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Original Article

Dermatology Section

Levocetirizine versus Bilastine as Monotherapy in the Management of Chronic Spontaneous Urticaria: A Randomised Controlled Trial

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ABSTRACT

Introduction: Chronic urticaria is defined as the almost daily occurrence of wheals and pruritus for a minimum of six weeks, adversely affecting the quality of life and necessitating management with a drug with better efficacy and a high safety profile. This study was designed to determine how monotherapy with newer antihistamines benefits chronic spontaneous urticaria by producing earlier and longer periods of remission. Additionally, the study aimed to assess the adverse effects associated with the drugs.

Aim: To compare the efficacy of Levocetirizine and Bilastine in chronic spontaneous urticaria.

Materials and Methods: The study was a single-blinded randomised controlled trial conducted in the Department of Dermatology at Madras Medical College, Chennai, Tamil Nadu, India over 24 months from January 2020 to December 2021. A total of 163 patients with chronic urticaria were randomly divided into two groups: Group A with 82 patients and group B with 81 patients. The patients were treated with tablet Levocetirizine 5 mg and tablet Bilastine 20 mg for six months (with up-dosing to four-fold maximum) in Group A and Group B, respectively. The treatment response was assessed using the Urticaria Activity Score (UAS) at each follow-up. Patients were followed-up for an additional six months to observe the time of recurrence. Total 15 patients were lost to follow-up and were consequently excluded from the statistical analysis.

Results: At the end of six months, the improvement observed in UAS was statistically similar in both groups (p-value=0.513). The time taken for remission was shorter with Levocetirizine (11.19±5.31 weeks) compared to Bilastine (14.59±5.02 weeks). Recurrence occurred earlier with Bilastine compared to Levocetirizine.

Conclusion: Levocetirizine and Bilastine are equally effective in controlling urticaria at the end of six months of treatment. Patients on Levocetirizine experienced earlier remission as well as late recurrence compared to those on Bilastine.

Keywords: Histamine antagonist, Hives, Urticaria activity score, Wheal

INTRODUCTION

Chronic urticaria causes significant morbidity, impairs sleep, and disrupts the daily functioning of the patient, necessitating treatment for a variable period depending on individual response. It is essential to analyse predisposing factors to prescribe a drug with better efficacy, a high safety profile, and fewer drug interactions [1]. For improved symptomatic relief, the therapy should have a rapid onset, a long duration of action, and be free from undesirable adverse effects. Current European Academy Of Allergy and Clinical Immunology (EAACI) guidelines recommend modern second-generation H1-antihistamines as the first-line management for chronic urticaria and suggest up-dosing of the same upto four-fold if unresponsive to standard doses [2].

Levocetirizine is a highly selective H1 receptor inverse agonist, the active R-enantiomer of the racemate Cetirizine with conformational stability, hence not converted to the inactive dextrocetirizine. It has two-fold affinity for the H1 receptor compared to Cetirizine. Its small volume of distribution confers improved safety as there is only lesser absorption through the blood-brain barrier and low cerebral receptor binding [3]. Metabolism is minimal with 85.8% being excreted unchanged in urine and faeces. It has a terminal elimination half-life of 5.7 hours [4]. The duration of action in inhibiting the histamine-induced flare response is much longer and presumed to be due to trapping of the drug by its strong and prolonged binding to H1 receptors. Also, it does not produce any deleterious effect on cognitive or psychometric functions.

Bilastine is a new H1 antihistamine approved for treating urticaria in adults and children older than two years of age [5]. It is highly selective for H1 receptors and has a good safety profile. It does not produce anticholinergic effects, nor does it impair vigilance or driving ability [6]. It has a chemical structure of benzimidazole-piperidinyl, an original molecule that binds to H1 receptors with an affinity higher than that of Cetirizine and Fexofenadine. In-vitro potency of the drug is also greater than that of Cetirizine and Fexofenadine [7]. It has negligible affinity for H2, H3, or H4, muscarinic, adrenergic, bradykinin, leukotriene, or calcium receptors. It has dose-dependent, long-lasting antihistaminic activity and higher activity in blocking histamine-induced bronchospasm [6]. It also inhibits Interleukin (IL)-4 and Tumour Necrosis Factor (TNF)-α release from human mast cells and granulocytes [7]. Absorption via the oral route is rapid in fasting conditions with a mean peak plasma concentration (Cmax) of 220 ng/mL. The mean oral bioavailability is about 61%, which is lower than that of other second-generation antihistamines. It has linear pharmacokinetics.

