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Comparative study of the efficacy and safety of intranasal azelastine hydrochloride and fluticasone furoate in the treatment of allergic rhinitis

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Abstract:

BACKGROUND: Allergic rhinitis (AR) is characterized by nasal itch, sneezing, watery or mucous rhinorrhea, nasal obstruction, and nasal or pharyngeal irritation. If untreated, AR can impair patients' quality of life (QOL). Azelastine hydrochloride (AH), histamine receptor antagonists, has anti-inflammatory and mast cell stabilizing properties. Fluticasone furoate (FF) is an anti-inflammatory agent with action on mast cells, eosinophils, neutrophils, macrophages, and lymphocytes. This study compares the efficacy and safety of these medications in AR.

MATERIALS AND METHODS: Patients in the study had been clinically diagnosed with AR. In each group, there were 75 randomized patients who were to receive either FF (27.5 μg/spray) or AH (0.10%) intranasally twice daily. Assessment in terms of symptoms (total nasal symptom score), signs (endoscopic staging), QOL, eosinophil count, and sensory attributes was done at baseline, day 7, and day 15. Adverse effects were recorded, and the cost incurred was analyzed. Paired and unpaired t-test were used to compare symptom scores, QOL scores, and absolute eosinophil count within and between the groups, respectively.

RESULTS: The total number of patients was 150 (76 males and 74 females); the mean age for FF group was 26.23 ± 5.2 years, and 26.96 ± 4.8 years for AH group. By day 7, there was a reduction of all scores in both medications, but the reduction in reduction was highly significant with FF ($P = 0.001$). There was a significant reduction ($P = 0.001$) in absolute eosinophil count both in blood and nasal smears by day 15 in both the groups; the reduction was significant ($P = 0.001$) with fluticasone. Adverse reactions were reported by 33.3% of patients receiving FF and 28% patients receiving AH.

CONCLUSION: Fluticasone furoate produced sustained relief of symptoms, signs, and sensory attributes with a greater reduction in eosinophil count in comparison with AH in patients with allergic rhinitis.

Keywords:

Allergic rhinitis, azelastine hydrochloride, intranasal fluticasone furoate

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Introduction

Allergic rhinitis (AR) is a chronic disease characterized by nasal itch, sneezing, watery or mucous rhinorrhea, nasal obstruction, and nasal or pharyngeal irritation.[1] It is an IgE-mediated hypersensitivity reaction to one or more allergens involving the nasal mucosa and surrounding tissues and affects approximately 20% of the general population.[2] Patients with AR can experience fatigue, sleep disturbances, social function impairment, depressed mood, anxiety, learning (cognitive) impairment and attention deficit, increased school absenteeism, and decreased work efficiency.[3] If untreated, AR can

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substantially impair the overall quality of life (QOL) of patients.[4] Apart from the local disease, AR can also cause chronic sinusitis and otitis media.

Treatment options include intranasal corticosteroids, antihistaminics, cromoglycate or oral antihistaminics, leukotriene antagonists, nasal decongestants, and allergen immunotherapy.[1] Azelastine hydrochloride (AH) and its metabolite, desmethylazelastine, are histamine (H_1) receptor antagonists; they also have anti-inflammatory and mast cell stabilizing properties.[5] Fluticasone furoate (FF) is a new topical corticosteroid with potent anti-inflammatory activity and low systemic absorption. It is said to have actions on multiple cell types such as mast cells, eosinophils, neutrophils, macrophages, and lymphocytes and mediators of inflammation such as histamine, eicosanoids, leukotrienes, and cytokines.[6]

Early initiation of treatment with the above drugs helps to control further progress of the disease and prevent complications. The primary goal of treating patients with AR is to provide symptomatic relief. This study was undertaken to compare the efficacy and safety of these drugs in the treatment of AR.

