Pharmacology and Clinical Pharmacy Research
ISSN:2527-7322 | e-ISSN: 2614-0020
doi: 10.15416/pcpr.v4i3.33204
Volume 6 No. 3 December 2021
ORIGINAL ARTICLE

A Comparative Study of Fluticasone Alone and Fluticasone Combined with Azelastine Nasal Spray in Patients with Allergic Rhinitis

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Abstract

In India, 20-30% of the population suffers from allergic rhinitis. Its prevalence increasing over the past many years and often adversely affects the quality of life. Little importance is given to allergic rhinitis and patients fail to correlate the ill-health to symptoms of allergic rhinitis in India. Studies have shown that patients with allergic rhinitis adversely affect the behavior, work performance, and lifestyle of patients. Hence this study was undertaken to compare the efficacy of fluticasone alone and in combination with azelastine. A total of 60 patients were randomly assigned into two groups (30 patients each), where the first group received fluticasone and the other group received fluticasone + azelastine. Drugs were administered as nasal spray and improvement were assessed using Total Nasal Symptom Score (TNSS) and Quality of life was assessed using Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at baseline and at 2 weeks. Descriptive statistics and student's t-test was used to analyze data. Both the groups had statistical improvement in TNSS and RQLQ scores when compared to baseline within the groups ($p < 0.0001$). Comparison of overall TNSS between the groups was statistically significant ($p < 0.001$), though total RQLQ scores were insignificant (< 0.02) when compared between two groups. It was observed that both drugs were safe and efficacious. By these results, we conclude that the combination therapy showed better improvement in TNSS when compared to fluticasone alone. Azelastine due to antihistaminic properties and fluticasone anti-inflammatory effect showed synergistic anti-inflammatory effect and improvement in quality of life.

Keywords: Fluticasone, Azelastine, Nasal Spray, Allergic Rhinitis

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Received: 26 April 2021. **Revised**: 2 September 2021. **Published:** 26 December 2021

Introduction

Allergic rhinitis, an inflammatory condition characterized by nasal itching, sneezing, rhinorrhoea and nasal congestion associated with activation of various immune cells which releases chemical mediators mainly histamine and cysteinyl leukotrienes.[1,2] Around 20–30 % Indian population suffers from allergic rhinitis and prevalence is increasing over past few years.[3]

The treatment includes combination of allergen avoidance and pharmacotherapy i.e, antihistaminics, corticosteroids and mast cell stabilizers. Newer second generation drugs like levocetrizine, desloratidine, and azelastine are preferred due to rapid onset of action and symptomatic improvement and decreased incidence of side effects compared to first generation antihistaminics.[4]

Intranasal corticosteroids are the first choice of drug.[5,6] Azelastine is the only intranasal antihistaminic with fast and longer duration of action attributed to its anti-inflammatory, mast cell stabilizing and anti-allergic effects.[7] Hence the current study was undertaken to see the effect of fluticasone versus fluticasone with azelastine, nasal spray in treatment of allergic rhinitis.

Methods

Study population

Patients of either sexes of more than 18 ears old with allergic rhinitis and willing to give written informed consent were included in the study. Diagnosis of allergic rhinitis is based on recent Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines which includes duration, symptoms and quality of life. Based on duration it is classified as “intermittent” or “persistent” disease and on severity of symptoms and quality of life as “mild” or “moderate to severe”.[8]

Patients with allergic rhinitis and on oral/ topical antihistamines or nasal decongestants in past 7 days, pregnant and lactating females, deviated nasal septum, nasal polyp, history of hypersensitivity reactions to azelastine or fluticasone, and who refused to give consent were excluded from the study. Based on the above inclusion and exclusion criteria, sixty patients were included in the study.

Study Design

The study was a randomized, prospective, comparative study in patients with allergic rhinitis visiting outpatient department of Ear, Nose, and Throat Department of Hassan Institute of Medical Sciences, Hassan from April to July 2018. Before commencement of study, the study protocol and informed consent were approved from Institutional Ethics Committee of Hassan Institute of Medical Sciences, Hassan. The procedure followed in the study was explained to the patients in their local language and written informed consent was taken from the patients before enrolment process.

