Original Article

Non-sedative Antihistamines: Assessment of Efficacy Based on Total Nasal Symptom Score in Patient with Allergic Rhinitis.

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Abstract

Background: *Allergic rhinitis is a common and chronic immunoglobulin E–mediated respiratory disorder following allergen exposure that can affect the quality of life and work activities. Antihistamine should be prescribed for the relief of persistent allergic symptoms & advised to avoid known allergens also.* ***Objectives:*** *The objective of the study is to assess the efficacy of non-sedating antihistamines in the treatment of allergic rhinitis based on the total nasal symptom score.* ***Materials and Methods:*** *This is a prospective study of patients with clinically diagnosed allergic rhinitis following inclusion & exclusion criteria at the study center. Patients' demographic profiles, symptoms and signs were obtained using a specially designed form. The symptoms were scored from baseline to end of treatment by using nasal symptom scoring protocol. The data were collated and analyzed using Microsoft excel & SPSS Version 17 statistical software.* ***Results:*** *Recruited 360 patients with allergic rhinitis, 96.66% presented with running nose as the chief complaint. A large number of patients have total nasal symptom scores of above 9 (n =170; 47.22%), whereas few (n = 42; 11.66%) had symptom scores of below 6 at a baseline level. Upon treatment with rupatadine, a significant reduction of TNSS (p< 0.05) was found from baseline over the 14-day treatment period. The incidence of adverse effects (fatigue 1.3%, headache 2.7%) was found to be less in the rupatadine group.* ***Conclusion:*** *non-sedative antihistamines effectively control persistent allergic rhinitis, where rupatadine is a drug of choice due to its better efficacy and having a low incidence of side effects.*

Key words: *Antihistamine, Efficacy, Nasal symptom score, Total Nasal Symptom Score (TNSS)*

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Introduction

Allergic rhinitis (AR) is one of the most prevalent atopic disorders which is associated with sleep disturbances that affect work productivity and interference with quality of life.[1] The prevalence of AR varies from population to population which presently affects up to 40% of the population worldwide[1-4] with data from Europe indicating between 23 and 30% and from US indicating between 10 and 30% of adults being affected respectively.[2] Allergic rhinitis is an immunoglobulin E–mediated disease which has been suggested that the increase in severity and persistence of symptoms may be associated with multiple sensitizations and prolonged exposure to traditional allergens [2,5] such as dust mites, insects, animal dander, fungal and mould spores, food, pollen, effects of weather including temperature and humidity, as well as participant's lifestyle.[2,3,5] Symptoms of Allergic rhinitis (AR) are clinically characterized by rhinorrhea, sneezing, nasal congestion and non-nasal symptoms such as itching and watery eyes or itching ears and palate, and signs of invasion of nasal mucosa by inflammatory cells.[1,3]

Several methods are available for the measurement of the nasal symptoms experienced by study participants. The Total Nasal Symptom Score (TNSS) is the sum of scores for each of nasal congestion, sneezing, nasal itching, and rhinorrhea at each time point, using a four-point scale (0–3), where 0 indicates no symptoms, a score of 1 for mild symptoms that are easily tolerated, 2 for awareness of symptoms which are bothersome but tolerable and 3 is reserved for severe symptoms that are hard to tolerate and interfere with daily activity. TNSS is calculated by adding the score for each of the symptoms to a

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total out of 12.[3,6] Treatment options for allergic rhinitis include control of environmental risks, pharmacological management, and allergen immunotherapy. Pharmacologic therapy includes antihistamines, decongestants, corticosteroids, intranasal cromolyn, intranasal anticholinergics, and oral leukotriene receptor antagonists (LTRAs).[7] In clinical practice antihistamines are first-line treatments largely used on an on-demand basis that relieves most of the manifestations of allergic rhinitis or conjunctivitis.[8] They are particularly effective at relieving sneezing, itching, and watery rhinorrhea.[9] The international guidelines state that first-generation antihistamines do not provide significant benefits because of their sedative action and anticholinergic side effects rather second-generation antihistamines represent the mainstay of treatment for allergic rhinitis.[7,10,11]

Compared with first-generation antihistamines, second-generation antihistamines have more complex chemical structures that decrease their movement across the blood-brain barrier, reducing central nervous system adverse effects such as sedation and have a longer duration of action up to 24 h allow once-daily administration.[5,7,9] Second-generation nonsedative oral antihistamines include fexofenadine, rupatadine, cetirizine, levocetirizine, desloratadine.[5] In this study we assessed the efficacy of second-generation antihistamines based on total nasal symptom score in patients with allergic rhinitis.

