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Comparative clinical evaluation of effect of topical verses systemic anti - allergic drug in allergic rhinitis: a prospective study

Sunil Kumar Singh Bhadouriya[1], Mohit Srivastava[2]*, Rohit Saxena[3], Abhinav Srivastava[4]

Department of ENT, [1]UPUMS, Saifai, Etawah; [2]Rama Medical College, Hapur, Ghaziabad; [3]SMS&R, Greater Noida; [4]Santosh Medical College, Ghaziabad, Uttar Pradesh, India

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***Correspondence:**
Dr. Mohit Srivastava,
E-mail: dr.mohit141180@gmail.com

ABSTRACT

Background: Nasal passages form one of the chief sources of contact of the human with his environment. Hence, it is natural that the mucosa of the area is the victim of assault with multitudes of potential allergens. Allergic rhinitis is an inflammatory disease with worldwide prevalence of 10-40%. Allergic rhinitis is a disease with low mortality but significantly lowers the quality of life and functioning. Both oral and intranasal antihistamines are approved for the first-line treatment of allergic rhinitis and both formulations result in a reduction in symptoms and an improvement in quality of life.
Methods: The following study was designed to assess the efficacy and safety of the azelastine nasal spray in comparison to levocetrizine in patients with allergic rhinitis. Out of the 68 patients, 34 cases were treated with topical azelastine (group A), while remaining 34 with systemic levocetrizine (group B). The effects of anti-allergic drugs have been studied on the basis of relief of symptoms and change in histopathology.
Results: The effect of levocetrizine has been studied on the basis of relief of symptoms and change in histopathology and found to have complete response in 58% and fair response in 23.5% patients of allergic rhinitis. The effect of topical azelastine nasal spray have complete response in 70.5% and fair response in 23.5% patients of allergic rhinitis.
Conclusions: Comparing the post therapy clinical and histopathological results in this study, azelastine nasal spray was found to be more effective and safe in the treatment of allergic rhinitis than levocetrizine.

Keywords: Rhinitis, Allergy, Antihistamines, Levocetrizine, Azelastine

INTRODUCTION

The term 'allergy', coined by von Pirquet, he proposed the term allergy, to describe a change of the living tissues, with increased or reduced sensitiveness due to the formation of specific antibodies.[1] On exposure to the foreign protein the allergen combines with cell– bound reagenic antibodies to release histamine and similar amines and other factors.[2] Allergy is used to define the series of events which occurs when an antigen, which is not harmful in itself, causes an immune response, leading to symptoms and disease in genetically predisposed individuals. The various manifestations of atopy and allergy are allergic rhinitis, allergic asthma, allergic conjunctivitis, allergic dermatitis, drug allergies, bee stings and urticaria/angioedema. Nasobronchial allergies i.e. asthma or rhinitis alone or asthma with rhinitis are the commonest allergic manifestations with 75.4% of patients belonging to this group.[3] Vangham and Bray stated that roughly 10% of general population is frankly allergic and 50% given history of transient episodes.[4] Allergic rhinitis is the most common allergy encountered in clinical practice and constitutes about 55% of allergies seen in India[5].Shambough stated that at least 90% of chronic nasal infections and 70% of chronic sinus