Sixty patients were randomly assigned into two groups of 30 patients each. A detailed history of patient, physical examination of nose was done at first visit (baseline), their Total Nasal Symptom Score (TNSS), and Rhinoconjunctivitis Quality of Life Questionnaire scoring (RQLQ) were performed. First group received fluticasone nasal spray 27.5µg one spray per nostril once daily and other group received fluticasone + azelastine nasal spray 27.5µg + 140 µg one spray per nostril twice daily. The condition of patients was followed up to 2 weeks. TNSS and RQLQ are the standard assessment scoring methods for allergic rhinitis.

TNSS used various symptoms like nasal congestion, runny nose, nasal itching, sneezing, difficulty in sleep, and these symptoms were

scored based on the severity scale as 0 to 3 where 0 = no symptom, 1 = mild, 2 = moderate, 3 = severe, and sum of these five symptoms were calculated as TNSS score.

RQLQ is disease specific quality of life questionnaire for measure of physical, emotional, and practical problems in patients with allergic rhinitis. It has 28 questions in 7 domains (sleep, non-hay fever symptom, practical problems, nasal symptoms, practical problems, activities, emotional). The patients scored on a 7-point scale as:
0 = no trouble
1 = hardly trouble at all
2 = somewhat trouble
3 = moderately trouble
4 = quite a bit trouble
5 = very trouble
6 = extremely trouble
The mean of all 28 responses was taken as overall RQLQ score and the domain scores is the mean of all the items in individual domain.

The primary outcome of measurement that used for efficacy assessment were the mean change of TNSS, from baseline to 2 weeks in both of the groups. The secondary outcome of measurement was the average change of TNSS from baseline to 2 weeks in individual symptom scores, mean change from baseline to 2 weeks in RQLQ including individual domain, and overall scores. For safety assessment, any adverse events during the treatment period like headache, dryness, stinging, burning, or irritation in nose with fluticasone and bitter taste, headache, and somnolence with azelastine were noted.[9,10] Statistical analysis was done using descriptive statistics and Students't' test.

Results and Discussion

Allergic rhinitis is a common seasonal inflammatory condition due to IgE mediated immunological response of nasal mucosa.[1] Trigger of allergic rhinitis includes pollens, house dust, mites, occupational triggers such as latex; tobacco smoke; automobile exhaust, oxides of nitrogen and sulphur dioxide; aspirin and other non-steroidal anti-inflammatory drugs.It is also associated with comorbid conditions like asthma, atopic dermatitis and nasal polyp. All these can lead to conjunctivitis, postnasal drip, eustachian tube dysfunction, otitis media, and sinusitis. These symptoms result in sleep disturbance, fatigue, depressed mood and cognitive function which impair the quality of life and productivity.[11]

Allergic rhinitis is a chronic inflammatory condition characterized by different cells. It includes chemotaxis, selective recruitment and trans-endothelial migration of cells. Release of cytokines and chemokines, activation and differentiation of eosinophils, T-cells, mast cells and epithelial cells. The major mediators released from activated cells are histamine and cysteinyl leukotrienes.[11] The diagnosis of allergic rhinitis is based on typical history of allergic symptoms like sneezing, rhinorrhoea, nasal itching, nasal blockade, diurnal rhythm, and conjunctivitis. All patients need nasal examination, peak nasal inspiratory flow to measure nasal obstruction.

According to the present study allergic rhinitis is most common among reproductive age group and predominantly seen in females. In this study, the average age of the patients were 35.7 years old and 31.6 years old, and mostly were females. The baseline of TNSS and RQLQ scores were different in both the groups. (Table 1) Similar study done by Ratneret al showed that the average age of the patients was 37.2 years and common among women.[12] In this study, combination therapy of fluticasone + azelastine nasal spray showed

Table 1. Demographic and Baseline Characteristics

Characteristics	Fluticasone Group	Fluticasone with Azelastine group
Number of Patients	30	30
Age in years (Mean ± SD)	35.77 ± 12.49	31.67 ± 14.03
Gender		
Male	11 (36.7%)	12 (40%)
Female	19 (63.3%)	18 (60%)
Range	16 - 60	15 - 75
Baseline TNSS	10.33 ± 3.27	11.27 ± 2.85
Baseline RQLQ score	54.07 ± 30.3	59.03 ± 29.34

