

Assessment of cost effectiveness of antihistaminics in allergic rhinitis patients in rural region by Nasal cytology: a simple and inexpensive tool

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ABSTRACT

Background: This study was to assess the usefulness of nasal smear as a quick, easy and inexpensive diagnostic method for allergic rhinitis and for assessment of the cost effectiveness of antihistaminics.

Methods: This study was conducted in rural setting of tertiary care hospital. Nasal smears were taken from 52 patients with a clinical history of nasal allergy having nasal congestion score of at least 3 or more. Nasal smears were stained with Hematoxylin-Eosin and examined by pathologists.

Results: A total of 52 patients 13 in each groups of the age group 18 to 65 years (Mean age, 33.73 ± 10.23 years); 48.08% are Female and 51.92% are Male were randomized and received either Cetirizine, Levocetirizine, Loratadine, or Fexofenadine over a period of one week. The association of eosinophil before and after the treatment was obtained using logistic regression analysis for each treatment separately. Eosinophil is marginally associated with Cetirizine before and after treatment.

Conclusions: Evaluation of eosinophils in nasal smear is an insensitive but cheaper test for the diagnosis of allergic rhinitis and use as a simple tool for comparison of cost effectiveness among commonly used oral antihistaminics. pharmacoeconomic analysis of present comparative clinical study shows that cetirizine is a better choice in comparison with levocetirizine, loratidine and fexofenadine due to its cost effectiveness.

Keywords: Allergic rhinitis, Antihistaminics, Cost effectiveness, Eosinophilia, Nasal cytology

INTRODUCTION

Allergic rhinitis (AR) is an IgE-mediated hypersensitivity reaction of nasal mucosa which is characterized by sneezing, itching, watery nasal discharge and a sensation of nasal obstruction. A characteristic feature of allergic inflammation is local accumulation of inflammatory cells including T lymphocytes, mast cells, eosinophils, basophils and neutrophils.¹ Release of various mediators from these cells is responsible for the symptoms of allergic rhinitis. Accumulation of additional inflammatory cells such as eosinophils and T cells occurs in response to various chemokines. These inflammatory cells can be

easily identified in nasal mucosa or secretions by performing nasal biopsies and then, preparing nasal smears to confirm the diagnosis of allergic rhinitis. Moreover, these methods are simple, reproducible, easy to perform and cost effective as compared to other diagnostic tests for allergic rhinitis.^{2,3}

The present study was planned to evaluate the diagnostic value of nasal smear as a simple, non-invasive and inexpensive method for diagnosing allergic rhinitis and used as a simple tool for comparing cost effectiveness among commonly used oral antihistaminic. Antihistaminic are effective in patients with allergic rhinitis having eosinophilia. When antihistaminic are given continuously

for seven days, Clinical improvement is accompanied by decreases in numbers of effector cells in target organs eosinophil. In this research we explore correlation of eosinophilia and antihistaminic therapy for allergic rhinitis. Our expectation is that a greater understanding of the underlying mechanisms of allergens will identify potential biomarkers that could predict or monitor the response to treatment. The nasal mucosa is the most accessible for the non-invasive study part of the respiratory system. The nasal cytology is a research method evaluating cells located within it, and it is mainly used as an additional test in allergic rhinitis. This method allows to assess the pathophysiological changes occurring in the nasal mucosa and monitor response to applied treatment and thus has both diagnostic and therapeutic values. An extremely precious feature of this research is its non-invasiveness and painlessness as it does not require any anaesthesia, and it is cheap and simple to make.

The aim of this study was to evaluate the cytological picture of nasal mucosa in allergic rhinitis and their correlation with antihistaminic treatment. In addition, the objective was also to determine the suitability of the nasal mucosa for the diagnosis of allergic rhinitis and assessment of cost effectiveness of antihistaminic in allergic rhinitis patients.