Materials and Methods

This was a randomized open-label parallel group study. Recruitment of patients was done over a period of 18 months. One hundred and fifty outpatients of both genders aged above 12 years, who had been clinically diagnosed with AR, but with no complications, were included in the study. Patients with a history of nasal trauma, deviated nasal septum, atrophic rhinitis, or patients who had undergone nasal biopsy and nasal surgery in the previous 2 months were excluded from the study. Those who had received systemic steroids in the preceding 30 days and immunotherapy in the past 2 years and pregnant and breastfeeding women were also excluded from the study.

Ethical approval was obtained from the Institutional Ethics Committee vide Letter No. DMC/KLR/MEU/IEC-CER/71/2013-14 dated 24/10/2013 and informed written consent was taken from all participants in the study. Simple randomization was done by recruiting alternate patients to FF and AH groups until we got 75 patients in each group, and they received either FF (27.5 μg/spray) intranasal spray (2 sprays/nostril/twice daily) or AH (0.10%) intranasal spray (2 sprays/nostril/twice daily). Assessment in terms of symptoms (total nasal symptom score [TNSS]), signs (diagnostic nasal endoscopic staging), absolute eosinophil count, QOL, and sensory attributes was done at the baseline, day 7, and day 15. Adverse effects were recorded, and the cost incurred was analyzed.

Symptom severity (runny nose, postnasal drip, sore throat, cough, sneezing, headache, nasal irritation, and poor smell) was determined by the TNSS[7,8] scored on a severity scale from 0 to 3; maximum possible TNSS was 24. Rhinoconjunctivitis QOL questionnaire (RQLQ)[8] is a disease-specific, validated quality-of-life questionnaire which measures the physical, emotional, and social problems in patients with allergy. In this scale, patients rate their experiences related to activities, sleep, nonnose or noneye symptoms, practical problems, nasal symptoms, and eye symptoms. Lund–Kennedy nasal endoscopic and sensory attribute score was also assessed.[9] Absolute eosinophil count in the blood and nasal smears was assessed using Hansel stain.[10]

To detect a mean difference of 1.0 in the TNSS on day 15 with the effect size of 0.67, α error of 5%, with 80% power, and 10% drop out rate, the sample size required in each group was 65. The demographic details were analyzed using descriptive statistics. The symptom scores (TNSS), QOL questionnaire scores (RQLQ), and absolute eosinophil count were analyzed using paired and unpaired student *t*-test for within and between the groups, respectively. $P < 0.05$ was considered statistically significant.

Results

A total of 150 patients were recruited and divided into two groups of 75 each [Figure 1]. FF was given to 52% of males and 48% of females and AH to 49.3% of males and 50.7% of females, respectively. The patients who had a previous history of AR were 56% and 45%**.** The most common symptoms presented by the patients were sneezing, rhinorrhea, and nasal obstruction. Baseline parameters were comparable in patients of both groups, as shown in Table 1.

A comparison with the baseline showed a significant decrease ($P = 0.001$) in the scores of all the individual parameters of the TNSS, Lund–Kennedy endoscopic staging score, and patient satisfaction score (RQLQ) by day 7 in both groups, and by day 15, the scores of the various parameters had reduced to zero with both the medications. An analysis between the groups showed a greater reduction in patients who had been given FF ($P = 0.001$) by day 7 as shown in Tables 2-4.

Within the group, there was a significant reduction in both the eosinophil counts by day 15 in comparison to the baseline. FF significantly reduced the absolute eosinophil count both in blood and nasal smears in comparison to AH by day 15 ($P = 0.001$), as shown in Table 5.

