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RESEARCH ARTICLE

Azelastine hydrochloride nasal spray and its combination with fluticasone propionate in the management of allergic rhinitis - A comparative study

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ABSTRACT

Background: Allergic rhinitis (AR) is a global health problem affecting 500 million of population. H_1-antihistamines are the first-line therapy although intranasal corticosteroids are the gold standard treatment in patients with more severe symptoms. **Aims and Objectives:** The aim of the study was to evaluate the efficacy and safety of azelastine hydrochloride nasal spray and its combination with fluticasone propionate nasal spray in the management of AR. **Materials and Methods:** A total of 70 patients clinically diagnosed as AR were randomized into two groups, Group A received azelastine hydrochloride nasal spray alone and Group B received a combination of azelastine hydrochloride with fluticasone propionate nasal spray for 2-weeks. Efficacy was assessed by mean change in the total symptom score (TSS) which was the sum of total nasal symptom score (TNSS) and total ocular symptom score (TOSS) at the end of 2 weeks from baseline. **Results:** Both groups showed statistically significant ($P < 0.0001$) improvements in the symptoms at the end of 2 weeks of treatment. In Group A, the baseline TNSS, TOSS, and TSS was 9.88 ± 0.99, 5.8 ± 1.32, and 15.68 ± 1.98, respectively, which was reduced to 5.78 ± 2.35, 1.60 ± 1.19, and 5.78 ± 2.35. In Group B, TNSS, TOSS, and TSS were reduced from 9.97 ± 0.92 to 2.71 ± 1.36, 6.08 ± 1.37 to 1.04 ± 0.87, and 16 ± 1.86 to 3.22 ± 1.64, respectively. There was a greater reduction in symptom score in Group B than Group A which was statistically significant ($P < 0.0001$). **Conclusion:** Combination of azelastine hydrochloride with fluticasone propionate nasal spray offers an advantage over the treatment with azelastine hydrochloride alone in regard to symptomatic improvement in AR.

KEY WORDS: Allergic Rhinitis; Nasal Sprays; Intranasal; Azelastine Hydrochloride; Fluticasone Propionate

INTRODUCTION

Allergic rhinitis (AR), an IgE-mediated hypersensitivity of the mucous membrane of nasal airways, is characterized by nasal symptoms such as nasal congestion, rhinorrhea, sneezing, and itchy nose.[1] It is frequently associated with ocular symptoms and has a negative impact on health-related quality of life. It is the most important reason for morbidity, medical expenditure, and insufficiency at work, school, and leisure activities.[2]

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AR is a global health problem and its prevalence continues to rise at a steady rate. Often underestimated and undertreated condition which currently affects >500 million people worldwide.[1,3,4] Global climate changes leading to elevated levels of carbon dioxide increased plant productivity and increase in airborne pollen may explain the increasing prevalence.[5]

Management of AR includes avoidance of allergen, pharmacotherapy, and allergen-specific immunotherapy.

According to the guidelines, H_1 antihistamines are the first-line therapy for all cases of AR, while the potent intranasal corticosteroids (INS) are the gold standard for moderate to severe cases.[6] Unfortunately, many patients do not attain optimal symptom relief with monotherapy and are discontented, experiencing breakthrough symptoms, subsequently, are in a quest of a new medication. Nasal obstruction and ocular symptoms are the most bothersome symptoms which are hard to control. Most of the physicians use multiple therapies to achieve faster and more profound symptom relief, in spite of limited evidence to support this practice.[7]

The antihistamine property of azelastine hydrochloride can be augmented by anti-inflammatory property of the INS to attain better symptom control in moderate to severe cases of AR.[8] Hence, this study was taken up to evaluate the efficacy and safety of azelastine hydrochloride nasal spray alone and its combination with fluticasone propionate.

MATERIALS AND METHODS

A prospective, open-label, parallel group, comparative 2 weeks clinical study conducted at the ENT Outpatient Department attached to Bangalore Medical College and Research Institute, Bengaluru. The study was conducted from May 2018 to October 2018 and was approved by the Institutional Ethics Committee. After the written informed consent was obtained from each patient, seventy patients clinically diagnosed with moderate to severe AR of either sex aged between 18 and 65 years were enrolled in this study. Patients with the history of hypersensitivity to study drugs, pregnant and lactating women were excluded from the study. Enrolled patients were randomly divided into two groups of 35 each.

- Group A: Azelastine hydrochloride (137 µg) nasal spray, two sprays in each nostril, twice daily.
- Group B: Combination of azelastine hydrochloride (137 µg) with fluticasone propionate (50 µg) nasal spray, two sprays in each nostril, twice daily.