infections can be shown to have underlying allergic factors responsible for chronicity.[6] Clinically allergic rhinitis manifests as itching, sneezing, rhinorrhea, congestion and itchy eyes. Symptoms begin at any Age but usually in adolescence and young adulthood. Onset of nasal allergy occurs frequently in first decade of life. In the second & third decades, smaller number develop allergic symptoms, & in the fourth, fifth & sixth decades the incidence sharply declines.[7] No Racial or Ethnic variations. A positive family history is present in 50% cases. Those without a family history develop allergy in 7-12% cases. Cookson et al noted the linkage of a specific chromosome region to allergic phenotype - the 11q13 gene locus.[8,9] Development of allergy in addition to genetic predisposition also depends upon exposure to environmental allergens, infection, endocrine, psychological, physical factors. Precipitating factors are inhalants, ingested foods, infectants, chemical substances, physical agent, and nonspecific irritants.[10] On anterior rhinoscopy the pale, boggy, bluish tinged mucosa is characteristic of the well-developed allergic rhinitis. Not all allergic individuals exhibit the classical pale, boggy, blue gray mucosa; it may vary from a normal watermelon red to pathologic pale, pinkish white. During an attack there is swelling of the erectile tissue of the turbinate's and increased secretions. The mucous membrane, especially over the inferior turbinate's, is often swollen as completely to occlude the passage. Allergic secretions tend to be ropier in their consistency than secretion of inflammatory origin. On posterior rhinoscopy the classical pale, boggy mulberry like posterior tips of the inferior turbinate's are significant and should suggest the possibility of an allergy. These however may be physiological for certain individuals.[11] Treatment of allergic rhinitis is far from satisfactory. Ideal treatment should be directed towards correction of etiological factor, avoidance of allergens and desensitization. However accurate determination of the cause is often difficult. Various methods of treatment are avoidance of precipitating factor, desensitization or hyposensitization, specific hypoventilation, antihistamines, corticosteroids, sodium cromoglycate, gamma globulin, thyroid hormone, injections of sphenopalatine ganglion with alcohol, zinc ionization, sub mucosal injections of corticosteroids, steroid aerosol, anti-leukotrienes, oral decongestant, intranasal decongestant, intranasal anticholinergics, immunotherapy and cauterization, submucosal diathermy and cryosurgery.[12-16] Various methods of treatment have been advocated, each with its own limitations and degree of success. Topical antihistamines, oral antihistamines are also recommended as first-line therapy in the treatment of allergic rhinitis.[17] Second-generation agents are generally preferred because they are less likely to cause sedation, performance impairment, and anticholinergic side effects, in both adults and children.[18] Unlike topical antihistamines, which mainly target nasal symptoms, oral antihistamines primarily target symptoms associated with histamine, such as sneezing, rhinorrhea, itchiness, watery eyes, and eye redness. Oral antihistamines have some effect on nasal congestion, although less than intranasal agents. Oral antihistaminic are approved for young children (desloratadine and cetirizine, age 6 months and up; loratadine and fexofenadine, age 2 years and up; levocetrizine, age 6 years and up). Although not as rapid as topical histaminic oral antihistamines have a relatively rapid onset of action, (ranges from one to three hours).[19] Levocetrizine works by blocking histamine receptors. It is a non-sedating histamine; worked by preventing the action of histamine. It does not prevent the actual release of histamine from mast cells, but prevents it binding to its receptors. This is in turn to prevent the release of other allergies chemicals and the blood supply to the area and provides relief from the typical symptoms of allergic rhinitis. There are a number of advantages of topical intranasal administration. Medication is more effectively delivered to the nasal mucosa, directly onto the target tissue harboring histamine-filled mast cells and inflammatory mediators. Topical administration is also associated with a faster onset of action and lower incidence of systemic side effects.[20] Azelastine is a second generation antihistaminic. This H1 blocker has good topical activity in addition inhibits histamine release and inflammatory reaction triggered by leukotriene and platelet activating factor; and has a bronchodilator property. After intranasal application it has been shown to down regulate intracellular adhesion molecule-1 (ICAM-1) expression on nasal mucosa. Azelastine have been shown to have a fast onset of action (15 minutes) and are also more effective than oral antihistamines for rhinitis symptoms.[21,22] In addition, they are more rapidly effective than topical steroids, but in the long term, their effects are less potent and less cost effective compared to those of topical steroids.[23,24] Stinging in the nose and altered taste perception are the local side effects. Some somnolence has been reported on nasal application.

METHODS

Study design

This prospective study was carried out in outpatient department of otorhinolaryngology Santosh medical college and hospital Ghaziabad from September 2008 to October 2009. This study was approved by institutional ethics committee.

Study population: Inclusion and exclusion criteria

75 patients between the ages of 13 to 48 years with allergic rhinitis who gave written informed consent were recruited from the outpatient department. All relevant information was recorded on a prescribed proforma. Patients treated with systemic and topical steroids during previous thirty days, antihistamines and decongestant during the past 7 days, were excluded from study. Patients with gross anatomical problem like deviated nasal septum, polyp, chronic sinusitis, throat problems and children less than 2 years were not included in the study. Patients with renal, hepatic and cardiovascular diseases were excluded from study.