Both the Cmax and the area under the curve increase proportionally to the administered dose. It is eliminated unchanged in urine and faeces - 33% and 67% of the administered dose, respectively. It does not undergo hepatic metabolism and does not alter the activity of cytochrome P450 enzymes. It has a slow elimination half-life of around 10-14 hours, and 96% of the administered dose is eliminated within a day [7]. Inhibitors or inducers of P-glycoproteins (P-gps) have interactions with Bilastine. Bilastine is a good substrate for P-gp, which limits its route across the blood-brain barrier and does not produce any significant effects on the QT interval, ensuring

neurological and cardiovascular safety. In many clinical studies, treatment with Bilastine 20 mg/day was as effective as Levocetirizine in chronic urticaria [6].

Studies on newer second-generation H1-antihistamines in chronic urticaria are very limited. Hence, present study was designed with a rationale to find out how monotherapy with newer antihistamines benefited in chronic spontaneous urticaria in producing earlier and longer periods of remission. The aim of the study was to compare the efficacy of Levocetirizine and Bilastine in chronic spontaneous urticaria. Also, the objective of the study was to assess the adverse effects associated with the drugs. The null hypothesis that there was no significant difference in the efficacy of Levocetirizine and Bilastine in the treatment of chronic spontaneous urticaria. The research hypothesis that there was a significant difference in the efficacy of Levocetirizine and Bilastine in the treatment of chronic spontaneous urticaria.

MATERIALS AND METHODS

The study was a single-blinded randomised controlled trial conducted in the Department of Dermatology, Madras Medical College, Chennai, Tamil Nadu, India for two years from January 2020 to December 2021 (24 months). Permission was taken from the Institutional Ethics Committee, Madras Medical College, Chennai (IEC number: 23012020). Single blinding was done by unwrapping the drugs from the original strips and providing the drugs in a pill organiser every two weeks. Randomisation was done by the opaque sealed envelope technique.

Inclusion criteria: Patients with newly diagnosed chronic spontaneous urticaria belonging to the age group 12-60 years attending the Dermatology Outpatient Department (OPD) during the study period. Patients who had not undergone any prior treatment for chronic urticaria in the past four weeks before enrollment. Those who were willing to give consent to participate in the study and for further follow-up.

Exclusion criteria: Patients with thyroid disorders, pregnant and lactating women, patients with other skin diseases such as psoriasis, immunobullous disorders, eczema, or dermatophytosis, stool examination positive for ova and cyst were excluded from the study.

Sample size calculation: According to Zuberbier T et al., study, considering a minimal mean difference of Total Symptoms Score (TSS) change at 28 days between Bilastine Group and Levocetirizine Group as 0.57 (1.95-1.38), an average standard deviation of TSS change at 28 days in both groups as 2.29 at 95% confidence interval with 80% power, the sample size is calculated as [8].

$$N=(Z_{1-\alpha/2}+Z_{1-\beta})^2*2*\sigma^2/(\mu_1-\mu_2)^2$$

$Z_{1-}\alpha_{/2}$-two tailed probability for 95% confidence interval=1.96.

$Z_{1-}\beta$-two tailed probability for 80% power=0.84.

μ1-μ2-mean difference of TSS change at 28 days between Bilastine Group and Levocetirizine group (1.95-1.38)=0.57.

σ-average standard deviation of TSS change at 28 days in Bilastine group & TSS change at 28 days in Levocetirizine group=2.29.

$N=(1.96+0.84)^2*2*(2.29)^2/(1.95-1.38)^2$.

$=81.5/0.33$.

$N=246.9$

Thus, the estimated sample size was 247.

In the current study, 163 patients were enrolled and randomised into two groups.