Demographic data, history of presenting illness, associated allergic disorders, concomitant medications, physical and clinical examination, nasal and ocular examination (symptom scores), and details of the drug prescription were recorded at the baseline visit (visit 1). Nasal spray was administered for a period of 2 weeks irrespective of the symptom control and follow-up was done at the end of 2 weeks (visit 2). A deviation of ± 2 days for follow-up was accepted. Study subjects were evaluated for nasal symptoms (nasal congestion, rhinorrhea, nasal itching, and sneezing) and ocular symptoms (itching/burning eyes, tearing/watering eyes, and eye redness) on a 4 point scale as given in Table 1. Efficacy was assessed by mean change in total symptom score (TSS) which is the sum of total nasal symptom score (TNSS) and total ocular symptom score (TOSS) at the end of 2 weeks from the baseline. Safety of the nasal sprays was assessed by any adverse effects spontaneously reported by the study subjects or elicited by the investigators were recorded [Figure 1].

Table 1: 4 point scale for symptom evaluation problem

0	Never	No problem
1	Rarely	Problem present but not disturbing
2	Quite often	Disturbing problem but not hampering any activity or sleep
3	Very often	Problem hampering some activities or sleep

Statistical Analysis

Data were analyzed in Microsoft office Excel 2010 and were expressed as mean and standard deviation. For normally distributed data paired *t*-test was used to compare the mean change in symptom scores within the groups and unpaired *t*-test between the groups. $P < 0.05$ was considered significant. Non-normally distributed data were analyzed using nonparametric test.

RESULTS

Among the 70 patients randomly allocated to the treatment groups, 68 patients completed the study according to the protocol. At the end of 1st week, two patients were lost to follow-up in azelastine hydrochloride group.

The two groups were homogenous with respect to baseline demographic data [Table 2].

Efficacy Analysis

Change in TNSS

TNSS was recorded at baseline and the end of 2 weeks for all the study subjects. Baseline TNSS for Group A and Group B was 9.88 ± 0.99 and 9.97 ± 0.92, respectively, which was comparable. At the end of 2 weeks of treatment, TNSS was 5.78 ± 2.35 in Group A and 2.71 ± 1.36 in Group B. The changes from the baseline in both the study groups were statistically significant. However, TNSS in Group B was significantly reduced than Group A at the end of 2 weeks ($P < 0.0001$) [Figure 2].

Change in TOSS

TOSS was calculated at baseline and the end of 2 weeks for all the patients. Baseline TOSS for Group A and Group B was 5.8 ± 1.32 and 6.08 ± 1.37, respectively, which was comparable. At the end of 2 weeks of treatment, TOSS was 1.60 ± 1.19 in Group A and 1.04 ± 0.87 in Group B. This reduction in TOSS was statistically significant in both the study groups ($P < 0.0001$). Mann–Whitney rank-sum test was used to compare the reduction in TOSS between the

Table 2: Baseline demographic and clinical data in study groups

Characteristics	Azelastine HCl group	Azelastine HCl+fluticasone propionate group	*P* value
Number of patients recruited	35	35	
Number of patients at follow-up	33	35	
Age (years)	29.14±13.8	32.6±12.99	0.366
Sex, *n* (%)			
Males	19 (54%)	18 (51%)	
Females	16 (46%)	17 (49%)	
TNSS at baseline	9.88±0.99	9.97±0.92	0.7125
TOSS at baseline	5.8±1.32	6.08±1.37	0.3819
TSS at baseline	15.68±1.98	16±1.86	0.42

All values are mean±standard deviation unless otherwise stated, TSS: Total symptom score, TOSS: Total ocular symptom score, TNSS: Total nasal symptom score, HCl: Hydrochloride

