ORIGINAL ARTICLE

Comparative Study of Topical Treatment in Allergic Rhinitis Using Azelastine and Fluticasone in a Combination Verses Fluticasone Propionate Alone

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Abstract

Background: Amongst the common problems faced globally, Allergic Rhinitis (AR) is very distressing at times. This is an inflammatory response to either known or unknown allergen. The symptomatic relief in AR using topical steroid Fluticasone propionate and antihistaminic Azelastine Hydrochloride in a combination has been studied. Very few studies showing comparison between these two drugs in a combination and steroid alone are available in the literature. *Aim and Objectives:* To study the effectiveness of topical treatment using corticosteroid Fluticasone propionate and antihistaminic in a combination versus Fluticasone propionate alone in patients of AR. *Material and Methods:* The cases presented with symptoms of allergic rhinitis were randomized in two groups at start of treatment. All cases of Group I were treated with Fluticasone propionate whereas of Group II with Fluticasone propionate and Azelastine hydrochloride combination. In each group, the individual symptom scores were recorded pre-treatment and post-treatment at the end of four weeks with the help of symptom evaluation scale. Based on these individual symptom scores, the Total Symptom Score (TSS) was calculated. The effectiveness of group specific drugs was evaluated by comparing individual and TSS. *Results:* After four weeks, both TSS and individual symptom score were reduced in either group ($p<0.05$). Further, Group II specific drug was found more effective than Group-I in relieving symptoms of AR. *Conclusion:* TSS decreased by an average of 84.14% in Group-I (i.e. treated with Fluticasone propionate) and by 91.16% in Group–II (i.e. treated with Fluticasone propionate and Azelastine hydrochloride I in a combination).

Keywords: Azelastine hydrochloride, Fluticasone propionate, Total Symptom Score

Introduction:

Allergic Rhinitis (AR) is seasonal or perennial, which includes various nasal and ocular symptoms [1, 2]. It affects up to 40% of the population [3]. More than half of the Indian population is having atopy and suffer from AR [4, 5]. It constitutes 10 to 20% sufferers of chronic rhinitis. Severe AR deteriorates the quality of life leading to impairment of daily activity and its prevalence is on increase [6]. AR represents as a part of systemic airway disease involving the entire respiratory tract and is no more a localized disorder of nasal cavity as thought earlier [7]. AR is a nasal airway disease in which production of inflammatory mediators and cell infiltration are prominent [8]. In topical treatment of AR, use of corticosteroid and antihistaminic therapies are well known. The topical steroid controls allergy by various mechanisms like suppressing the release of histamine and kinins, reducing the resultant edema by interference in adhesion of leukocyte to the capillary wall and reduction of capillary membrane permeability [9, 10]. Also, Azelastine topical antihistaminic controls allergy by way of blocking the histamine release as well as inhibiting the pre formed histamine. It also inhibits inflammatory mediators including leukotrienes, cytokines, adhesion molecules kinins [11-14]. Hence, the topical antihistaminic preparation

combined with steroid, works in synergism. Very few studies like Ratner *et al*.[15], Berger *et al*.[16] are done like in Ratner *et al*.[12], effectiveness of topical Fluticasone propionate, topical Azelastine and combination of both were studied on 151 patients at Texas, USA and follow up period was 2 weeks. In Berger *et al.* [16], 13 which was open label study, effectiveness of topical Fluticasone propionate versus topical Azelastine and Fluticasone propionate combination were studied on 405 children (between 6-12 years) at California, USA and follow up period was 3 months.

The present study was carried out to evaluate effectiveness of corticosteroid Fluticasone propionate and antihistaminic in a combination versus Fluticasone propionate alone applied as topical nasal spray on Indian patients of AR.

Material and Methods:

The double blind, randomized study of 220 cases who presented in ENT outpatients department of a tertiary care hospital from 1st December 2016 to 30th June 2018 was conducted after clearance from Institutional Ethics Committee.