The cases were followed up for 4 weeks in the short duration of this study. In spite of best persuasion only 68 cases (90.6%) returned for follow up. The follow up study was made on 68 cases only. After obtaining a detailed medical history, clinical examination was done. Complete blood count, absolute eosinophil count and paranasal sinus radiograph of the patients were taken and treatment planning commenced. Nose, throat and ears were thoroughly examined to rule out any infective or obstructive cause. Out of the 68 patients, 34 cases were treated with topical azelastine (group A), while remaining 34 with systemic levocetrizine (group B). One puff of topical azelastine spray (0.1%) was prescribed twice daily for 4 weeks. In another group B levocetrizine was prescribed. The patients were asked to take 5 mg dose of the drug once in the evening. In children less than 11 years up to 6 years 2.5 mg dose was prescribed. Follow up visits were scheduled every week for 4 weeks.

Ethical aspects

The study protocol was approved by Institute Ethical committee.

Statistical study

Data was entered in Microsoft excel sheet and data analysis was done by using statistical software SPSS version 17. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 75 patients were recruited in the study. Out of 75 patients recruited in study, 68 patients completed entire 4 weeks of study. The group comprised of 40 males and 28 females, with the mean age of 31.5 years. In majority of the cases (50.6%) physical agents were the main cause of the disease. Most of these were sensitive to change in atmospheric temperature, 33.3% were found allergic to inhalants, another 8% cases had multiple sensitivity and no specific causative factor was found in remaining 8% cases. Nature of discharge was watery profuse in 53.3% cases, watery scanty in 42.6% cases and mucoid in 4% cases. Out of the 68 patients, 34 cases were treated with topical azelastine (group A), while remaining 34 with systemic levocetrizine (group B). The Post therapy symptomatology was kept in three categories, in which there was complete absence of symptom considered as good, relief in the symptoms as fair and no improvement as poor. Sneezing was completely absent or markedly reduced in majority of cases, the next common symptom was nasal obstruction, in fairly good number of cases it became absent or reduced to a great extent and only two cases with azelastine and one with levocetrizine noticed no relief in the symptoms. Table 1 is showing degree of relief following levocetrizine therapy amongst 34 cases of allergic rhinitis. Table 2 is showing degree of relief following azelastine therapy amongst 34 cases of allergic rhinitis.

Table 1: Showing degree of relief following levocetrizine therapy amongst 34 cases of allergicrhinitis.

S.No.	Symptoms	No. of Cases	Complete response (%)	Fair response (%)	Poor response (%)
1.	Sneezing	34	20 (58.8)	10 (29.4)	04 (11.7)
2.	Nasal obstruction	28	13 (46.4)	14 (50)	02 (7.1)
3.	Rhinorrhoea	20	08 (40)	09 (45)	03 (15)

Table 2: Showing degree of relief following azelastine therapy amongst 34 cases of allergic rhinitis.

S.No.	Symptoms	No. of Cases	Complete response (%)	Fair response (%)	Poor response (%)
1.	Sneezing	34	25 (83.3)	07 (20.5)	02 (5.8)
2.	Nasal obstruction	30	22 (73.3)	06 (20)	02 (6.6)
3.	Rhinorrhoea	20	14 (70)	05 (25)	01 (5)

Table 3: Showing results in post therapy histopathologically with levocetrizine.

S.No.	No. of cases	Results			
		Good	Fair	Poor	Nil
1.	34	20	08	01	05
2.	(%)	58.8	23.5	2.9	14.7

Results of histopathology were based upon the reduction in cellular infiltration, few mucous and serous glands no evidence of prominent dilated duct, decrease or absence of eosinophil infiltration, reduction in stromal oedema. Figure 1 is showing intense inflammatory reaction in stroma. Figure 2 is showing eosinophils in nasal biopsy section.

Table 3 and 4 shows that the result in histopathology after therapy was better with azelastine than levocetrizine.

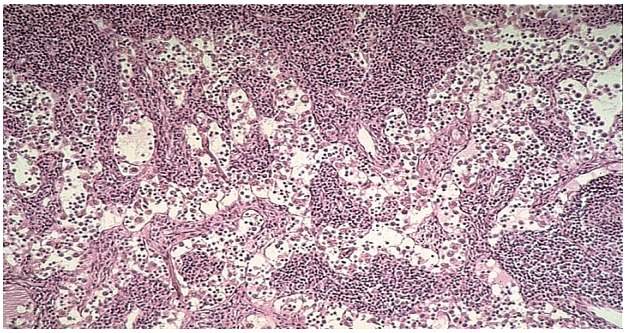

Figure 1: Photomicrograph showing intense inflammatory reaction in stroma (H&E, 100 X).