Materials and Methods

This study was a prospective cross sectional study conducted on 360 diagnosed patients clinically with allergic rhino-sinusitis at the ENT out- patient dept. of Khulna Medical College Hospital, Khulna carried out over a 5 months period from November 2020 to March 2021. Consenting adult patients age >18 years of both sexes who presented with two or more of the following symptoms: nasal blockage/obstruction, excessive sneezing, excessive nasal itching, and watery nasal discharge were included in this study whereas patients with co-morbid conditions like Diabetes mellitus (DM), Hypertension (HTN), heart diseases, asthma, history of nasal tumors, nasal polyps, were excluded from the study. Ethical approval was obtained from the Institutional Ethics Committee and informed written consent was also obtained from each patient before recruitment. A specially designed questionnaire was used to record participant demographic profile and their symptoms were scored using Lund's symptom score protocol. The severity of the symptoms was assessed by calculating the total nasal symptoms score (TNSS)) from baseline visit to end of the study visit (after 2 weeks of treatment) in which all participants were evaluated for the degree of running nose, nasal itching, nasal obstruction, sneezing of different episodes. The data was tabulated as mean ± standard deviation (SD) and percentage by using Microsoft Excel 2007 and the Statistical Package for Social Sciences (SPSS) Version 17.0 statistical software. Results were analyzed using a two-tailed student t-test. A P-value of <0.05 was considered statistically significant.

Results

Three hundred sixty (360) participants were recruited into the study group where female (52.22%) were more affected than male (47.77%). The majority of the participants were aged between 18 to 37 years (58.33%) with fewer individuals in other age group. Among them most of the patient came from urban area (56.66%) and had positive family history of atopy (54.16 %). Table-I shows these demographic characteristics of the study population.

Table I: Demographic characteristics of the participants.

Characteristics of the participants		Number of participants (n= 360)	Percentage (%)
Age (years)	< 18	50	13.88%
	18–37	210	58.33%
	38–57	62	17.22%
	>57	38	10.55%
Gender	Female	188	52.22%
	Male	172	47.77%
Family history of atopy	Present	195	54.16%
	Absent	165	45.83%
Residence	Urban	204	56.66%
	Rural	156	43.33%

Figure 1 shows self-reported triggers of allergic symptoms in the study population. Dust was the commonest etiologic factor for allergic rhinitis accounting (50.55%), second-most was group pollen (17.22%), food (12.5%) and smoke (10.27%) & others were (9.44%).

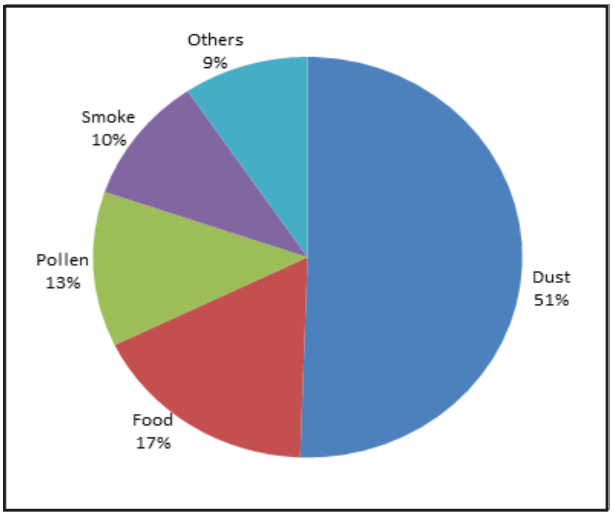

Figure 1: Triggers of allergic symptoms in the participants

Figure 2 shows baseline symptoms of allergic rhinitis among the study population where most common symptom presented in the severe form was nasal itching (n = 155), but the majority of the patients had complaints of running nose (96.66%) followed by nasal itching (93.88%), nasal obstruction (90%), sneezing (88.33%).