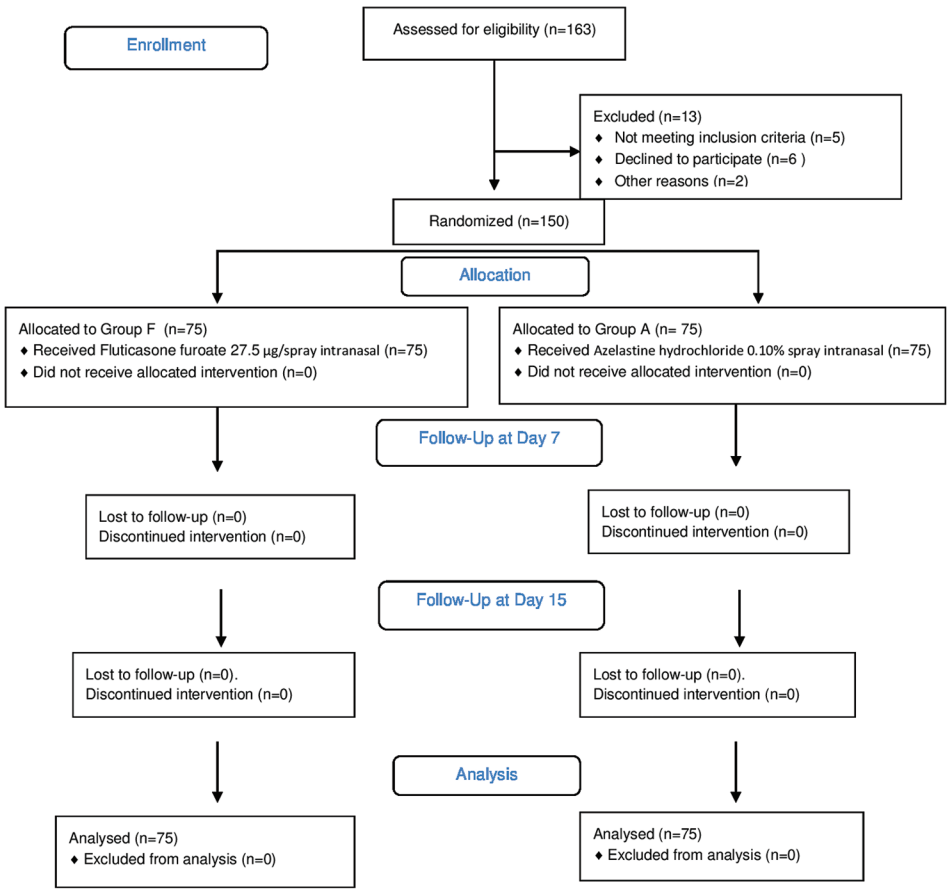

Figure 1: Consort flow chart representing recruitment, randomization, and follow-up

Table 1: Baseline characteristics of allergic rhinitis patients by treatment group

Baseline characteristics	Fluticasone furoate group Mean±SD, median (range)	Azelastine hydrochloride group Mean±SD, median (range)	*P*-value
Total nasal symptom score (runny nose, postnasal drip, sore throat, cough, sneezing, headache, nasal irritation, and poor sense of smell)	10.13±0.79, 10 (8-11)	10.07±0.70, 10 (9-11)	0.58
Lund-Kennedy endoscopic staging score	5.13±0.68, 5 (4-6)	4.92±0.69, 5 (4-6)	0.60
Absolute eosinophil count in blood (cells/mm^3)	421.67±32.66	426.27±32.79	0.07
Absolute eosinophil count in nasal smears (cells/100 HPF)	5.17±0.92, 5 (2-6)	4.95±1.35, 5 (2-6)	0.09
Quality of life questionnaire	36.63±3.07, 36 (30-43)	36.80±2.47, 37 (32-42)	0.70
Sensory attributes	34.12±4.23, 33 (27-45)	34.71±3.55, 35.5 (27-41)	0.42

SD=Standard deviation

Sensory attributes of 116 patients [Table 6] were assessed; 58 patients in each group within 2 min of drug administration and on follow-up visits. Table 6 shows significant intragroup reduction. The reduction in the scores of FF was greater in comparison with AH at the end of day 7, which was statistically significant (P = 0.001).