All cases presented with seasonal and perennial AR were included in the study after informed consent. Cases with nasal obstruction due to structural abnormality such as gross deviated nasal septum, extensive antrochoanal and ethmoidpolyps and malignancy were excluded. Also those on systemic or oral corticosteroids and antihistamines taken before 30 days of study, having diabetes irrespective of its status of control and with pregnancy or women planning for pregnancy or lactating were excluded. All cases selected, and evaluated as per inclusion and exclusion criteria were investigated by means of proper history taking, clinical examination and relevant laboratory investigations like hemoglobin, total leukocyte count and Absolute Eosinophil Count (AEC).

All cases were randomized in two groups namely Group-I and II with the help of computer assisted randomization. The prescription drug was replaced with Group I and Group II labels by non-medical staff thus confirming double blinding while advising the topical treatment. All the participants were treated using group specific topical nasal spray 2 puff in each nostril for a period of four weeks. Every patient was instructed to hold breath for a while before applying two consecutive puffs in each nostril and repeat the same twice a day during treatment period.

All cases were assessed on 4 point scale (0 to 3) for symptoms like nasal blockade, rhinorrhea, sneezing, nasal itching etc (Table 1). The rating of the 4 point symptom score was explained to every patient. Pre-treatment symptoms scores were recorded. The daily symptom scores on a scale (0-4) were recorded in a diary by the patient himself. This diary was maintained during entire study period, thus increasing the credibility of the subjective scale. This self-assessment rating by patients is recommended by the US Department of Health and Human Services, Food and Drug Administration (FDA), AR: Clinical Development Programs for Drug products. Individual symptom scores as well as AEC before and after 4 weeks of treatment were recorded in either group. The mean values of individual symptom scores and AEC were obtained and compared between before and after treatment. The Total Symptom Score (TSS) was derived after addition of all individual symptom scores. Subsequently group specific mean total symptom score was obtained and compared. Effectiveness of treatment was assessed by comparing the individual symptom score, total symptom score and absolute eosinophil count before and after treatment.

Table 1: Total Symptom Score (TSS)

Symptom Evaluation Scale	Symptoms	Description of symptoms*
0	Absent	No symptoms
1	Mild	Symptoms present but not troublesome
2	Moderate	Symptoms frequently troublesome but not disturbing daily activity or sleep
3	Severe	Symptoms disturbing daily activity and sleep

***if p< 0.05, statically significant*

Ethical approval:

All procedures performed on human participants were in agreement with ethical standards of the Institutional and/or National Ethics Committee

Informed Consent:

Informed consent was obtained from all the cases in the study.

Statistical Methods:

Chi-square and Unpaired't' test was used to find significance of age, sex, duration of illness and intermittent or persistent symptoms and co-morbidity between Group I & II. Mann Whitney U test was used to find proportion of significance in individual symptom score pre-treatment and post-treatment between group I and II and Wilcoxon signed Rank test used to find the significance of total symptoms score pre-treatment and post-treatment. All data analysis had been done by using SPSS (version 22) for windows.

Results:

All enrolled cases completed the study and were followed up for period of four weeks. The age was between 10 to 75 years in all 220 cases studied. In all, there were 124 (56.00%) males and 96 (44.00%) females. The mean age of Group I and II was 33.94 and 33.49 respectively (Table 2). Out of 220 (100%) cases, symptoms were intermittent in 141 (64.09%) and persistent in 79 (35.90%). Amongst these 141 cases, having intermittent symptoms, 68 (30.90%) were from Group I and 73 (33.18%) from Group II. Similarly amongst 79 (35.90%) cases having persistent symptoms, 42 (19.09%) were from Group I and 37 (16.81%) from Group II (Table 2). Mean duration of symptoms taken together was 3.15 years in Group I and 3.49 years in Group II (Table 2). The number of cases having bronchial asthma were 13 (5.45%) and 11 (5.00%) in Group I and Group II respectively.

