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TOPICAL TREATMENT USING ANTIHISTAMINIC, STEROID AND A COMBINATION OF BOTH IN ALLERGIC RHINITIS-A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

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ABSTRACT: This study evaluates the effectiveness of corticosteroid fluticasone propionate, antihistaminic azelastine, and a combination of both as well as to find out the prognostic significance of absolute eosinophil count (AEC) in the topical treatment of allergic rhinitis. All cases presenting with symptoms of nasal allergy were included maintaining double-blind status. A total of 225 participants of groups I, II and III were treated with topical azelastine, fluticasone propionate and combination of both. The individual symptom score was recorded before and after treatment at the end of four weeks with the help of symptom evaluation scale. The effectiveness of group-specific drugs was evaluated by comparing individual and total symptom scores. AEC was repeated at the end of four weeks in all cases. After intervention the reduction of total symptom score (TSS) and AEC was 9.26 ± 0.01, 11.73 ± 0.54, 11.08 ± 1.61 and 205.59 ± 81.18, 176.05 ± 38.23, 195.75 ± 29.22 in group I, II and III respectively. Similarly for sneezing it was 0.21±0.41, 0.24 ± 0.43 and 0.13 ± 0.38, for nasal obstruction 0.4 ± 0.57, 0.08 ± 0.13 and 0.33 ± 0.6, for nasal discharge 0.72 ± 0.83, 0.04 ± 0.20 and 0.21 ± 0.41 and for nasal itching 0.11 ± 0.39, 0.04 ± 0.20 and 0.25 ± 0.44 in group I, II and III respectively. Fluticasone propionate (interventional agent of group II) was found to be the most efficacious in reducing TSS (95.52%), AEC (79.82%), and all individual symptom scores except in case of a symptom of sneezing, the combination of azelastine and fluticasone propionate (interventional agent of group III) was most efficacious and statistically significant.

INTRODUCTION: The allergic rhinitis (AR) is seasonal or perennial, and has various nasal and ocular symptoms. It affects up to 40% of the population; however, more than 50% of the Indian population is having atopy and suffering from AR. Quality of life & impairment of daily activity is the consequences of severe AR.

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It is a part of systemic airway disease rather than a localized disorder of the nasal cavity. The topical treatment of AR using corticosteroid and antihistaminic is well known.

The topical steroid controls allergy by suppressing the release of histamine and kinins, reducing the resultant edema [1]. Whereas, antihistamines control allergy by blocking histamine release as well as inhibits preformed histamine. Thus, synergism is found between antihistamines & steroid when used topically [2, 3]. The present study was carried out amongst cases of AR to evaluate the effectiveness of azelastine, fluticasone propionate, and a combination of both as well as to assess their effect

on absolute eosinophil count (AEC) when used topically.

Study Design: It is a prospective, double-blind, randomized controlled comparative study to find out the effectiveness of topical treatment using antihistaminic, steroid, and combination of both in 225 cases of AR at ENT department of a tertiary care teaching hospital.

MATERIALS AND METHODS: All cases presenting with symptoms of nasal obstruction, sneezing, itching sensation in the nose, watery nasal discharge as well the cases with other symptoms like watering of eyes and itching in eyes, palate, ears and showing willingness for clinical trial irrespective of age and sex were included in the study. The cases with symptoms of nasal obstruction due to structural abnormalities such as the grossly deviated nasal septum, extensive nasal polyps, tumor, and requiring surgical management were excluded from the study. Also, those using systemic or oral corticosteroids and/or anti-histamines during the past 30 days of the entry visit were excluded as they may confuse the results of the trial. Further, any case with a history of surgery or having a disease known to affect the gastrointestinal absorption of drugs, diabetics irrespective of the status of its control and women with pregnancy or lactation were excluded. For treatment purposes, the participants were handed over to supporting staff. A total of 225 participants, with the aid of 3 envelopes containing the treatment specific chits (75 chits representing each group) were enrolled in treatment groups I, II, and III. All participants were subjected to investigations viz. hemoglobin percentage, differential count, and absolute eosinophil counts (AEC). The prescription drug label was replaced with a group-specific new label to maintain double-blind status. Participants of groups I, II and III were treated using topical azelastine, fluticasone propionate and combination of both in preparation on a domiciliary basis.

In all cases, the individual symptom score was recorded before and after treatment at the end of four weeks with the help of a 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 total symptom scores. AEC was repeated at the end of four weeks in all cases.

