy and safety of Bilastine 20 mg with cetirizine 10 mg and placebo in allergic rhinitis and found that once daily dosing of Bilastine 20 mg was proven to be superior than placebo and comparable to cetirizine 10 mg in reducing the Seasonal Allergic Rhinitis (SAR) troubling symptoms and it exhibited less adverse effect when compared to cetirizine [19].

In the clinical research done by Sastre J et al., they compared the efficacy and safety of Bilastine 20 mg with Cetirizine 10 mg in the treatment of allergic rhinitis and concluded that both the drugs are equally effective [20].

A study done by Bachert C et al., compared the efficacy of Bilastine with Desloratadine and concluded that Bilastine 20 mg once daily was efficacious, safe and not different from desloratadine 5 mg once daily in the treatment of allergic rhinitis symptoms [21].

The above-mentioned studies highlight the equal efficacy of Bilastine with cetirizine and desloratadine in the treatment of allergic rhinitis. Additionally, these show that Bilastine does not cause suppression of central nervous system.

Sedative effects are less in Bilastine compared to Levocetirizine which are subjective. So Chronopharmacology of Bilastine can be assessed in future. Thus, further researches can be done with larger sample size and with different study designs.

Limitation(s)

Double Blinding was not possible and observer's bias could not be eliminated. Though sedative effects were monitored, the present study failed to record and analyse it statistically. This was the major limitation of this study.

CONCLUSION(S)

The second-generation antihistaminic drugs are efficacious in reducing the symptoms of allergic rhinitis. In this clinical research, both Bilastine and levocetirizine were equally efficacious. There were changes in the symptoms and laboratory values (serum IgE and AEC count pre and post treatment) noted between the groups. Though there was clinical significance in treatment of allergic rhinitis between the groups, there was no statistical significance which would confirm Bilastine to be superior to Levocetirizine for the allergic rhinitis patients.

Acknowledgement

The authors are thankful to Professor Dr. T. Chakradhar, Head of the Department, Department of Pharmacology, Osmania Medical College for the expert advice. The authors would also like to thank Dr. Santha Sheela Kumari for statistical help.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 01, 2021
- Manual Googling: Apr 08, 2021
- iThenticate Software: Jun 01, 2021 (19%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Dec 28, 2020**
Date of Peer Review: **Feb 11, 2021**
Date of Acceptance: **Apr 20, 2021**
Date of Publishing: **Aug 01, 2021**