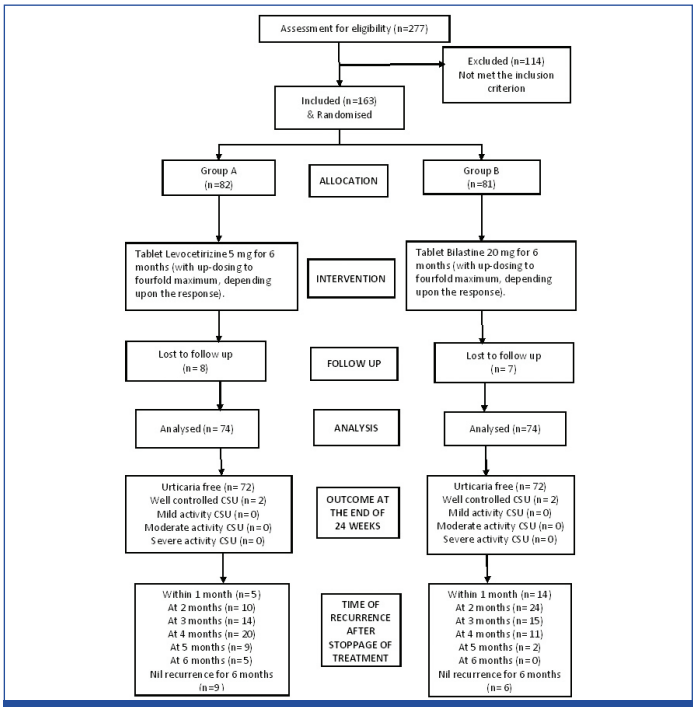
Study Procedure

Sampling technique: Simple random sampling. A total of 163 patients were enrolled in the study and simple random sampling technique was used after satisfying the inclusion criteria. They were randomly divided into two groups:

Group A (82 patients) - was treated with tablet Levocetirizine 5 mg for six months (with up-dosing to four-fold maximum, depending on the response).

Group B (81 patients)- was treated with tablet Bilastine 20 mg for six months (with up-dosing to fourfold maximum, depending on the response).

Total of 15 patients were lost to follow-up during the course of the study (eight patients from Group A and seven patients from Group B) and were excluded from the statistical analysis. There were remaining 148 patients, with 74 patients in each group [Table/Fig-1]. Detailed clinical history, including occupation and basic demographic details, was taken. General examination, systemic examination, and dermatological examination were conducted. UAS [Table/Fig-1,2] was calculated for each patient before the initiation of treatment and during each follow-up [9,10].



[Table/Fig-1]: Flowchart of the final Consolidated Standards of Reporting Trails (CONSORT) diagram displaying steps of the study.

Investigations including complete blood count, absolute eosinophil count, Erythrocyte Sedimentation Rate (ESR), thyroid function tests, liver function tests, renal function tests, random blood sugar, and stool examination for ova and cyst were performed.

The patients were followed-up during the six months of treatment at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24. The response to treatment was assessed by calculating the UAS before the initiation of treatment and at every follow-up (at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24). Clinical effectiveness and the period of remission were noted. The patients were followed-up for a further six months after the completion of treatment, and the time taken for recurrence was noted.

Primary outcome: Urticaria free/well-controlled urticaria. The disease activity was assessed using UAS7 disease activity score bands [Table/Fig-2] [9].

UAS7 bands	Disease activity
0	Urticaria-free
1-6	Well controlled CSU
7-15	Mild activity CSU
16-27	Moderate activity CSU
28-42	Severe activity CSU

[Table/Fig-2]: UAS7 disease activity score bands.
CSU: Chronic spontaneous urticaria; Secondary outcome: Mild activity CSU (according to UAS); Moderate activity CSU; Severe activity CSU

The severity of urticaria was assessed using Urticaria Activity Score (UAS) [Table/Fig-3] [2].

Score	Severity	Wheals	Pruritus
0	None	None	None
1	Mild	<20 wheals/24 hour	Present but not annoying or troublesome
2	Moderate	20-50 wheals/24 hour	Troublesome but does not interfere with sleep
3	Severe	>50 wheals/24 hour or large confluent areas of wheals	Severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep

[Table/Fig-3]: Urticaria Activity Score (UAS) [3].

STATISTICAL ANALYSIS

The data collected were entered into Microsoft Excel 2019 and then loaded into Statistical Package for Social Sciences (SPSS) software version 23.0 for statistical analysis. Both quantitative and qualitative variables were present in the study. Qualitative data were expressed using percentages, and quantitative data were described using mean standard deviation. To compare the distribution of qualitative variables between the groups, the Chi-square test was applied. To compare the mean between the two groups, an Unpaired t-test was applied. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Out of 163 patients, 15 patients were lost to follow-up (8 from Group A and 7 from Group B) and were excluded from the statistical analysis. The most common age group affected was 20-30 years (33.8%), with a female-to-male ratio of 1.3:1 [Table/Fig-4]. Absolute eosinophil count was raised in only 17 patients (11.5%) [Table/Fig-5]. With respect to the cause, 137 patients (92.5%) of the cases were idiopathic, and 2 (1.3%), 3 (2.1%), and 6 (4.1%) gave a history of triggers following the consumption of fish/meat/brinjal, respectively. With respect to occupation, 10 patients (6.7%) were drivers, and 8 (5.4%) were tailors, which were associated with vibration [Table/Fig-6].