Statistical Methods: Chi-square and ANOVA test was used to find the significance of age, sex, duration of illness and intermittent or persistent symptoms and co-morbidity between groups I, II, and III. Mann Whitney U-test was used to find significance in individual symptom score pre-treatment and post-treatment between the groups and Wilcoxon signed-rank test used to find the significance of total symptoms score pre-treatment and post-treatment as per the dataset.

All data analysis had been done by using SPSS (version20.0) for windows.

TABLE 1: TOTAL SYMPTOMS SCORING (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

OBSERVATIONS AND RESULTS: All enrolled cases completed the study and were followed up for a period of four weeks. The age was between 15 to 65 years in all 225 cases studied. In all, there were 125 (55.56%) males and 100 (44.44%) females. The mean age of groups I, II, and III was 31.31, 33.19, and 33.39, respectively **Table 2**.

Out of 225 (100%) cases, symptoms were intermittent in 133 (59.11%) and persistent in 92 (40.89%). Out of these 133 (59.11%) cases, having intermittent symptoms, 45 (33.83%) were from group I, 42 (31.58%) were from group II and 46 (34.59%) from group III. Similarly, amongst 92 (40.89%) cases having persistent symptoms, 30 (32.61%) were from the group I, 33 (35.87%) were from group II, and 29 (31.52%) were from group III **Table 2**. The mean duration of symptoms taken together was 2.6 years in group I and 2.49 years in group II and 3.42 years in group III **Table 2**. The number of cases having bronchial asthma was 9 (4%), 14 (6.2%), and 12 (5.3%) in groups I, II, and III, respectively.

TABLE 2: COMPARISON AMONG PATIENT'S BASELINE CHARACTERISTICS

Variables	Total N=225	Azelastine Group I n=75 Mean (SD)	Fluticasone Group II n=75 Mean (SD)	Azelastine & Fluticasone Group III n=75 Mean (SD)	ANOVA F-value/ Chi Square	p-value
Age (in years)						
Mean (SD)	32.34 (10.99)	31.31 (9.9)	33.19 (8.89)	33.39 (12.88)	0.86	0.42
Range (SD)	15-65	15-65	15-65	15-65		
Gender						
Male	125(55.56%)	35(28%)	51(40.8%)	39(31.2%)	7.49	0.24
Female	100(44.44%)	40(40%)	24(24%)	36(36%)		
Symptoms						
Intermittent	133(59.11%)	45(33.83%)	42(31.58%)	46(34.59%)	0.48	0.79
Persistent	92(40.89%)	30(32.61%)	33(35.87%)	29(31.52%)		
Duration of Illness (yrs) Mean (SD)	Nil	2.6(1.34)	2.49(1.36)	3.42(2.06)	7.64	0.0006*
Co-Morbidity Bronchial Asthma	Nil	9(4%)	14(6.2%)	12(5.3%)	Nil	

*significant when p<0.05

Analysis of Individual Symptom Score, TSS, and AEC: In this study, the individual symptoms were sneezing, nasal obstruction, nasal itching, nasal discharge, palatal itching, itching of the eye, itching of ears, and watering of the eye. The percentage of individual symptom scores before to after treatment showed improvement in all groups. The symptom score of nasal obstruction improved by 83.6%, 96.7%, and 86.6 in groups I, II, and III. The symptom score of nasal discharge improved by 71.8%, 98.36%, and 91.1 in groups I, II, and III. The symptom score of nasal itching improved by 89.4%, 97.1%, and 82.01 in groups I, II, and III. The symptom score of sneezing improved by 91.1%, 91.3%, and 95.05% in group-I, II, and III. The symptom score of itching in eyes improved by 96.4%, 98.95%, and 96.5% in groups I, II, and III. The symptom score of watering from eyes improved by 87.5%, 94.4%, and 93.3% in groups I, II, and III. The symptom score of itching in ears improved by 88.89%, 97.3%, and 95.08% in groups I, II, and III. The symptom score of palatal itching improved by 89.7%, 96.27%, and 95.04% in groups I, II, and III **Table 4**. The percentage change of median TSS was 85.03%, 95.52%, and 90.89% in groups I, II, and III, respectively **Table 3**. The absolute eosinophil count improved by 71.55%, 79.82%, and 77.27% in groups I, II, and III **Table 4**.