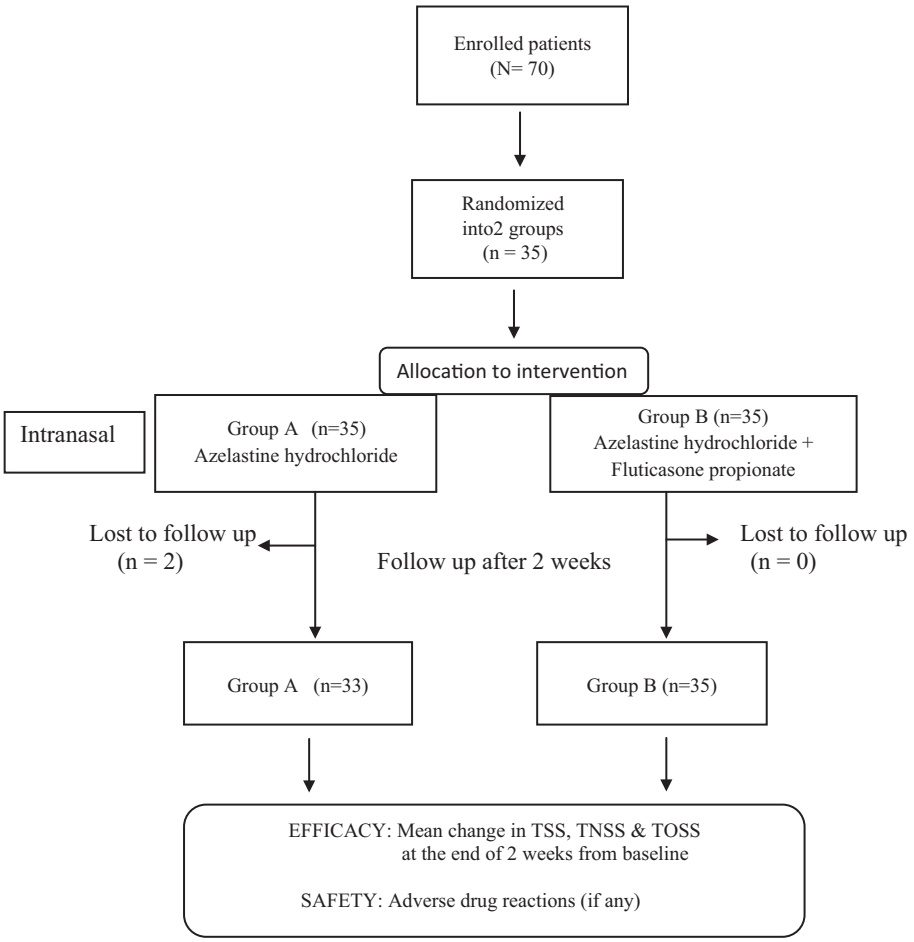


Figure 1: Study flowchart

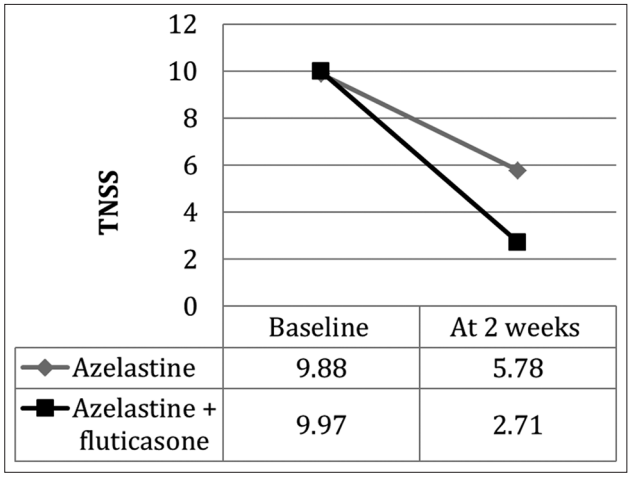
two groups and depicted a greater reduction in Group B than Group A ($P < 0.0016$) [Figure 3].

Change in TSS

TSS was calculated at baseline and the end of 2 weeks for all the study subjects. Baseline TSS for Group A and Group B was 15.68 ± 1.98 and 16 ± 1.86, respectively, which was reduced at the end of 2 weeks of treatment to 5.78 ± 2.35 in Group A and 3.22 ± 1.64 in Group B. The changes from baseline in both the study groups were statistically significant ($P < 0.0001$). Between the two groups, the Mann–Whitney rank-sum test applied which depicted a greater reduction of TSS in Group B than Group A ($P < 0.0001$) [Figure 4].

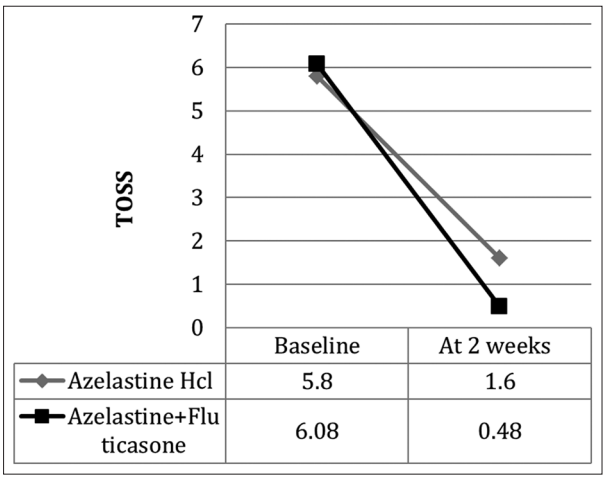
Safety Analysis

Both the nasal sprays were well tolerated in the study subjects. The most common adverse effect was bitter taste (6% in Group A and 11.4% in Group B) and headache (3% in Group A and 8.5% in Group B). No serious adverse events reported.