Age group (In years)	Group A		Group B		Group A+B		χ^2	p-value
	n	%	n	%	n	%		
1-20	5	6.8	7	9.5	12	8.1	3.213	0.523
20-30	24	32.4	26	35.1	50	33.8		
30-40	27	36.5	18	24.3	45	30.4		
40-50	10	13.5	15	20.3	25	16.9		
50-60	8	10.8	8	10.8	16	10.8		
Gender								
Male	36	48.6	28	37.8	64	43.2	1.76	0.184
Female	38	51.4	46	62.6	84	57		

[Table/Fig-4]: Distribution of age and sex between the two groups.

Absolute eosinophil count	Group A		Group B		χ^2	p-value
	n	%	n	%		
Abnormal	9	12.2	8	10.8	0.066	0.797
Normal	65	87.8	66	89.2		

[Table/Fig-5]: Distribution of absolute eosinophil count between the groups.

Occupation	Group A		Group B		Group A+B		χ^2	p-value
	n	%	n	%	n	%		
Driver	6	8.1	4	5.4	10	6.7	0.431	0.934
Tailor	4	5.4	4	5.4	8	5.4		
Welding	1	1.4	1	1.4	2	1.4		
Miscellaneous	63	85.1	65	87.8	128	86.5		
Triggers								
Fish	2	2.7	0	0	2	1.3	3.007	0.391
Meat	2	2.7	1	1.4	3	2.1		
Brinjal	2	2.7	4	5.4	6	4.1		
Idiopathic	68	91.9	69	93.2	137	92.5		

[Table/Fig-6]: Distribution according to occupation and triggers between the groups.

Symptoms and triggers: Total of 60 patients (41.2%) reported a duration of symptoms for six months to one year, followed by 46 patients (31.1%) who had symptoms for 1-3 years. Total 9 (6.1%) patients (6.1%) had urticaria for more than 10 years [Table/Fig-7]. All the patients had a history of both itching and wheals; only 11 patients (7.4%) had a history of angioedema associated with wheals, but it was not life-threatening. None of the patients complained of pain over the lesions [Table/Fig-8].

Duration of illness	Group A		Group B		Group A+B		χ^2	p-value
	n	%	n	%	n	%		
6 weeks to 6 months	4	5.4	5	6.8	9	6.1	0.413	0.981
6 months to 1 year	32	43.2	29	39.2	61	41.2		
1 to 3 years	23	31.1	23	31.1	46	31.1		
3 to 10 years	11	14.9	12	16.2	23	15.5		
>10 years	4	5.4	5	6.8	9	6.1		

[Table/Fig-7]: Distribution according to duration of illness between the groups.

Signs	Group A		Group B		Group A+B		χ^2	p-value
	n	%	n	%	n	%		
Itching	74	100	74	100	148	100	-	-
Wheals	74	100	74	100	148	100	-	-
Pain	0	0	0	0	0	0	-	-
Angioedema	7	9.5	4	5.4	11	7.4	0.884	0.347

[Table/Fig-8]: Distribution according to the presence of signs among the participants.

Co-morbidities: Total 10 (6.7%) patients had diabetes mellitus type 2, 1 (0.7%) had diabetes mellitus with hypertension, 1 (0.7%) had only hypertension, 4 (2.7%) had hypothyroidism, and 2 patients (1.4%) had hyperthyroidism [Table/Fig-9]. Total 81 (54.7%) patients (54.7%) had moderate activity of urticaria at the time of presentation. Among the patients in Group A, 12 (16.2%), 46 (62.2%), and 16 (21.6%) had severe, moderate, and mild activity, respectively, and among the patients in Group B, 30 (40.5%), 35 (47.3%), and 9 (12.2%) had severe, moderate, and mild activity as per the UAS, respectively. Severity was higher among the patients in Group B than in Group A.

Co-morbidities	Group A		Group B		Group A+B		χ^2	p-value
	n	%	n	%	n	%		
Diabetes mellitus (type 2)	4	5.4	6	8.1	10	6.7	2.400	0.791
Diabetes and hypertension	1	1.4	0	0	1	0.7		
Hypertension	1	1.4	0	0	1	0.7		
Hypothyroid	2	2.7	2	2.7	4	2.7		
Hyperthyroid	1	1.4	1	1.4	2	1.4		
Nil	65	87.8	65	87.8	130	87.8		

[Table/Fig-9]: Distribution according to the presence of co-morbidities.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

In the first and second weeks of the trial, patients in Group A received 5 mg of Levocetirizine, and everyone in Group B received 20 mg of Bilastine once a day. At week 4, there was an increase in dosage among a certain proportion of patients, with 32 (43.2%) receiving 10 mg dosage of Levocetirizine in Group A and 39 (52.7%) receiving 40 mg (20 mg twice a day) of Bilastine in Group B. During each follow-up, the dosage received by the patients increased.