TABLE 3: ANALYSIS OF TOTAL SYMPTOM SCORE BEFORE TO AFTER TREATMENT

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	Azelastine Group I, n=75	10.89 ± 1.11	1.63 ± 1.10	9.26 ± 0.01	85.03	<0.0001*
	Fluticasone Group II, n=75	12.28 ± 1.2	0.55 ± 0.66	11.73 ± 0.54	95.52	<0.0001*
	Azelastine & Fluticasone Group III, n=75	12.19 ± 2.63	1.11 ± 1.02	11.08 ± 1.61	90.89	<0.0001*

* Statistically highly significant by Mann-Whitney Test

TABLE 4: GROUP WISE INDIVIDUAL SYMPTOM SCORE AND ABSOLUTE EOSINOPHIL COUNT BEFORE AND AFTER TREATMENT

Variables	Treatment Group I (Azelastine) n=75		Treatment Group II (Fluticasone) n=75		Treatment Group III (Azelastine & Fluticasone) n=75		Kruskal- Wallis Stat		p-value	
	Before	After	Before	After	Before	After	Before	After	Before	After
Sneezing	2.37 (0.71)	0.21 (0.41)	2.76 (0.52)	0.24 (0.43)	2.63 (0.51)	0.13 (0.38)	1.97	3.63	0.0005*	0.16
Nasal obstruction	2.44 (0.64)	0.4 (0.57)	2.44 (0.5)	0.08 (0.13)	2.47 (0.68)	0.33 (0.6)	0.75	16.90	0.69	<0.0001*
Nasal discharge	2.56 (0.64)	0.72 (0.83)	2.44 (0.58)	0.04 (0.20)	2.36 (0.82)	0.21 (0.41)	3.16	49.03	0.21	<0.0001*
Nasal itching	1.04 (0.78)	0.11 (0.39)	1.4 (0.64)	0.04 (0.2)	1.39 (0.91)	0.25 (0.44)	9.78	17.1	0.0075*	0.002*

Itching of eyes	1.12 (0.59)	0.04 (0.2)	1.24 (0.59)	0.07 (0.25)	1.15 (0.90)	0.04 (0.2)	0.45	0.76	0.080	0.68
Watering of eyes	0.32 (0.47)	0.04 (0.2)	0.72 (0.78)	0.04 (0.2)	0.75 (0.86)	0.05 (0.23)	13.53	0.21	0.0012*	0.90
Itching of ears	0.36 (0.56)	0.04 (0.2)	0.48 (0.58)	0.013 (0.12)	0.61 (0.82)	0.03 (0.16)	3.5	1.23	0.17	0.6
Palatal itching	0.68 (0.62)	0.07 (0.25)	0.8 (0.75)	0.03 (0.16)	0.84 (0.91)	0.05 (0.23)	0.57	1.33	0.75	0.51
Absolute eosinophil count	722.71 (195.74)	205.59 (81.18)	872.51 (195.22)	176.05 (38.23)	861.2 (128.59)	195.75 (29.22)	36.56	9.88	<0.0001	0.0071*

*significant when p<0.05

TABLE 5: COMPARISON OF PRESENT STUDY WITH OTHER SIMILAR STUDIES

	Group I		Group II			Group III	
	Ratner *et al*	**Present study**	**Havle *et al.***	**Raisha *et al.***	**Present study**	**Raisha *et al.***	**Present study**
Nasal obstuction	19.2%	83.6%	91.3%	74.15%	96.7%	88.2%	86.6%
Nasal discharge	20.5%	71.8%	98.36%	68.61%	98.36%	92.13%	91.1%
Nasal itching	25.4%	89.4%	89%	68.06%	97.1%	81.74%	82.01%

Out of 225 (100%) cases, only 9 (4%) experienced side effects of the drug, which were mild and resolved spontaneously without requiring concomitant therapy or discontinuation from the study. 3 (1.33%) cases of group I, 2 (0.89%) of group II and 4 (1.78%) of group III presented with mild side effects. Amongst these 3 cases in group I, epistaxis was noted in 1, nasal stuffiness in 1, irritation of throat in 1. Similarly, amongst 2 cases in group II, epistaxis was noted in 1, headache in 1. Similarly, amongst 4 cases in group III, epistaxis was noted in 1, headache in 1, nasal stuffiness in 2.