Mean ± SD
TNSS- Total Nasal Symptom Scores
RQLQ - Rhinoconjunctivitis Quality of Life Questionnaire scores

Table 2. Comparison of Total Nasal Symptom Score

Treatment Groups	Total Patients	Mean ± SD	p value
Fluticasone	30	4.20 ± 2.16	< 0.01*
Fluticasone with Azelastine	30	6.43 ± 2.64	

Mean± SD, * p<0.001 highly significant

greater efficacy compared to fluticasone alone in patients with allergic rhinitis patients. There are few studies which also noted similar improvement in TNSS compared to baseline to 14 days treatment.[12] Runny nose, sneezing, and nasal congestion were the most common and severe symptom, whereas nasal itching and difficulty in sleeping were moderate symptom at baseline visit (Figure 1, Figure 2).

Intranasal corticosteroids like fluticasone propionate, mometasone furoate are the first drug of choice in the current guidelines for treatment of moderate to severe allergic rhinitis when nasal congestion is prominent symptom. They inhibit inflammatory process and reduce nasal mucosa permeability, number of inflammatory cells and release of mediators.[5,6]

Azelastine is the only intranasal antihistamine which has fast and long acting effect based on triple mode of action i.e anti-inflammatory, mast cell stabilizing and anti-allergic effects. It inhibits leukotriene action associated with dilatation of vessels, increased vascular permeability and edema resulting in nasal congestion, itching, sneezing mucus production, and recruitment of inflammatory mediators.[7]

The individual components in TNSS of fluticasone + azelastine group were comparatively decreased (runny nose: 2.5 to 1.2; sneezing: 2.2 to 0.9; nasal congestion: 2.6 to 1.6; nasal itching: 1.5 to 0.4; difficulty in sleep: 2.3 to 1.0). The overall TNSS were also decrease in both groups from baseline to 2 weeks (fluticasone group: 10.33 to 6.13; fluticasone + azelastine: 11.27 to 4.83). (Figure 1 and Figure 2) Moreover, overall TNSS were statistically significant in fluticasone + azelastine compared to fluticasone alone (Table 2). (p>0.0010)

Table 3. Individual Domain Scores of RQLQ in Fluticasone alone and Fluticasone + Azelastine

Individual Domains	Baseline	2 Weeks
Sleep		
Fluticasone alone	6.3 ± 5.6	3.4 ± 3.1*
Fluticasone + Azelastine	7.0 ± 5.3	3.1 ± 2.3♦
Non-Hay Fever Symptoms		
Fluticasone alone	9.0 ± 7.1	4.6 ± 3.7*
Fluticasone + Azelastine	10.7 ± 7.7	4.7 ± 3.4♦
Practical Problems		
Fluticasone alone	8.0 ± 4.8	4.7 ± 3.2*
Fluticasone + Azelastine	8.6 ± 5.0	3.7 ± 2.0♦
Nasal Symptoms		
Fluticasone alone	11.3 ± 5.8	6.5 ± 3.5*
Fluticasone + Azelastine	12.5 ± 5.2	5.5 ± 2.4♦
Practical Symptoms		
Fluticasone alone	5.7 ± 5.3	3.1 ± 3.4*
Fluticasone + Azelastine	5.4 ± 5.3	2.5 ± 2.6♦
Activities		
Fluticasone alone	7.0 ± 4.5	4.0 ± 2.7*
Fluticasone + Azelastine	7.4 ± 4.4	3.2 ± 1.9♦
Emotional		
Fluticasone alone	6.6 ± 4.7	3.6 ± 2.6*
Fluticasone + Azelastine	7.2 ± 4.2	3.0 ± 1.9♦

Mean± SD; * p>0.0001compared with baseline; ♦ p>0.0001 compared with baseline

Table 4. Comparison of Overall Total RQLQ Scores between Two Groups

Treatment Groups	Total Patients	Mean ± SD	p value
Fluticasone	30	24.0 ± 13.78	< 0.02*
Fluticasone + Azelastine	30	33.03 ± 16.88	