TSS Analysis:

The mean TSS at four weeks after treatment was compared with pre-treatment score in all cases. Pre-treatment TSS was 11.23±1.23 and 12.23 ±1.68 in Group I and II respectively. Similarly, four weeks post-treatment TSS was 1.78 ± 1.09 and 1.08 ± 0.78 in Group I and II respectively. This also means, TSS reduced by 9.45 ± 0.14 in Group I, where as it reduced by 11.15 ± 0.9 in Group II (Fig. 1). Using Wilcoxon matched paired test, the percentage change of median total symptom score was 84.14% in Group I compared to 91.16% in Group II.

Table 2: Age, Gender, Symptoms and Co-morbidity

Variable	Group I (n= 110)	Group II (n= 110)	Total (n=220)	Test Value	P value*
Age (years)				t=0.24	0.79
Mean ±SD	33.94 ± 13.45	33.49 ± 13.89	33.71 ± 13.67		
Range	15–65	10–75	10–75		
Gender	Numbers			χ^2=0.07	0.78
Male	61 (27.54%)	63 (28.46%)	124 (56.00%)		
Female	49 (22.45%)	47 (21.55%)	96 (44.00%)		
Symptoms	Numbers			χ^2=0.49	0.48
Intermittent	68 (30.90%)	73 (33.18%)	141 (64.09%)		
Persistent	42 (19.09%)	37 (16.81%)	79 (35.90%)		
Duration (years) Mean ±SD	3.15 ± 1.77	3.49 ± 1.99	3.32 ± 1.88	t=1.33	0.18
Co-morbidity Bronchial asthma	13 (05.45%)	11 (05.00%)	24 (10.45%)	χ^2=0.21	0.67

Note: p-Value was derived from independent t-test and chi-square test
**Significantly different from control at P<0.05*

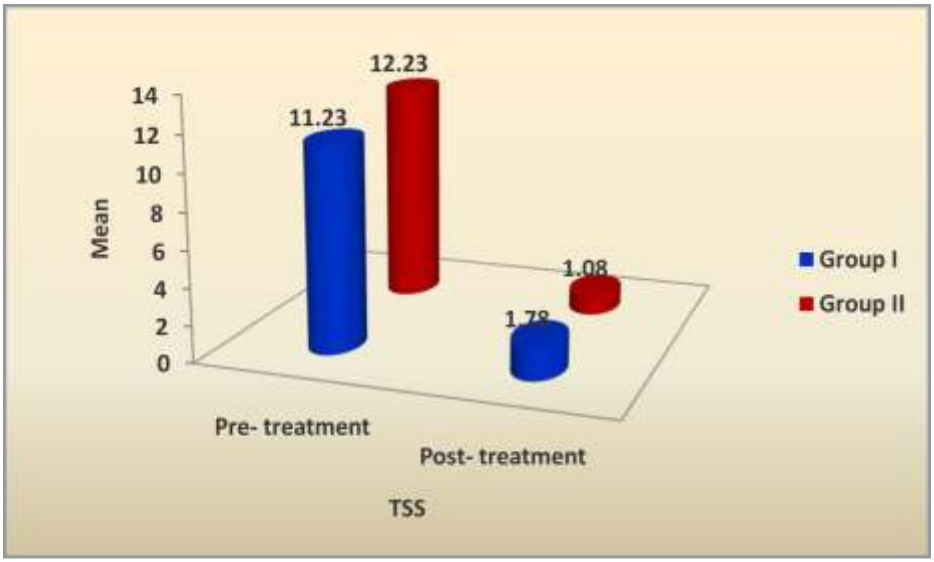

Fig. 1: Graph showing Total Symptom Score (TSS) Analysis Pre-treatment and Post-treatment of Group I and II

Table 3: Total Symptom Score Analysis

Variable	Group*	Pre-treatment (Mean ±SD)	Post treatment (Mean ±SD)	Change from Pre-treatment (Mean ±SD)	% Change from pre-treatment	P value#
Total symptom score	I	11.23±1.23	1.78 ± 1.09	9.45 ±0.14	84.14	<0.0001
	II	12.23 ±1.68	1.08 ± 0.78	11.15 ± 0.9	91.16	<0.0001