METHODS

The study enrolled a total of 52 allergic rhinitis patients. All patients enrolled in the study were patients of the Department of otorhinolaryngology, MIMER medical college, Talegaon Dabhade. The study was approved by the Institutional Ethical Committee (IEC). In order to ensure better reliability of the results, only patients clinically diagnosed with allergic rhinitis were eligible on the basis of nasal congestion score. They are divided into four different groups as per antihistaminic treatment.

- Group I consisted of a total of 13 patients, including 6 male and 7 females who received Ceterizine.
- Group II consisted of a total of 13 patients, including 4 male and 9 females who received Levoceterizine.
- Group III consisted of a total of 13 patients, including 7 male and 6 females who received Loratidine.
- Group IV consisted of a total of 13 patients, including 10 male and 3 females who received fexofenadine.

Exclusion criteria for patients in all groups, participating in the study were current respiratory tract infection, Patients with history of hypersensitivity to antihistaminics. Concomitant medication that could affect the efficacy of study drugs. chronic use of inhaled or systemic corticosteroids, Pregnant or lactating women, usage of nasal corticosteroids within 14 days, usage of antihistamines within 14 days preceding the survey. Each test was preceded by obtaining informed consent from the patient, In the case of the examination in the nasal cavity of the secretions, the sample was taken after purging the nose. In each patient, the material for cytological

examination has been collected from the middle third of the inferior turbinate. The samples were taken from one nasal cavity with nasal scraping method (using a nasal curette) and then transferred to a microscopic slide. The samples were spread onto a slide glass, air-dried, fixed, and stained with Haematoxylin and Eosin stain (Merck Limited). The samples were then evaluated for the presence or absence of eosinophil by examining 45x magnification high power fields (HPFs) with Nikon Eclipse 50 I Pentahead microscope (Nikon Corporation, Japan).⁴ The analysis was based on identifying in successive fields of the presence of particular cell types: ciliated and non-ciliated columnar cells, mucous (goblet) cells, basal, and squamous cells, neutrophils and eosinophils. No adverse effects were observed in any patient which could result from the research itself.

Efficacy variable

- Mean change in % of eosinophil in nasal smear from Baseline to End of treatment.
- Cost effectiveness analysis.⁵⁻⁷

Statistical analysis was performed using the statistical software Microsoft SPSS 19.0. (SPSS Inc., Chicago, USA). Data was summarized using Mean, Median and Standard Deviation. Mean change in Nasal smear for eosinophil before and after treatment were done. Statistical differences were considered statistically significant for which the level of statistical significance fulfilled the condition of $p < 0.05$. Logistic regression analysis and odds ratio were used for analysis of qualitative data. The statistician was blinded to the groups during analysis.

RESULTS

A total of 52 patients 13 in each groups of the age group 18 to 65 years (Mean age, 33.73 ± 10.23 years); 48.08% are Female and 51.92% are Male were randomized and received either Cetirizine, Levocetirizine, Loratidine, or Fexofenadine over a period of one week. Mean compliance with treatment was 100% for all four treatment groups. The baseline demographic data and clinical characteristics of all 52 patients participated in this study have been compared in the Table 1. The association of eosinophil before and after the treatment was obtained using logistic regression analysis for each treatment separately in the Table 2. Eosinophil is marginally associated with Cetirizine before and after treatment and has been have been compared in the Figure 1 and Figure 2.