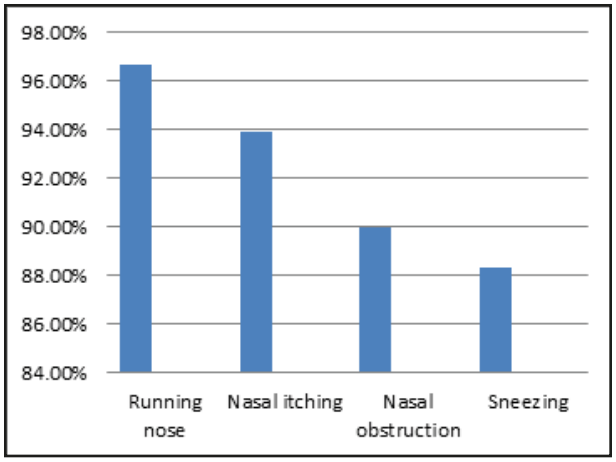

Figure II: Baseline symptoms of allergic rhinitis

Table II shows a cross tabulation of baseline & after treatment of total nasal symptom scores of participants. A large number of patients with results have total nasal symptom scores of above 9 (n= 170; 47.22%), whereas (n = 42; 11.66%) had symptom scores of below 6 at the baseline category.

After 2 (two) weeks of treatment only 13 (3.61%) patients had symptom scores of below 6. Therefore baseline TNSS (mean ±SD) was 8.76±2.55 and after 2 weeks of treatment TNSS (mean ±SD) reduce to 4.12±1.58.

Table II: Baseline & after treatment of Total Nasal Symptom Score (TNSS)

TNSS n= 360	Baseline (n= 360) '0' week	After treatment (n= 360) 2 weeks
Mild < 6	42 (11.66 %)	13 (3.61 %)
Moderate 6-9	148 (41.11%)	03 (0.83%)
Severe >9 upto 12	170 (47.22 %)	Nil
Mean ± SD	8.76 ± 2.55	4.12 ± 1.58

Effect of different antihistamines on total nasal symptom scores of participants from baseline to end of the study showed in Table III. TNSS in rupatadine groups at baseline mean ±SD (8.66±2.64) and after 2 weeks of treatment mean ±SD (3.3±0.57) revealed statistically significant results (p value= .000897; p< 0.05).

Table III: Effect of antihistamines on TNSS from baseline to end of the study

Antihistamine	Baseline '0' week (n= 360)				After treatment 2 weeks (n= 360)				P value
	Mild <6	Moderate 6 -9	Severe 9 -12	Mean ±SD	Mild <6	Moderate 6 -9	Severe 9 -12	Mean± SD	
Rupatadine n= 72	8	29	35	8.66±2.6	3	Nil	Nil	3.3±0.5	.000 897
Levocetirizine n= 72	12	29	31	8.37±2.7	4	2	Nil	4.5±1.9	.001 094
Cetirizine n= 72	7	28	37	8.87±2.5	2	1	Nil	4±2.64	.001 515
Desloratadine n= 72	5	32	35	8.86±2.2	2	Nil	Nil	3.5±0.7	.001 619
Fexofenadine n= 72	10	30	32	8.40±2.8	2	Nil	Nil	2.5±0.7	.004 183

Table IV: Percentage of adverse effects during the study by treatment group

Adverse effects	Rupatadine n= 72	Levocetirizine n= 72	Cetirizine n= 72	Fexofenadine n= 72	Desloratadine n= 72
Somnolence	Nil	02 (2.7%)	08 (11.11%)	04 (5.5%)	06 (8.3%)
Fatigue	01 (1.3%)	02 (2.7%)	08 (11.11%)	02 (2.7%)	03 (4.1%)
Headache	02 (2.7%)	03 (4.1%)	03 (4.1%)	02 (2.7%)	01 (1.3%)
Weakness	Nil	01 (1.3%)	08(11.11%)	03 (4.1%)	02 (2.7%)
Dizziness	Nil	01 (1.3%)	02 (2.7%)	01(1.3%)	02 (2.7%)

Among different antihistamines rupatadine have good effect on TNSS than others. Percentage of adverse effects is negligible in rupatadine group. Only 1.3% & 2.7% patient complaints of fatigue & headache respectively in this group. Other adverse effects of different antihistamines are tabulated in percentage showed in Table IV.