DISCUSSION: AR is either intermittent and persistent or seasonal and perennial. When symptoms are presently less than 4 days a week or for less than 4 consecutive weeks in a year, it is grouped as intermittent. Similarly, when the symptoms are presently more than 4 days a week or for more than 4 consecutive weeks in a year, it is grouped as persistent. Similarly, quantitatively AR can be mild, moderate, and severe, depending on the symptomatology and quality of life [2].

Treatment of AR aims at adequate and faster relief of the symptoms using antihistamine, corticosteroid or both in a combination either topically or systemically [4]. 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. Also, azelastine topical antihistamine control allergy by blocking the histamine release as well as inhibiting the preformed histamine. It also inhibits inflammatory mediators, including leukotrienes, cytokines, and adhesion molecules kinins. Hence, the topical antihistaminic preparation combined with a steroid, works in synergism [2]. In group-I cases receiving topical azelastine, the significant reduction of TSS (P=<0.0001) was 85.03%, and in a similar study by Dykewicz *et al*., it is 91% [5]. In group II and III cases receiving topical corticosteroid and both in combination, the significant reduction of TSS was 95.52% and 90.89%, respectively, and in a study by Raisha *et al.,* it is 84.14% and 91.16% respectively [1]. There was a significant difference in reduction in the symptom of nasal obstruction (p<0.0001), which was 83.6% in group I, 96.7% in group II and 86.6 in group III.

Whereas, in a similar study by Ratner *et al*., [7,] it is 19.2% in group I. And in a study by Havle *et al*. [6] Raisha *et al.,* it is 91.3% and 74.15% in group II respectively. In a similar study by Raisha *et al.*, it is 88.2% in group III. There was a significant difference in reduction in a symptom of nasal discharge (p<0.0001), which was 71.8% in group I, 98.36% in group II and 91.1 in group III.

Whereas, a similar study by Ratner *et al*., [5] it is 20.5% in group I. And by Havle *et al.,* Raisha *et al.,* it is 98.36% and 68.61% in group II respectively. In a similar study by Raisha *et al.*, it is 92.13% in group III, respectively. There was a significant difference in reduction in the symptom of nasal itching (p<0.002) that was 89.4% in group I, 97.1% in group II and 82.01 in group III. Whereas, a similar study by Ratner *et al*., [7,] it is

25.4% in group I. And by Havle *et al.*, Raisha *et al.*, it is 89%and 68.06% in group II, respectively.

In a similar study by Raisha *et al*., it is 81.74% in group III, respectively. There was a significant difference in the reduction of absolute eosinophil count ($p<0.0071$) by 71.55% in group-I, 79.82% in group-II, and 77.27% in group-III. The symptom of sneezing shows improvement in 91.1% in group-I, 91.3% in group-II, and 95.05% in group-III. The symptom of itching in eyes shows improvement in 96.4% in group-I, 98.95% in group-II, and 96.5% in group-III. The symptom of watering of eyes shows improvement in 87.5% in group I, 94.4% in group-II, and 93.3% in group-III. The symptom of itching in ears shows improvement in 88.89% in group-I, 97.3% in group-II, and 95.08% in group-III. The symptom of palatal itching shows improvement in 89.7% in group-I, 96.27% in group-II, and 95.04% in group-III. Although these symptoms of sneezing, itching in eyes, watering of eyes, itching in ears, palatal itching showed a reduction in symptoms after treatment; however, it was statistically insignificant.

CONCLUSION: All cases of group I, II, III were treated topically using azelastine, fluticasone propionate, and combination of both, respectively. All these drugs were efficacious in reducing total symptom score (TSS) as well as individual symptom score and absolute eosinophil count (AEC) in cases of allergic rhinitis. Amongst all, fluticasone propionate (interventional agent of group II) was found to be the most efficacious in reducing TSS (95.52%), AEC (79.82%), and all individual symptom scores except symptom of sneezing which showed maximum improvement by a combination of azelastine and fluticasone propionate (interventional agent of group III). The reduction of a nasal symptom of obstruction ($p<0.0001$), discharge ($p<0.0001$), and itching ($p<0.002$) and TSS ($P=<0.0001$) as well as AEC ($p<0.0071$) was statistically significant in all groups. Amongst symptom score and AEC, the later being an objective parameter, must be used in assessment of prognosis while treating allergic rhinitis.

Ethical Approval: All procedures performed on human participants were in agreement with the ethical standards of the Institutional and/or National Ethics Committee. The prior Institutional Ethics Committee Approval was sought to vide IEC letter number: KIMSDU/IEC/03/2019.

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