At weeks 10 and 12, the patients who received an increased dosage were more in Group B than in Group A, with a p-value of less than 0.05 [Table/Fig-10]. Additionally, the dose escalation was higher in Group B at weeks 14, 16, 18, 20, and 22 compared to Group A [Table/Fig-11,12]. The proportion of patients requiring a higher dosage of the drug was higher with Bilastine compared to Levocetirizine (p-value <0.05). The data regarding the distribution of activity of urticaria at each follow-up is provided in the following tables [Table/Fig-13-17]. At week 24, in Group A, 72 patients (97.3%) were urticaria-free, and two patients (2.7%) had well-controlled urticaria. In Group B, 72 patients (97.3%) were urticaria-free, and one patient (1.4%) had well-controlled urticaria. Both groups were statistically similar with respect to the outcome at the end of 24 weeks. Both Levocetirizine and Bilastine were equally effective in controlling urticaria at the end of 24 weeks of treatment (p-value >0.05) [Table/Fig-17]. The time taken for remission was shorter with Levocetirizine (11.19±5.31 weeks) compared to Bilastine (14.59±5.02 weeks) (p-value <0.05) [Table/Fig-18]. Recurrence was earlier with Bilastine than Levocetirizine (p-value <0.05). Within the 1st and 2nd months after the stoppage of treatment, 19.4% and 33.3% had a recurrence in Group B, compared to 6.9% and 13.9% in Group A [Table/Fig-19]. Drowsiness was commonly reported with Levocetirizine, and headache with Bilastine. Both drugs did not cause serious adverse effects. In Group A, 10 patients (13.5%) reported drowsiness, 3 (4.1%) reported gastrointestinal symptoms, and three patients (4.1%) reported headache, respectively. In Group B, 7 (9.5%) patients (9.5%) reported headache, 5 (6.8%) reported drowsiness, and 2 (2.7%) patients reported gastrointestinal symptoms [Table/Fig-20].

Variables		Group A (Levocetirizine)		Group B (Bilastine)			χ^2	p-value
		n	%		n	%		
Week 1	5 mg	74	100	20 mg	74	100	-	-
Week 2	5 mg	74	100	20 mg	74	100	-	-
Week 4	5 mg	42	56.8	20 mg	35	47.3	1.327	0.249
	10 mg	32	43.2	40 mg	39	52.7		
Week 6	5 mg	35	47.3	20 mg	29	39.2	0.991	0.319
	10 mg	39	52.7	40 mg	45	60.8		
Week 8	5 mg	18	24.3	20 mg	24	32.4	9.507	0.009
	10 mg	54	73	40 mg	39	52.7		
	15 mg	2	2.7	60 mg	11	14.9		
Week 10	5 mg	18	24.3	20 mg	23	31.1	15.90	0.001
	10 mg	51	68.9	40 mg	30	40.5		
	15 mg	5	6.8	60 mg	21	28.4		
Week 12	5 mg	15	20.3	20 mg	10	13.5	10.45	0.015
	10 mg	48	64.9	40 mg	36	48.6		
	15 mg	11	14.9	60 mg	27	36.5		
	20 mg	0	0	80 mg	1	1.4		

[Table/Fig-10]: Distribution of intervention dosage between the two groups between week 1 and week 12.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

Variables		Group A (Levocetirizine)		Group B (Bilastine)			χ^2	p-value
		n	%		n	%		
Week 14	5 mg	21	28.4	20 mg	8	10.8	13.74	0.003
	10 mg	37	50	40 mg	32	43.2		
	15 mg	14	18.9	60 mg	25	33.8		
	20 mg	2	2.7	80 mg	9	12.2		
Week 16	5 mg	21	28.4	20 mg	9	12.2	16.12	0.001
	10 mg	38	51.4	40 mg	30	40.5		
	15 mg	13	17.6	60 mg	22	29.7		
	20 mg	2	2.7	80 mg	13	17.6		
Week 18	5 mg	18	24.3	20 mg	6	8.1	14.94	0.002
	10 mg	39	52.7	40 mg	32	43.2		
	15 mg	13	17.6	60 mg	21	28.4		
	20 mg	4	5.4	80 mg	15	20.3		