Discussion

The most common allergic disease affecting the general population worldwide is allergic rhinitis leads to inflammation of the upper airway mucous membranes due to binding of antigens to specific IgE.[12] In this study, the majority of patients with allergic rhinitis were females. This is consistent with several studies worldwide,[4,13-16] Greater cough reflex sensitivity of the airway, hormonal influence, physiological differences between men and women in airway reactivity to allergens are common attributing factor for higher prevalence rate in female.[4] 58.33% patients with allergic rhinitis were in the age group of 18 to 37 years. This is similar with other studies.[4,14-18] A larger proportion of the patients (54.16%) have family history of allergic disease or atopy. This is similar to findings by Ajiya, et al., Azam et al.[4,19] irrespective of the varying prevalence across the worldwide populations and societies it have shown that the strongest risk factor for the development of allergic symptoms has been a strong family history of allergic disease.[4] The most common triggering factor of allergic rhinitis is dust particle (50.55%) which is concomitant with other observation done by Ajiya et al., Nepali, et al.[4,20] The majority of patients in this study presented with complaints of running nose 96.66% which is consistent with other study done by Azam et al.[19] However, the symptom with most severity was nasal itching (n= 155) followed by nasal obstruction (n=144) & sneezing (n= 122). These findings differs from other reported findings in Nijeria, India, Brazil, Nepal.[4,12,16,20]

Studies on antihistamines are usually conducted in countries where the presence of seasonal rhinitis is quite significant. The TNSS is a widely accepted and reliable parameter to assess the efficacy of a drug in the treatment of allergic rhinitis. A decrease in the score suggests an overall clinical improvement in the condition. In several studies, the difference in TNSS for each subject was calculated, seeking to establish the reduction gradient in the score.[1,4,6,13-15,17,21] In the present study, a significant ($p<0.05$) and progressive decrease in the TNSS was observed from baseline over the 14 day treatment period with different non-sedative antihistamines. Rupatadine was found to be more significant (P-value .000897) in reducing TNSS and improving signs of allergic rhinitis after 2 weeks of treatment. The proportion of patients with a complete response for TNSS was statistically higher in levocetirizine also. Another trial of desloratadine, cetirizine, fexofenadine also showed significant reduction in symptom score & improvement in nasal symptoms of allergic rhinitis. Some other studies showed that rupatadine offers an effective response in the treatment of persistent allergic rhinitis due to its fast response onset and sustained improvements throughout the two-week period.[10,14,16,17,22] Similar findings for the effectiveness of levocetirizine are shown in other studies.[8,18,21,22] Rupatadine is known as a dual blocker since this drug not only block the action of histamine but also of other inflammatory mediators such as PAF, LTs, and chemokines.[1,10]

It is well recognized that second-generation antihistamines have generally non-sedating property; however it does not mean that somnolence is never occur with these therapies.[17] In our study somnolence is reported in a small minority of patients, it should be noted that in our trial, at the end of each weekly treatment period, patients were actively asked to report any adverse symptom or event that they may have experienced. Incidence of somnolence was more in cetirizine group (11.11%) followed by desloratadine (8.3%), fexofenadine (5.5%), levocetirizine (2.7%) whereas no somnolence was reported in rupatadine group. Other adverse effects were fatigue, headache, weakness, dizziness reported by the patients of different treatment group. Similar trials also carried out with other

studies done by Marmouz et al., Shamizadeh et al. Gupta et al., Snidvongsa et al.[12,15,17,23] None of the adverse effects reported was severe that required termination of treatment or reduction in dose. The increase in the incidence of somnolence or sleepiness, as a treatment-related adverse event, could be associated with the administration of the drug in the morning. So bed time is more preferable for antihistamine prescribing.

The use of some antihistamines is confined to selected countries like the Philippines and Thailand where bilastine is an afordable innovator drug though its use is minimal, due to limited availability in Thailand. Moreover, the drug pricing differs between countries, and is highly dependent on the healthcare structure.[24]

We faced some limitations during our study time. Firstly the sample is small in size to evaluate the actual number of adverse events reported by the patients through follow up visit or via contact over telephone; moreover patients allergic to various allergen may be free of symptoms when their environment has been adjusted. Though diagnosis and treatment of allergic rhinitis still depends on a good clinical evaluation[19] it should significantly correlate with exposure to particular allergens. Focused assessment on populations comprises of children are required to provide specific recommendations. Also, further studies are required for additional assessments of the effect of rupatadine & other antihistamines on patients reported clinical outcomes.

Conclusion

Non sedative antihistamines provide effective relief of the symptoms of allergic rhinitis. However, clinical benefit occurs significantly more with rupatadine due to its H1- antihistamine & additional PAF antagonistic property. We studied that the superior efficacy of rupatadine compared to others at improving total nasal symptom score of allergic rhinitis over 14 days of treatment. Our study outcome based on a sensitive and clinically relevant model play an important role for the treating physician to select the most appropriate antihistamine for particular patients.

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