Average cost-effectiveness calculations

The average cost effectiveness = Net Cost (Rupees ₹) / Net Health Benefit = ₹ / % Mean change in nasal smear eosinophil

The average cost effectiveness of intervention for Cetirizine = Net Cost/ Net Health Benefit = ₹26.25 / 0.4= ₹ 65.625 per cure

Table 1: Comparison of demographic data and clinical characteristics of the patients participated in the study (n=52).

| Parameters | Cetirizine n=13 | Levocetirizine n=13 | Loratadine n=13 | Fexofenadine n=13 | F | p* |
|-------------|--------------------|------------------------|--------------------|----------------------|-------|-------|
| Age (years) | 31.85±9.45 | 39.38±14.39 | 32±1.011 | 31.69±7.22 | 1.858 | 0.149 |
| Sex | | | | | | |
| Male (%) | 6 (46.16%) | 4 (30.77%) | 7 (53.84%) | 10 (76.92%) | | |
| Female (%) | 7 (53.84%) | 9 (69.23%) | 6 (46.16%) | 3 (23.08%) | | |
| NCS | 4.46 ± 0.66 | 3.87 ± 0.68 | 4 ± 0.82 | 4.15 ± 0.55 | 1.905 | 0.141 |

The values are expressed as mean±SD, NCS = Nasal congestion score, *one way ANOVA

Table 2: Comparison of Eosinophil in Nasal secretion smear baseline and at the end of each treatment.

| Groups(n=13) | Baseline | End of treatment | | Total | Odds | p |
|----------------|----------|------------------|---------|-------|------|--------|
| | | Absent | Present | | | |
| Cetirizine | Absent | 7 | 2 | 9 | 10.5 | 0.094* |
| | Present | 1 | 3 | 4 | | |
| Total | | 8 | 5 | 13 | | |
| Levocetirizine | Absent | 5 | 2 | 7 | 2.5 | 0.433 |
| | Present | 3 | 3 | 6 | | |
| Total | | 8 | 5 | 13 | | |
| Loratadine | Absent | 5 | 3 | 8 | 6.67 | 0.155 |
| | Present | 1 | 4 | 5 | | |
| Total | | 6 | 7 | 13 | | |
| Fexofenadine | Absent | 2 | 4 | 6 | 5.79 | 0.237 |
| | Present | 2 | 5 | 7 | | |
| Total | | 4 | 9 | 13 | | |

n=13 patient

The association of eosinophil before and after the treatment was obtained using logistic regression analysis for each treatment separately. Eosinophil is marginally associated with Cetirizine before and after treatment.

Table 3: Pharmacoeconomic assessments (cost effectiveness analysis).

| Methods | Cetirizine | Levocetirizine | Loratidine | Fexofenadine |
|--|--|--------------------|--------------------|---------------------|
| Method 1 Cost consequence Analysis (CCA) | Net Cost (at the end of 1 week treatment) | | | |
| | ₹ 26.25 | ₹ 29.46 | ₹ 39.84 | ₹ 75.58 |
| | Net health benefit (% Mean change in nasal smear eosinophil) | | | |
| | 40 | 40 | 42.85 | 44.45 |
| Method 2 | | | | |
| Average Cost | ₹ 26.25 / 0.4 | ₹29.46 / 0.4 | ₹39.84 / 0.4285 | ₹75.58 / 0.4445 |
| Effectiveness Ratios (net cost/ net health benefit) | = ₹ 65.625 per cure | = ₹ 73.65 per cure | = ₹ 92.97 per cure | = ₹ 170.03 per cure |

Using this same means of calculation, the average cost effectiveness for intervention has been done for other treatment groups. The average cost effectiveness of intervention for Levocetirizine was ₹ 73.65 per cure, Loratadine was ₹ 92.97 per cure and for Fexofenadine was ₹ 170.03 per cure (Table 3).

Cost effectiveness analysis

In Noncompeting choice, Cetirizine should be covered first because it has the best (lowest) cost-effectiveness ratio compared to the other interventions (i.e. ₹ 65.625 / %

effect vs ₹ 73.65 / % effect or ₹ 92.97 / % effect or ₹170.03 / % effect). This would be a more efficient way of spending money rather than starting with one of the other interventions that has a higher average cost-effectiveness ratio without any additional benefit (Table 3).