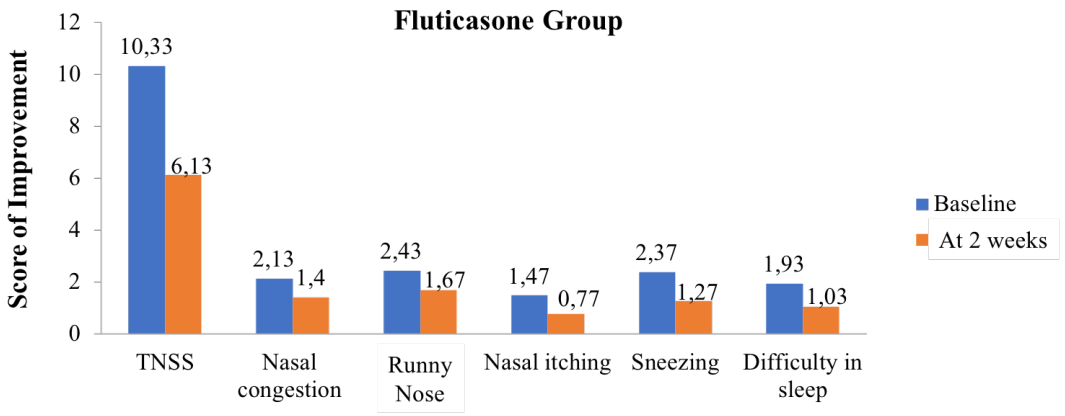

Figure 1. Total TNSS and Individual Symptoms in Fluticasone Group

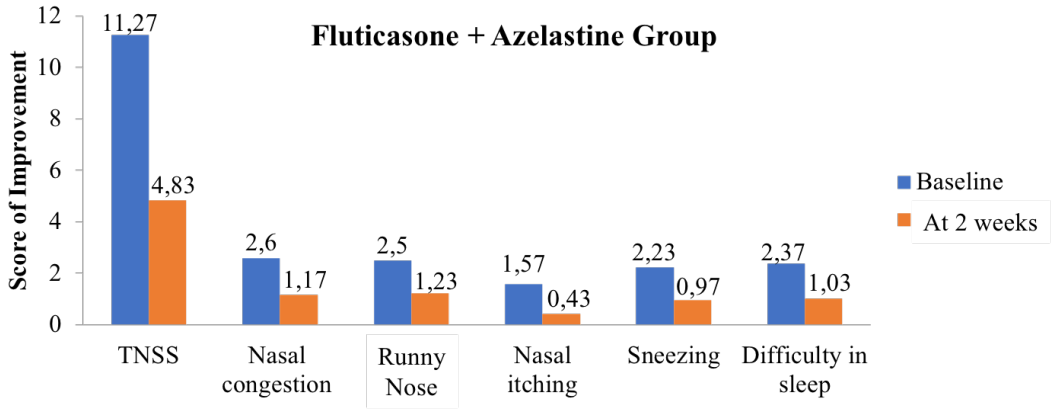

Figure 2. Total TNSS and Individual Symptoms in Fluticasone + Azelastine Group

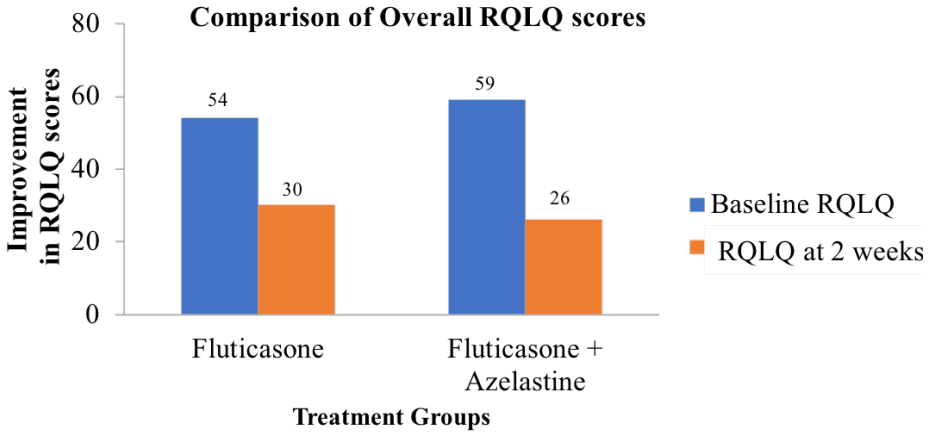

Figure 3. Comparison of Overall RQLQ Scores

Another study done by Ratneret al, also showed similar results (runny nose: 4.9 to 1.7; sneezing: 4.5 to 2.1; nasal congestion: 5.4 to 1.7; nasal itching: 4.7 to 1.9). Similar decrease in the score was seen between the groups from 19.6 to 5.2 in fluticasone group and from 19.5 to 7.4 in combination therapy.[12]