[Table/Fig-11]: Distribution of intervention dosage between the two groups between week 14 and week 18.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

Variables		Group A (Levocetirizine)		Group B (Bilastine)			χ^2	p-value
		n	%		n	%		
Week 20	5 mg	20	27	20 mg	9	12.2	11.56	0.009
	10 mg	38	51.4	40 mg	31	41.9		
	15 mg	11	14.9	60 mg	21	28.4		
	20 mg	5	6.8	80 mg	13	17.6		
Week 22	5 mg	18	24.3	20 mg	13	17.6	11.07	0.011
	10 mg	41	55.4	40 mg	28	37.8		
	15 mg	9	12.2	60 mg	25	33.8		
	20 mg	6	8.1	80 mg	8	10.8		
Week 24	5 mg	18	24.3	20 mg	12	16.2	9.66	0.022
	10 mg	41	55.4	40 mg	30	40.5		
	15 mg	10	13.5	60 mg	25	33.8		
	20 mg	5	6.8	80 mg	7	9.5		

[Table/Fig-12]: Distribution of intervention dosage between the two groups between week 20 and week 24.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

Variables		Group A (Levocetirizine)		Group B (Bilastine)		χ^2	p-value
		n	%	n	%		
Week 1	Urticaria free	-	-	-	-	7.28	0.063
	Well controlled urticaria	4	5.4	2	2.7		
	Mild activity	44	59.5	40	54.1		
	Moderate activity	24	32.4	21	28.4		
	Severe activity	2	2.7	11	14.9		
Week 2	Urticaria free	0	0	1	1.4	1.24	0.743
	Well controlled urticaria	19	25.7	21	28.4		
	Mild activity	33	44.6	30	40.5		
	Moderate activity	33	29.7	22	29.7		
	Severe activity	-	-	-	-		
Week 4	Urticaria free	0	0	1	1.4	16.30	0.001
	Well controlled urticaria	22	29.7	30	40.5		
	Mild activity	47	63.5	25	33.8		
	Moderate activity	5	6.8	18	24.3		
	Severe activity	-	-	-	-		

[Table/Fig-13]: Distribution according to the grades of urticaria at one week, two week and four weeks.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

Variables		Group A (Levocetirizine)		Group B (Bilastine)		χ^2	p-value
		n	%	n	%		
Week 6	Urticaria free	1	1.4	5	6.8	6.23	0.101
	Well controlled urticaria	43	58.1	31	41.9		
	Mild activity	26	35.1	30	40.5		
	Moderate activity	4	5.4	8	10.8		
	Severe activity	-	-	-	-		
Week 8	Urticaria free	15	20.3	14	18.9	11.12	0.011
	Well controlled urticaria	33	44.6	16	21.6		
	Mild activity	26	35.1	43	58.1		

	Moderate activity	0	0	1	1.4		
	Severe activity	-	-	-	-		
Week 10	Urticaria free	35	47.3	22	29.7	19.39	0.001
	Well controlled urticaria	27	36.5	15	20.3		
	Mild activity	12	16.2	36	48.6		
	Moderate activity	0	0	1	1.4		
	Severe activity	-	-	-	-		

[Table/Fig-14]: Distribution according to the grades of urticaria at 6th week, 8th week and 10th week.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

Variables		Group A (Levocetirizine)		Group B (Bilastine)		χ^2	p-value
		n	%	n	%		
Week 12	Urticaria free	43	58.1	18	24.3	18.36	0.001
	Well controlled urticaria	19	25.7	28	37.8		
	Mild activity	12	16.2	28	37.8		
	Moderate activity	-	-	-	-		
	Severe activity	-	-	-	-		
Week 14	Urticaria free	53	71.6	24	32.4	22.76	0.001
	Well controlled urticaria	13	17.6	31	41.9		
	Mild activity	8	10.8	19	25.7		
	Moderate activity	-	-	-	-		
	Severe activity	-	-	-	-		
Week 16	Urticaria free	48	64.9	37	50	3.95	0.138
	Well controlled urticaria	18	24.3	22	29.7		
	Mild activity	8	10.8	15	20.3		
	Moderate activity	-	-	-	-		
	Severe activity	-	-	-	-		

[Table/Fig-15]: Distribution according to the grades of urticaria at 12th week, 14th week and 16th week.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