In competing choice method of cost-effectiveness analysis the incremental cost-effectiveness ratio has been done. This would allow to determine the marginal or incremental cost for an additional unit of health benefit when choosing between different interventions. But in this study there were no any additional health benefit by choosing other

antihistaminics vs cetirizine so incremental cost-effectiveness ratio has not been done.⁷

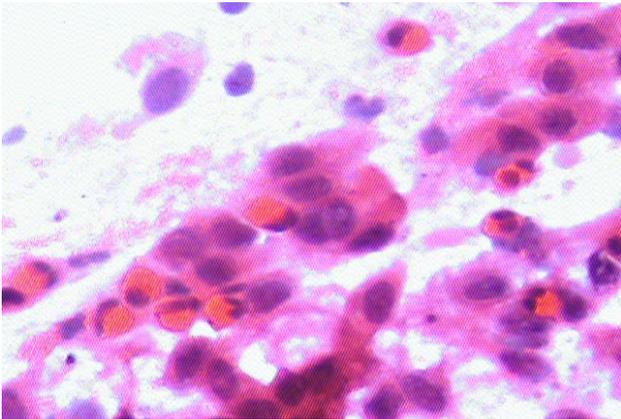


Figure 1: Microphotograph of nasal smear at baseline of an AR patient (ABT13, FL308/13) receiving Cetirizine, showing clumps of mucosal epithelial cells along with eosinophils (H and E 40X).

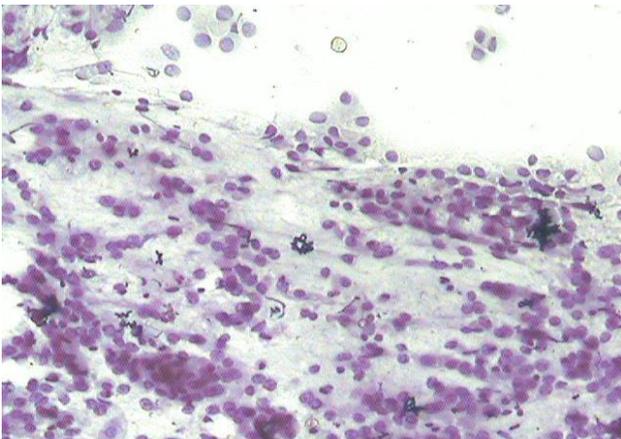


Figure 2: Microphotograph of nasal smear at the end of treatment of an AR patient (AAT13, FL326/13) receiving Cetirizine, showing clumps of mucosal epithelial cells, no eosinophil seen (H and E 10X).

DISCUSSION

The demographic characteristics of the study participants and the baseline symptom scores i.e. Nasal Congestion Score prior to dosing were comparable among the four treatment groups (Table 1). Rhinitis is a heterogeneous disorder characterized by one or more of the following nasal symptoms: sneezing, itching, rhinorrhea, and/or nasal congestion. Studies reflect a more accurate prevalence of rhinitis but are likely to continue to underreport this disease.^{8,9} Approximately 50% of all cases of rhinitis are caused by an IgE mediated reaction to allergens. In this case symptoms arise as a result of local inflammation induced by aeroallergens such as pollens, molds, animal dander and house dust mites. The immune response involves the release of inflammatory mediators and the activation and recruitment of different