Nasal stuffiness was one of the most common adverse effects encountered; 33.33% with FF and 28% with AH, 12% and 8% of patients reported minimal throat irritation till day 7 with the respective medications. One intranasal spray of FF was required for each patient, at the cost of Indian Rupees (INR) 235.75. Similarly, each patient had used one intranasal AH spray at the cost of INR 187.25.

Discussion

One hundred and fifty patients were recruited for the study. The mean age was 26.23 ± 5.21 and 26.96 ± 4.82 years in FF and AH, respectively, which is similar (28–32 years) to other studies.[11] The probable reason is the lifestyle activity which increases their exposure to a wide variety of allergens compared to the older age group. Most of the patients presented with the three main symptoms of AR, i.e., sneezing, nasal obstruction, and rhinorrhea. Baseline demographic profiles and parameters were comparable between the groups. Around 50% of patients in our study had a

Table 2: Comparison of total nasal symptom score among alleregic rhinitis patients by the day of treatment and treatment group

Characteristics	Nasal symptoms score			*P*-value
	Day 0 Mean±SD, median	Day 7 Mean±SD, median	Day 15 Mean±SD, median	
Fluticasone furoate	10.13±0.79, 10	2.89±0.70, 3	0	0.001
Azelastine hydrochloride	10.07±0.70, 10	3.84±0.78, 4	0	0.001
P	0.58	0.001	1.000	

SD=Standard deviation ; Symptoms= Runny nose, postnasal drip, sore throat, cough, sneezing, headache, nasal irritation, poor sense of smell

Table 3: Comparison of Lund-Kennedy endoscopic staging score among alleregic rhinitis patients by the day of treatment and treatment group

Characteristics	Endoscopic staging score			*P*-value
	Day 0 Mean±SD, median (range)	Day 7 Mean±SD, median (range)	Day 15 Mean±SD, median (range)	
Fluticasone furoate	5.13±0.68, 5 (4-6)	1.35±0.55, 1 (0-2)	0	0.001
Azelastine hydrochloride	4.92±0.69, 5 (4-6)	2.24±0.75, 2 (1-3)	0	0.001
P	0.60	0.001	1.000	

SD=Standard deviation

Table 4: Comparison of total nasal symptom score among alleregic rhinitis patients by the day of treatment and treatment group

Treatment group	Quality of life score			*P*-value
	Day 0 Mean±SD, median (range)	Day 7 Mean±SD, median (range)	Day 15 Mean±SD, median (range)	
Fluticasone furoate	36.63±3.07, 36 (30-43)	11.75±2.32, 12 (7-17)	0	0.001
Azelastine hydrochloride	36.80±2.47, 37 (32-42)	17.32±2.95, 17 (11-23)	0	0.001
P	0.70	0.001	1.000	

SD=Standard deviation

Table 5: Comparison of absolute eosinophil count in blood and nasal smears of allergic rhinitis patients by the day of treatment and treatment group

Treatment group	AEC - blood cells/mm^3		*P-value*	AEC - nasal smears cells/HPF		*P*-value
	Day 0 Mean±SD	Day 15 Mean±SD		Day 0 Mean±SD	Day 15 Mean±SD	
Fluticasone furoate	421.67±32.66	199.60±20.75	0.001	5.17±0.92	0.25±0.43	0.001
Azelastine hydrochloride	426.27±32.79	220.33±23.26	0.001	4.95±1.35	0.60±0.49	0.001
P	0.07	0.001		0.09	0.001	

SD=Standard deviation, AEC=Absolute Eosinophil Coun

Table 6: Comparison of sensory attribute scores for allergic rhinitis patients by the day of treatment and treatment group

Treatment group	Sensory attributes score checked immediately following drug administration			*P*-value
	Day 0 Mean±SD, median (range)	Day 7 Mean±SD, median (range)	Day 15 Mean±SD, median (range)	
Fluticasone furoate (*n*=58)	34.12±4.23, 33 (27-45)	9.74±2.37, 9 (6-16)	0	0.001
Azelastine hydrochloride (*n*=58)	34.71±3.55, 35.5 (27-41)	11.71±2.69, 11.5 (6-19)	0	0.001
P	0.42	0.001	1.000	

SD=Standard deviation

previous history of AR with aggravated symptoms in winter and in the presence of dust and smoke.