In another study done by Hampel et al, also the total TNSS improved by 28.4% in combination therapy (azelastine + fluticasone), 20.4% in fluticasone group, 16.4% in azelastine group, and 11.2% in placebo group. The combination therapy showed statistically significant improvement in the TNSS compared to either agent alone in patients with moderate-to-severe seasonal allergic rhinitis.[13] In our study, patients also had greater relief of symptoms of allergic rhinitis in combination therapy compared to individual drug and these changes were observed in few studies which stated that combination therapy of fluticasone + azelastine was superior in relieving nasal itching, runny nose, and sneezing.

The RQLQ was used to measure physical, emotional, and practical problems with allergic rhinitis. The RQLQ scores decreased and statistically significant compared to baseline and 2 weeks in individual domain in both groups (Table 3). Also, the overall RQLQ score within the two groups were improved significantly from baseline to 2 weeks (fluticasone group: 54.03 to 30.06; fluticasone + azelastine group: 59.03 to 26.0; $p>0.0001$) (Figure 3). This is in accordance with the similar study done by Ratner et al, which also noted statistically significant improvement in RQLQ scores when compared from mean baseline to 14 days treatment in individual domain of RQLQ scoring.[12]

However, between the two groups, the total RQLQ scores was not statistically significant ($p <0.02$), though there was clinical significant results when azelastine was given along with fluticasone, compared to fluticasone alone. (Table 4).

Study done by Behncke et al showed that azelastine hydrochloride nasal spray was compared to fluticasone propionate nasal spray in geriatric patients also showed improvement from baseline in the RQLQ score after 3 and 6 weeks of treatment, though there were no significant differences between treatment groups showing non-inferiority in the efficacy of antihistaminics and corticosteroid therapy.[14] Hence in the present study we have used combination therapy to improve the efficacy and duration of treatment.

A study done by Sami et al, used another scoring method i.e, total Modified Sino-Nasal Outcome Test (MSNOT-20) score which is based onthe sum of symptom severity rating from each of the 20 diseases specific questionnaire. Following treatment, there was a statistically significant decrease in the total MSNOT-20 score. The subgroup analysis of nasal, paranasal symptoms and sleep disturbances also decreased significantly when in combination therapy of azelastine hydrochloride and fluticasone propionate in allergic rhinitis.[15]

The improvement in combination therapy might be due to different mechanism of action of the drugs and also intranasal drug delivery targets nasal mucosa and reduces the risk in allergic rhinitis. Azelastine has triple mode of action i.e anti-inflammatory, mast cell stabilizing and anti-allergic effects. It inhibits leukotriene action associated with dilatation of vessels, increased vascular permeability resulting in nasal congestion, itching and sneezing. A study by Dhanush HC et al[16] also observed the significant reduction in individual symptoms of allergic rhinitis among the patients treated with topical azelastine.

Fluticasone inhibit the onset of inflammatory response and reduce nasal mucosa permeability, number of inflammatory cells and release of mediators.[17]

The advantage of intranasal drug delivery is to decrease risk of systemic side effects and drug interactions.[18] Even Bhadouriya et al also suggested that the topical azelastine relieves the symptoms of allergic rhinitis rapidly and effectively.[19] Also another study by Dalvi et al showed clinically significant reduction the symptoms of sneezing and nasal obstruction with fluticasone + azelastine spray than azelastine alone.[20] All the drugs were well tolerated. Few patients complained of a bitter taste in combination of fluticasone + azelastine and no other side effects were noted significantly. This result is similar with a study of Ratner et al that showed the most common adverse effect in fluticasone + azelastine was bitter taste and headache.[12]

Conclusion

The combination therapy of fluticasone and azelastine showed significant improvement in TNSS in patients with allergic rhinitis. The quality of life of patients with allergic rhinitis was similar in both the groups.

Funding

Nil

Acknowledgement

Nil

Conflict of Interest

Nil

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