**Group I – Fluticasone propionate Group II – Fluticasone propionate with Azelastine hydrochloride # P<0.0001 statistically highly significant by Wilcoxon signed Rank test*

Table 4: Individual Symptom Score and Absolute Eosinophil Count Before and After Treatment of Each Group I and Group II

Variable	Pre-treatment			Post-treatment		
	Group I (n=110) Mean ± SD	Group II (n=110) Mean ± SD	P value*	Group I (n=110) Mean ± SD	Group II (n=110) Mean ± SD	P value*
Sneezing	2.43 ± 0.71	2.62 ± 0.79	0.062	0.21 ±0.36	0.11 ± 0.41	0.041
Nasal obstruction	2.36 ± 0.66	2.41 ± 0.61	0.561	0.61 ± 0.21	0.27 ± 0.13	<0.0001
Nasal Discharge	2.29 ± 0.49	2.31 ± 0.58	0.78	0.72 ± 0.43	0.18 ± 0.20	<0.0001
Nasal itching	1.19 ± 0.61	1.26 ± 0.54	0.368	0.38 ± 0.61	0.23 ± 0.19	0.014
Itching of eye	1.11 ± 0.57	1.19 ± 0.61	0.316	0.08 ± 0.10	0.03 ± 0.10	0.0003
Watering of eye	0.45 ± 0.51	0.63 ± 0.23	0.061	0.04 ± 0.11	0.04 ± 0.13	0.781
Palatal itching	0.72 ± 0.43	0.81 ± 0.56	0.182	0.08 ± 0.13	0.03 ± 0.14	0.006
Itching of ears	0.44 ± 0.21	0.51 ± 0.44	0.134	0.04 ± 0.17	0.01 ± 0.10	0.01
Absolute eosinophil count	783.11 ± 91.59	821.32 ± 125.59	0.061	218.19 ± 25.61	189.23 ± 28.34	0.012

**Statistically significant when p< 0.05*

Individual Symptom Score and AEC Analysis:

In this study, the symptoms were nasal obstruction, nasal itching, nasal discharge, palatal itching, itching of eye, itching of ears, sneezing and watering of eye. Amongst all cases, sneezing was the most common symptom having pre-treatment 2.43 ± 0.71 and 2.62 ± 0.79 of Group I, II respectively (P=0.062). Whereas, after treatment Mean ± SD became 0.21 ± 0.36 and 0.11 ± 0.41 of Group I, II respectively (P=0.041). Itching of ear was the least common with pre-treatment 0.44 ± 0.21 and 0.51 ± 0.44 of Group I, II respectively (P=0.134). Whereas after treatment became 0.04 ± 0.17 and 0.01 ± 0.10 of Group I, II respectively (P=0.01). Therefore Group I and II specific drugs were effective in reducing symptoms but Group II specific drug was better. Regarding the symptom of watering of eye, the pre-treatment was 0.45 ± 0.51 and 0.63 ± 0.23 in Group I, II respectively (p=0.061). The after treatment was almost similar in Group I, II (P=0.781). This also means that both Group I and II were equally effective in reducing this symptom.

The mean individual symptom score and AEC between the groups remained almost similar before start of treatment; however after treatment, it was found to be reducing individual symptom score and absolute eosinophil count (Table 4). Thus, confirming the effectiveness.

Side Effects of Drugs:

In the present study, out of 220 patients, none experienced serious side effects, only 12 (5.45%) patients experienced side effect of the drug which were mild and resolved, neither requiring concomitant therapy nor discontinuation from the study. Five (2.27%) cases of Group I and 7 (3.18%) cases of Group II presented with mild side effects. Amongst these 5 (2.27%) cases, epistaxis was noted in 2(0.9%), nasal stuffiness in 1(0.45%), irritation of throat in 1(0.45%) and headache in 1(0.45%). Similarly amongst 7 (3.18%) cases, epistaxis was noted in 3(1.36%), nasal stuffiness in 1(0.9%), irritation of throat in 2(0.9%) and headache in 1(0.9%).