Variables		Group A (Levocetirizine)		Group B (Bilastine)		χ^2	p-value
		n	%	n	%		
Week 18	Urticaria free	58	78.4	45	60.8	10.73	0.005
	Well controlled urticaria	13	17.6	29	39.2		
	Mild activity	3	4.1	0	0		
	Moderate activity	-	-	-	-		
	Severe activity	-	-	-	-		
Week 20	Urticaria free	67	90.5	59	79.7	7.063	0.029
	Well controlled urticaria	4	5.4	14	18.9		
	Mild activity	3	4.1	1	1.4		
	Moderate activity	-	-	-	-		
	Severe activity	-	-	-	-		
Week 22	Urticaria free	69	93.2	69	93.2	0.476	0.788
	Well controlled urticaria	3	4.1	4	5.4		
	Mild activity	2	2.7	1	1.4		
	Moderate activity	-	-	-	-		
	Severe activity	-	-	-	-		

[Table/Fig-16]: Distribution according to the grades of urticaria at 18th week, 20th week and 22th week.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

Urticaria	Group A		Group B		χ^2	p-value
	n	%	n	%		
Urticaria free	72	97.3	72	97.3	1.33	0.513
Well controlled urticaria	2	2.7	1	1.4		
Mild activity	0	0	1	1.4		
Moderate activity	-	-	-	-		
Severe activity	-	-	-	-		

[Table/Fig-17]: Distribution according to the grades of urticaria at 24th week.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

Groups	Time taken for remission (in weeks)		df	p-value*
	Mean	SD		
Group A	11.19	5.31	146	0.001
Group B	14.59	5.02		

[Table/Fig-18]: Comparison of mean time taken for remission (in weeks) between the two groups.
SD=Standard deviation; df=of freedom; Test applied=unpaired t-test

Recurrence	Group A		Group B		χ^2	p-value
	n	%	n	%		
Nil	9	12.5	6	8.3	22.73	0.001
Within ≤ 1 month	5	6.9	14	19.4		
2nd month	10	13.9	24	33.3		
3rd month	14	19.4	15	20.8		
4th month	20	27.8	11	15.3		
5th month	9	12.5	2	2.8		
6th month	5	6.9	0	0		

[Table/Fig-19]: Distribution of recurrence between the groups.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

Side-effects	Group A		Group B		χ^2	p-value
	n	%	n	%		
Drowsiness	10	13.5	5	6.8	3.50	0.321
Gastroinstestinal	3	4.1	2	2.7		
Headache	3	4.1	7	9.5		
No side-effects	58	78.4	60	81.1		

[Table/Fig-20]: Distribution of side-effects between the groups.
n=Number of patients; χ^2=Chi-square distribution; Test applied=Pearson's Chi-squared test

DISCUSSION

In the present study, the aim was to find the efficacy of Levocetirizine and Bilastine as monotherapy in chronic spontaneous urticaria. It was inferred that all the patients in Group A (Levocetirizine) and Group B (Bilastine) were urticaria-free or had well-controlled activity at the end of six months, making both drugs equally effective with a p-value of >0.05.Over a period of 6 months of follow-up, Group B patients showed earlier recurrence compared to Group A with a p-value of <0.05. Thus, Levocetirizine produced earlier remission and showed late recurrence in contrast to Bilastine.

In present study, the most commonly affected age group was 20-30 years (33.8%), followed by 30-40 years (30.4%). This was in contrast to Wertenteil S et al.,'s study, where chronic urticaria was more prevalent among the older age group of 40-49 years, followed by 50-59 years [10]. The gender distribution overall was 56.8% females and 43.2% males, which was in the ratio of 1.3:1. This was similar to many studies where there was a female preponderance in the ratio of 2:1 [11,12]. The age and gender distribution in both groups were found to be statistically similar.

In present study, all the patients had a history of both itching and wheals; only 7.4% had a history of angioedema associated with wheals but not life-threatening.

In the study by Jaros J et al., 50% of the patients presented with only wheals, 10% with angioedema, and 40% with both [13]. A family history of urticaria was evident in only 7.4% in present study, in contrast to Asero R's study where only 4% had a family history of urticaria [14]. The duration of urticaria prior to treatment was

between six weeks to six months in 9 (6.1%) patients, six months to one year in 61 (41.2%), 1-3 years in 46 (31.1%), 3-10 years in 23 (15.5%), and for >10 years in 9 (6.1%) patients. This is in contrast to the study conducted by Toubi E et al., where the persistence of symptoms at the end of one year, two years, three years, and five years was 75%, 52%, 43%, and 14%, respectively [15]. AEC was raised in only 11.5% of the patients. However, in a study conducted by Naveen N and Puneetha B the mean AEC was significantly higher in patients with chronic urticaria compared to the control group [16].