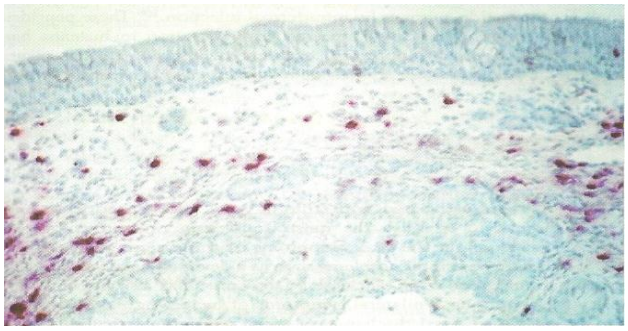

Figure 2: Eosinophils in nasal biopsy section.

Table 4: Showing results in post therapy histopathologically with azelastine.

S.No.	No. of cases	Results			
		Good	Fair	Poor	Nil
1.	34	24	08	01	01
2.	(%)	70.5	23.5	2.9	2.9

Table 5: Showing degree of relief (from sneezing) following levocetrizine therapy and azelastine therapy amongst 34 cases of allergic rhinitis.

	Sneezing			P value
	Complete response (%)	Fair response (%)	Poor response (%)	
Levocetrizine therapy (n=34)	20 (58.8)	10 (29.4)	04 (11.7)	0.1999811
Azelastine therapy (n=34)	25 (83.3)	07 (20.5)	02 (5.8)	Not significant

Table 6: Showing degree of relief (from nasal obstruction) following levocetrizine therapy and azelastine therapy amongst 34 cases of allergic rhinitis.

	Nasal obstruction			P value
	Complete response (%)	Fair response (%)	Poor response (%)	
Levocetrizine therapy (n=28)	13 (46.4)	14 (50.0)	2 (7.1)	0.0258589
Azelastine therapy (n=30)	22 (73.3)	6 (20.0)	2 (6.6)	Significant

Table 7: Showing degree of relief (from rhinorrhoea) following levocetrizine therapy and azelastine therapy amongst 34 cases of allergic rhinitis.

	Rhinorrhoea			P value
	Complete response (%)	Fair response (%)	Poor response (%)	
Levocetrizine therapy (n=20)	08 (40.0)	09 (45.0)	03 (15.0)	0.0565303
Azelastine therapy (n=20)	14 (70.0)	05 (25.0)	01 (5.0)	Borderline significant

Table 8: Showing results in post therapy histopathology with levocetrizine therapy and azelastine therapy.

	Results in post therapy histopathology				P value
	Good (%)	Fair (%)	Poor (%)	Nil (%)	
Levocetrizine therapy (n=34)	20 (58.8)	08 (23.5)	01 (2.9)	5 (14.7)	0.3100875
Azelastine therapy (n=34)	24 (70.5)	08 (23.5)	01 (2.9)	01 (2.9)	Not significant

Table 5 is showing degree of relief from sneezing following levocetrizine therapy and azelastine therapy. Table 6 is showing degree of relief from nasal obstruction following levocetrizine therapy and azelastine therapy which was statistically significant (p value less than 0.05).

Table 7 is showing degree of relief from rhinorrhoea following levocetrizine therapy and azelastine therapy which was borderline significant (p=0.056). Table 8 is showing results in post therapy histopathology with levocetrizine therapy and azelastine therapy which was not found statistically significant (p=0.31).

None of the cases in the present study had any major complications except in four cases that had mild bleeding after the nasal biopsy that was controlled by anterior nasal packing and systemic hemostatic and antibiotic drugs. No serious adverse event was reported in both groups. Few adverse events were noticed in cases with azelastine therapy and almost nil after effect was seen with levocetrizine therapy. None of the adverse events which were reported were severe enough to warrant termination of the treatment. With systemic levocetrizine therapy, 4 cases reported to have resistant rhinitis which was probably related to overuse of the drug. Stinging discomfort or dryness locally in the nose was encountered infrequently. With topical azelastine therapy only two cases reported crusting and dryness of nose; on the other hand almost all the cases treated with azelastine felt such benefit that they continued the given treatment.

DISCUSSION

In our prospective study the clinical changes in response to topical azelastine (Group A) with systemic levocetrizine (Group B) were evaluated. Most of the cases suffering from allergic rhinitis were in the age group of 21-30 years (51 cases) with the mean age of 31.5 years. This observation is in accordance with that of Negus and Hagy.[25]

In the present study, allergic rhinitis was found to occur more in males (60%) as compared to females (40%), which is in agreement with other studies.[26] Negus (1955) observed, both sexes were equally affected. The low incidence in female may be due to that in our country, females are less exposed, to outside atmospheric inhalants, allergens and temperature variations as they usually stay at home, but now this trend is changed.