inflammatory cells to the nasal mucosa.¹⁰ Infiltration of inflammatory cells is evident in both seasonal and perennial form, although the magnitude of these cellular changes is somehow different in seasonal and perennial allergic rhinitis.¹¹ Although the type of infiltrating cells and pattern of inflammation is varied among different studies but generally accepted, allergic rhinitis (AR) is characterized the recruitment of eosinophils into the nasal mucous. Increased numbers of eosinophils are reported within nasal lavage,^{12,13} secretions, smear, brush and biopsy samples in perennial AR compared with healthy nasal mucous. Nasal cytological examination for these cells not only establishes the diagnosis of allergic rhinitis but is also useful in the follow up of patients and evaluation the efficacy of treatment.¹⁴ In general, numbers of eosinophils tend to be lower in perennial disease, in contrast to seasonal disease and depends on the level of seasonal allergen exposure.^{15,16} Allergic rhinitis is considered to be male predominant diseases, in this study there was a mild predominance for males. Although the onset of allergic rhinitis can occur at any time of life, 70% of these develop it before 30 years of age and in this study mean age were years 33.73 ± 10.23 years of age. In spite of new techniques for allergic rhinitis diagnosis, still nasal smear specifically for eosinophilia has some role either in diagnosis or treatment evaluation.^{17,18} The diagnosis of allergy in allergic rhinitis, is a difficult challenge and requires careful and broad analysis. This is due to both the diversity of the symptoms of the disease and absence of specific and reliable laboratory tests. Despite the fact that nasal cytology is a simple, non-invasive, repetitive, and cheap method, its use in medicine is relatively rare. Cytological examination of nasal mucosa has a long history. Most of the research papers had paid attention to the presence of eosinophils and their relation to the allergy, and the first of them had been conducted more than a century ago by Gollash in patients with asthma.¹⁹ Then, in the twentieth century, Eyer mann has proven the presence of eosinophils in 72% out of 92 patients with rhinitis.²⁰ Malmberg and Holopainen demonstrated the correlation between nasal eosinophilia and allergic rhinitis.²¹ Relationship between allergic rhinitis and nasal eosinophilia has been also studied by Kajosaari and Saarinen. In this survey, a group of 178 patients with allergic rhinitis was observed; the presence of eosinophils and mast cells in cytograms obtained from the nasal mucosa (using nasal smear taken by wiping the mucosa with a cotton-tipped applicator) was an important indicator of allergic rhinitis, characterized by a high specificity but a low sensitivity.²² Nowacki et al, analyzed the usefulness of cytology of the nasal mucosa in predicting the occurrence of allergic rhinitis. It has been shown that eosinophilia in nasal cytology, of at least 8%, was associated with a high risk of developing AR. Therefore, it has been proposed that the increased nasal eosinophilia can be taken as an indicator of the risk of allergic march. The average percentage of eosinophils at baseline was significantly higher in allergic rhinitis patients.²³ The present study has determined the correlation of allergic rhinitis with the degree of eosinophilia. As a positive test,

A smear was considered positive for eosinophilia with at least more than five eosinophils in each high power field of microscopic slide. By analyzing individual studies evaluating the problem of eosinophilia in the cytological picture, one can see the differences in the very definition of the term “significant eosinophilia.” This range is wide and it is ranging from 4% of all cells in Miller et al, Vaidya et al, found eosinophilia in at least 5% of these cells in the cytogram.^{24,25}

A similar analysis was made by Miller et al, however assuming 4% as a criterion for eosinophilia. In their work, the sensitivity of the study in allergic rhinitis was 70%, with a specificity of 94%.²⁴ In the Bakhshae et al, study, eosinophilia diagnosis was assessed as a highly specific (88.5%) but less sensitive (51.3%) in the cytological examination of the nasal mucosa in patients with AR, with eosinophil counts of at least 10% number of cells in the smear.¹

CONCLUSION

Based on the results of the study, the presence of eosinophil in nasal cytology is a good indicator of the likelihood of allergic rhinitis and in combination with other diagnostic tests leading to proper diagnosis. Nasal cytology with eosinophilia assessment can be a useful tool for early diagnosis of allergic rhinitis patients. Nasal cytology with allergic rhinitis is a helpful diagnostic test, usefulness of nasal cytology is limited due to the low sensitivity of the method and this inexpensive tool can be used for cost effective analysis of different drugs used commonly for the treatment of allergic rhinitis. It is worth emphasizing that until now, there have not been established any standards for testing and analysis of samples and that there is no consensus defining the value of “significant eosinophilia” in the nasal cytology.

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