Our study showed that FF administered intranasally significantly reduced all the parameters of TNSS and the Lund–Kennedy endoscopic staging score ($P = 0.001$) by day 7 compared to the baseline, and by day 15, patients were symptom free. It also significantly improved the patient's satisfaction with treatment [Table 4] ($P = 0.001$) by day 7 as assessed by RQLQ, which denotes improvement in QOL. There was a significant reduction in ocular manifestations of AR, which is one of the parameters of RQLQ. A study demonstrated that patients treated with fluticasone nasal spray had a greater reduction in the total symptom score and an improvement in the QOL in comparison with the placebo ($P < 0.001$).[12]

In the present study, intranasal azelastine hydrochloride significantly decreased all the parameters of TNSS and the Lund–Kennedy endoscopic staging score ($P = 0.001$) by day 7 compared to baseline, with a reduction of the scores to zero by day 15. It also significantly improved patient's QOL by day 7 ($P = 0.001$). Other studies have shown that azelastine therapy improved TNSS significantly more than a placebo, cetirizine, and loratadine.[13,14]

The analysis between the groups showed that FF significantly ($P = 0.001$) decreased the total nasal symptom, Lund–Kennedy endoscopic score, and QOL score (RQLQ) compared to AH by day 7 [Tables 2-4]. When three different topical preparations of corticosteroids were compared with four different preparations of antihistaminics, it was clear that the topical nasal corticosteroids significantly improved the symptoms than antihistaminics.[15] Another study reported an improvement in symptoms with fluticasone compared to loratadine ($P = 0.001$).[16] In a 6-week, placebo-controlled study, a once-daily dose of 256 μg of budesonide nasal spray was ($P < 0.01$) more effective than azelastine.[14]

In this study, the medications reduced the absolute eosinophil count both in blood and in the nasal smears by day 15 compared to baseline, which was statistically significant ($P = 0.001$). We also observed that FF produced a significant ($P = 0.001$) reduction in both these parameters compared with AH. Absolute eosinophil count in the nasal smears ranged between zero and one in both groups by day 15, but the number of patients with a count of zero was more with FF (56) than AH (30).

The assessment of sensory attributes in patients using these drugs showed that the scores reduced significantly by day 7 (i.e., patients in both groups tolerated the drug well), but this was significant ($P = 0.001$) with FF in comparison with AH [Table 6]. Patient preference with regard to specific sensory attributes of a drug may determine adherence to therapy.[17,18] Important sensory attributes include minimal odor, irritant effect, absence of taste, and product moistness.

The adverse effects observed with FF were nasal stuffiness (33.33%) and irritation of nasal mucosa (12%). Studies have shown adverse effects such as mild mucosal irritation and epistaxis.[11] With AH, nasal stuffiness was 28% and nasal irritation 8%. Other studies have reported a bitter taste in the mouth and drowsiness as adverse effects.[14,15] The adverse effects noted in our study were mild to moderate. Patients in both the groups required only one metered dose nasal spray of FF or AH at the cost of 235.75 and 187.25 rupees per patient, respectively.

Conclusion

Fluticasone furoate produced sustained relief of symptoms and signs, with an improvement of QOL. There was also a significant reduction in eosinophil count in allergic rhinitis patients compared to Azelastine hydrochloride. A reduction in sensory attributes indicates that the patients tolerated fluticasone even though it was rather expensive.

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Conflicts of interest
There are no conflicts of interest.

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