Discussion:

AR is grouped into either intermittent or persistent. When symptoms are present less than 4 days a week and for less than 4 consecutive weeks it is grouped as intermittent. Similarly when the symptoms are present more than 4 days a week and for more than 4 consecutive weeks it is grouped as persistent. The severity of AR can be classified as mild, moderate and severe [17]. Severity refers to the symptomatology and impairment of quality of life.

AR is treated using systemic antihistaminic, topical nasal corticosteroid sprays, topical nasal antihistamine sprays and subcutaneous injection of allergens. Treatment of AR aims at adequate and faster control of the symptoms [8].

Cases in Group I showed significant reduction of TSS by 84.14% (P=<0.0001) which was in accordance with study by Dykewicz *et al*. [18] 91% and Havle *et al*. [19] 95.55%. Similarly Group I cases showed significant reduction in individual symptoms which was in accordance with Dykewicz *et al*.[18].

A double-blind, placebo-controlled study in which effectiveness of topical Fluticasone were studied on 241 patients (>12 years of age) at Missouri, USA and follow up period was 4 weeks. In study by Havle *et al*. [19], a single blind, randomized control study in which the efficacy of Olopatadine hydrochloride nasal spray was compared with fluticasone propionate steroidal nasal spray on 150 patients at karad-Maharashtra, India and Ratner *et al*. [15] (Table-5).

Table 5: Efficacy of Fluticasone Propionate in Comparison with Other Studies

Studies	Ratner *et. al.* [15]	Dykewicz *et. al.* [18]	Havle *et. al.* [19]	Present study
Sneezing	31.8%	85%	91.30%	91.35%
Nasal obstruction	21.1%	92%	96.72%	74.15%
Nasal discharge	23%	90%	98.36%	68.61%

Cases in Group II showed reduction of TSS significantly by 91.16% (P=<0.001) whereas, similar studies by Berger *et al*. [16], Sami *et al*.[20], who analyzed effectiveness of topical Fluticasone with Azelastine in a combination on 53 patients at UK to identify AR and its response to treatment and follow up period was one month. Carr *et al.* [21], who analyzed effectiveness of topical Fluticasone with Azelastine in a combination on 3398 patients (>12 years old) with moderate-to-severe Seasonal AR, a randomized, double-blind study was carried out at California, USA and follow up period was 14 days. Bousquet *et al*. [22], who analyzed effectiveness of topical Fluticasone with Azelastine in a combination on 82 patients, a randomized, double-blind study was carried out at Ontario, USA and follow up period was 4 hours and Ratner *et al*.[15] showed reduction of TSS by 73.4%, 64%, 57%, 32.4% and 37.9% respectively. The cases of Group II showed improvement in the individual symptoms such as sneezing, itching of nose and nasal blockage by 95.80%, 97.47% and 88.79% respectively. Whereas Ratner *et al*.[15] showed improvement in above symptoms that are 46.4%, 39.9%, 31.2% respectively.

In this study both groups showed reduction of sneezing. There was significant difference in reduction in symptom of sneezing that was 91.35% in Group I and 95.80% in Group II. Whereas, similar study by Ratner *et al*. [15], it was 31.8% and 46.4% respectively. In Group II, the symptom of nasal obstruction was improved by 88.79% and in Group I, it was 74.15%. Whereas, in study by Ratner *et al*. [15]. It was 31.2% and 21.1% respectively. In this study, percentage improvement of TSS in Group I cases as well as in Group II cases was 84.14% and 91.16%. Whereas, in similar studies by Berger *et al*.[16] it was 66% and 73.4%, in Ratner *et al*. [15] it was 27.1% and 37.9% and in Carr *et al*.[21] it was 49% and 57%.

Conclusion:

Group I and II specific drugs in this study were effective in controlling symptoms of AR. Group I and II specific drug i.e. Fluticasone propionate and Fluticasone propionate with Azelastine hydrochloride combination used topically reduced total symptom score-TSS by 84.14% and 91.16% respectively in cases of AR.Thus, combination of corticosteroid Fluticasone propionate and antihistaminic Azelastine was effective than Fluticasone propionate alone in patients of AR.

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