In the present study, incidence of allergic rhinitis in relation to occupation revealed that housewives, office workers and students were the commonest sufferers. It is probable that these people are subjected to emotional stress, family troubles, examination worries, and work load.

In the present study a positive family was obtained in 29.3% cases. Genetic analysis of DNA from family members implicated genetic linkage with a gene (or genes) on chromosome 11q.[27] An exciting recent development is the co-localization on chromosome 11q of the gene for the high affinity IgE receptor disorders of which, at least in part, may contribute to the atopic trait.[28]

The classical symptoms of allergic rhinitis were sneezing (90.6%), nasal discharge (69.33%) and nasal obstruction (77.3%) found amongst 68 cases in varying degree of severity. Lindquist et al in 1986 stated that in allergic rhinitis sneezing was the predominant feature followed by nasal obstruction and rhinorrhea.[29] Present study is in accordance with his observation. The nasal discharge was watery in the majority of the cases (53.3%). This observation is in accordance with that of Binder et al.[30]

In the present study allergic rhinitis cases we got more successful results with topical azelastine nasal spray (91%) when compared to (81%) in cases of systemic anti-allergic levocetrizine. Moreover, there were almost no side effects like rebound swelling or recurrence reported with azelastine nasal spray therapy, however the possibility of overuse related rebound swelling, should be kept in mind before prescribing azelastine topically nasal spray in allergic rhinitis cases.

Bunnang et al reported significantly greater improvement in blocked nose, runny nose and runny eyes during the first 2 weeks of budesonide treatment than during the same period on astemizole.[31]

Wight et al managed 59 cases of allergic rhinitis with azelastine 400 mg and 800 mg topically per day.[32] He observed more or less same benefit in the cases with either dose of budesonide and no increase in adverse effects occurred with higher dose therapy.

Mc. Arthur carried out a comparative study azelastine and beclamethasone sprays in 88 adults with allergic rhinitis.[33] In this study the results with azelastine were good improvement in 69% of cases, fair in 22% of cases and there was poor improvement in 9% of cases.

When we compared the overall outcome in the two groups, we found topical azelastine spray relieves symptoms of allergic rhinitis rapidly and effectively. Thus we can expect better results in allergic rhinitis with topical azelastine nasal spray which has proven to be more effective than systemic levocetrizine in the present study. The results of our study are in agreement with previous study where efficacy of azelastine nasal spray was significantly superior in improvement of nasal symptom severity.[35] Intranasal agents may be preferred in patients in whom nasal congestion is particularly bothersome or in cases where a more rapid onset of action is desired.[34-37] Oral agents would be a better choice in young children, in cases of poor medication compliance, and in patients who are bothered most by histamine-associated symptoms, such as itching, sneezing or red and watery eyes. The topical effect of nasal drugs

in allergic rhinitis, however, needs to be studied further. There are certain limitations of our study; first, the sample size is small due to less time of study. Each patient recruited in our study had to come for follow-up every week for 4 weeks. Secondly a clear-cut clinical efficacy evaluation cannot be made in the present study as no control group was available.

CONCLUSION

Comparison will help us to formulate a set line of treatment in allergic rhinitis taking into consideration the season, type of presentation and histopathological response with clinical response. From present study, following conclusions were drawn: In this study the incidence of allergic rhinitis were found to be more below 30 years (68%). Incidence of allergic rhinitis was found to be more in males (60%) than in females. Office workers, students and house wives were more affected than others (82.6%). The chief symptoms with which the patients presented were sneezing (96%), Nasal obstruction (78.6%) and less common symptom was rhinorrhoea (69.33%). The effect of systemic levocetrizine anti-allergic drug has been studied on the basis of relief of symptoms and change in histopathology and found to have complete response in 58% and fair response in 23.5% patients of allergic rhinitis. The effect of topical azelastine nasal spray anti-allergic drugs has been studied on the basis of relief of symptoms and change in histopathology and found to have complete response in 70.5% and fair response in 23.5% patients of allergic rhinitis. Comparing the post therapy clinical and histopathological results in this study, topical azelastine nasal spray found to be more effective and safe in the treatment of allergic rhinitis than systemic levocetrizine as an anti-allergic drug.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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