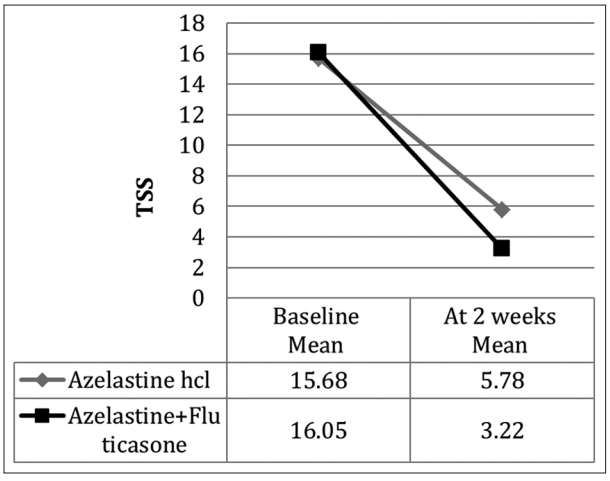
	Baseline	At 2 weeks
Azelastine	9.88	5.78
Azelastine + fluticasone	9.97	2.71

Figure 2: Total nasal symptom score at baseline and the end of 2 weeks of treatment in the study groups



	Baseline	At 2 weeks
Azelastine Hcl	5.8	1.6
Azelastine+Fluticasone	6.08	0.48

Figure 3: Total ocular symptom score at baseline and the end of 2 weeks of treatment in the study groups



	Baseline Mean	At 2 weeks Mean
Azelastine hcl	15.68	5.78
Azelastine+Fluticasone	16.05	3.22

Figure 4: Total symptom score at baseline and the end of 2 weeks of treatment in the study groups

DISCUSSION

AR remains a challenge to the physicians to treat the symptoms and ensure a good quality of life. In AR cytokines, chemokines, neuropeptides, and adhesion molecules are involved in a complex network to produce the specific symptoms of AR and the non-specific hyper-reactivity.[9] Most of the patients with AR do not attain optimal symptom relief with monotherapy leading to changing medication or combination therapy. Routinely prescribed combination of oral antihistamines with INS is as effective as corticosteroid alone.[10]

Several clinical trials have already demonstrated the efficacy of azelastine hydrochloride nasal spray and its combination with fluticasone propionate with a better safety profile. However, despite extensive literature search and, to the best of our knowledge, there are no available research articles that evaluate the efficacy of azelastine hydrochloride nasal spray and its combination with fluticasone propionate in Indian population. Hence, this study was undertaken.

In the present study, the efficacy of the nasal sprays was assessed by TNSS, TOSS, and TSS. There were significant changes in all the parameters in both the groups at the end of 2 weeks from the baseline. However, the mean changes in all the three parameters were more with the combination group than azelastine hydrochloride nasal spray alone. This may be attributed to the augmented anti-inflammatory property of the corticosteroid with that of the primary antihistamine activity of azelastine. A randomized double-blind study by Ratner *et al*. demonstrated that there was a significant improvement in TNSS with a combination of azelastine and fluticasone when compared to azelastine nasal spray.[11]

Azelastine hydrochloride nasal spray is the only topically administered 2nd generation antihistamine without any adverse cholinergic effects. It selectively antagonizes the H1 receptor and is 10 times more potent than chlorpheniramine. It has one of the fastest onsets of action of 15 min with nasal spray among the currently available rhinitis medication. It also exhibits long-acting effects based on the triple mode of action - anti-allergic, anti-inflammatory, and mast cell stabilizing properties. Azelastine has inhibitory effects on a wide range of chemical mediators including leukotrienes and kinins, as well as inflammatory cytokines and chemokines (e.g., intercellular adhesion molecule –1).[12]

INS act by suppressing inflammation in the nasal mucosa leading to a reduction or resolution of symptoms. At present, they are the most effective treatment for AR and are the first-line therapy in moderate-to-severe cases of AR or in individuals who are still symptomatic regardless of the regular use of antihistamines. INS relieves all nasal symptoms, including nasal blockage and a meta-analysis done by Juel-Berg *et al.,* in 2017, showed that INS are superior to antihistamines in improving nasal symptoms and quality of life in patients with AR.[13] On the other hand, INS may require some time to achieve peak efficacy. However, after initial administration, asselstine's antihistamine effect

would manifest rapidly and can be sustained with regular use.

The primary antihistamine property of azelastine could have been augmented by the anti-inflammatory property of the INS throughout the 2 week study period. This would have led to attain an optimum symptom control in patients with AR.

The present study was prospective, comparing two nasal sprays available in the market. Despite the fact that small sample size and short duration of the study, the results of the study add to the existing literature.

CONCLUSION

In our study, both the treatment groups demonstrated significant therapeutic benefit in patients with AR. However, clinical benefit occurs significantly more with the combination of azelastine hydrochloride and fluticasone propionate nasal spray. Hence, the combination therapy is safe and effective to reduce symptoms of AR.

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