Before starting treatment, among the patients in Group A, 16.2%, 62.2%, and 21.6% had severe, moderate, and mild activity, respectively, and among the patients in Group B, 40.5%, 47.3%, and 12.2% had severe, moderate, and mild activity, respectively. Severity was higher among the patients in group B than in group A with a p-value of less than 0.05. 46.6% of patients had moderate urticaria and 18.44% had severe urticaria in Naveen N and Puneetha B study, as compared to 77% in Kessel A et al.,'s and 64.29% in Zaky A and Knalifa S study [16-18].

In the first week of the trial, everyone in Group A received 5 mg of Levocetirizine, and everyone in Group B received 20 mg once a day of Bilastine. A similar dose was received by the patients in the second week as well. In week 4, there had been an increase in dosage among a certain proportion of patients in both groups. 43.2% received a 10 mg dosage of Levocetirizine in Group A, and 52.7% received 40 mg (20 mg twice a day) of Bilastine in Group B. During each follow-up, the dosage received by the patients had increased. At weeks 10 and 12, the dosage received by the patients was higher with Bilastine than Levocetirizine with a p-value of less than 0.05. Also, the dose escalation was higher with Bilastine at weeks 14, 16, 18, 20, 22, 24 compared to Levocetirizine.

At week 24, in Group A, 97.3% were urticaria-free, and 2.7% had well-controlled urticaria. In Group B, 97.3% were urticaria-free, and 1.4% had well-controlled urticaria. Both groups were statistically similar with respect to the outcome at the end of 24 weeks. These observations align with a study by Zuberbier T et al., which indicated that Bilastine reduced patients' mean TSS significantly more than placebo [8]. In contrast, Podder I et al., found Bilastine to be more effective, differing from present study [19]. The mean time taken for remission in Group A and Group B was 11.19±5.31 weeks and 14.59±5.02 weeks, respectively. The time for remission was longer with Bilastine than with Levocetirizine, with a p-value of less than 0.05.

In present study, the proportion of patients with early recurrence was higher with Bilastine than with Levocetirizine. Out of 148 patients, 129 (89.5%) experienced recurrence. This contrasts with a study by Kim JK et al., where only 13% of cases had recurrence [20].

With Levocetirizine, 13.5% reported drowsiness, 4.1% reported gastrointestinal symptoms, and 4.1% reported having a headache. This differs from studies by Hindmarch I et al., and Gandon JM et al., where Levocetirizine did not induce sedative effects [21,22]. Sedation was reported in 25% of patients in a study by Sarkar TK et al., [23]. With Bilastine, 9.5% reported headaches, 6.8% reported drowsiness, and 2.7% reported gastrointestinal symptoms. Many studies indicate less sedation with Bilastine [19]. Therefore, Bilastine is considered a safer drug for use by drivers and pilots compared to Levocetirizine. Monotherapy with Levocetirizine or Bilastine in chronic urticaria is well-tolerated and does not lead to serious adverse effects with long-term use.

When monotherapy or combination therapy fails to control symptoms, an advanced approach with immunosuppressants or biologic therapy (such as Omalizumab or Ligelizumab) may be necessary [24].

Limitation(s)

Serum Immunoglobulin (Ig) E levels and autologous serum skin tests were not conducted, which could have added more significance to the study. Antithyroid peroxidase antibodies were not tested, preventing investigation into the aetiology of autoimmune thyroid disorders. Treatment was based solely on monotherapy with second-generation antihistamines, despite many studies recommending combination treatments for more effective chronic urticaria management. Adverse effects were assessed based on symptoms alone.

CONCLUSION(S)

Levocetirizine and Bilastine are equally efficacious in controlling chronic spontaneous urticaria at the end of six months of treatment. Both are found to have good tolerability. Patients on Levocetirizine experienced earlier remission as well as late recurrence compared to those on Bilastine. Both drugs did not produce any serious adverse effects. Drowsiness was commonly reported with Levocetirizine, while headache was more commonly reported with Bilastine. The quality of life of patients with urticaria is severely affected, and the search for an optimal drug to control the symptoms with minimal side effects continues. Prompt and effective management of the disease, along with identifying a cause, will help mitigate the disease burden.

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