Original Research Article

Effect of Treatment of Allergic Rhinitis on Bronchial Asthma and vice versa Using Combination of Drug Therapy

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Received: 06-11-2021 / Revised: 28-11-2021 / Accepted: 26-12-2021

Abstract

Introduction: Allergic rhinitis and bronchial asthma are considered to be sequential forms of the same allergic syndrome. However, treating inflammation associated with rhinitis shows some improvement in asthma or vice versa is still debatable. **Aim:** To study the effect of treatment of Allergic Rhinitis on Bronchial Asthma and vice versa using combination of drug therapy. **Materials and Methods:** Patients having symptoms of both allergic rhinitis and bronchial asthma were selected and divided in two groups of 50 each. Group 1 consisted of patients in which nasal symptom preceded pulmonary symptoms. Group 2 consisted of patients in which pulmonary symptoms preceded nasal symptoms. All patients of group 1 were treated with a combination of intranasal fluticasone and fexofenadine and response on asthma symptoms were assessed after 12 weeks using pulmonary function test (PFT) and asthma control test (ACT). All patients of group 2 received a combination of inhaled budesonide and salbutamol/formeterol and response on allergic rhinitis symptoms were assessed after 12 weeks using Total nasal symptom score (TNSS) and Visual Analogue Score (VAS). **Observations and Results:** The mean age of the patients were 24.5±1.54 years, 61 males and 39 females. In group 1 patients, after 12 weeks the mean value of FEV1/FVC increased from 63.44 to 68.056 and mean ACT score increased from 16.67 to 19.78 (both p value <0.05). In group 2, the mean value of TNSS decreased from 8.818 to 2.9 and the mean VAS score of all symptoms decreased post treatment (both p value <0.05). **Conclusion:** Thus in our study we found that both the diseases were closely linked therapeutically pointing towards the need of combined approach in management of both the diseases.

Keywords: Allergic Rhinitis, Bronchial Asthma, Combined Airway Disease, Intranasal Corticosteroid.

Introduction

Allergic rhinitis is a commonly associated comorbid condition with bronchial asthma. The connection between the upper and lower airway diseases has become a topic of great interest in the last few years. It is established that nasal allergy and asthma frequently occur together, with approximately 20–50% of allergic rhinitis patients having concomitant asthma and upwards of 80% of asthmatics having chronic nasal symptoms. However, whether nasal disease precedes pulmonary disease or vice versa, it is still not clear.

Several studies have been done in past to study the therapeutic relationship between both the diseases. Topical Glucocorticosteroids are the most effective drugs when used in the nose and the bronchi for the treatment of rhinitis and asthma respectively. The intranasal treatment of allergic rhinitis using glucocorticosteroids was found to improve asthma symptoms in most of the studies. Drugs administered by the oral route may have an effect on both nasal and bronchial symptoms. Oral H_1-antihistamines represent the first-line treatment in allergic rhinitis and although some studies have found a modest effect on asthma symptoms, these drugs are not recommended for the treatment of asthma[1].

The combination of oral H_1-antihistamines and decongestants was found to be more effective on asthma symptoms[2]. However, only few studies have investigated the effect of treating allergic rhinitis on asthma and vice versa using combination of two drugs. Also, there are relatively less studies about the effects on nasal disease by treatment with inhaled glucocorticosteroids and SABA/LABA in asthma.

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Materials And Methods

This was a prospective study and was carried out in a tertiary care centre from October 2017 to March 2020. A total of 100 patients attending the outpatient department and indoor patients with symptoms of both allergic rhinitis (nasal symptoms) and bronchial asthma (pulmonary symptoms) were included in this study, after taking proper written consent.

Diagnosis of allergic rhinitis was made according to recent ARIA guidelines and of Bronchial asthma according to recent GINA guidelines. The patients who were selected for the study were evaluated with proper history and detailed examination. Proper ethical clearance was obtained from the institutional ethical committee.

Inclusion Criteria

- Age >11 years
- Patients having both nasal (allergic rhinitis) and pulmonary (asthma) symptoms.

Exclusion Criteria

- Patient having symptoms of only allergic rhinitis or only bronchial asthma
- Patient of systemic illnesses such as heart diseases, uncontrolled diabetes and hypertension.

They were divided into two groups according to the history of symptoms.

Group 1: It consisted of patients in which nasal symptoms (allergic rhinitis) preceded pulmonary symptoms (bronchial asthma).

Group 2: It consisted of patients in which pulmonary symptoms (bronchial asthma) preceded nasal symptoms (allergic rhinitis).

All the patients of group 1 were treated with intranasal corticosteroids (fluticasone propionate) and oral antihistamine (fexofenadine) according to ARIA guidelines and response of treatment on asthma symptoms were assessed using spirometry (Pulmonary Function Test) and Asthma Control Test (ACT).

All the patients of group 2 were treated with inhaled corticosteroids (budesonide) and Short Acting Beta Agonists (SABA) / Long-Acting Beta Agonists (LABA) (salbutamol/formeterol) according to GINA guidelines and response on allergic rhinitis symptoms were assessed using Total nasal symptom score (TNSS) and Visual Analogue Score (VAS).

Asthma Control Test (ACT)

Asthma control test is a type of questionnaire-description score used to access the level of asthma control. It is self-administered tool by the patient. It consists of 5 questions with 4-week recall (on symptoms and daily functioning). Scaling is done on a 5-point scale (for symptoms and activities: 1 = all the time to 5 = not at all; for asthma control rating: 1 = not controlled at all to 5 = completely controlled)

The scores range from 5 (poor control of asthma) to 25 (complete control of asthma), with higher scores reflecting greater asthma control. An ACT score >19 indicates well-controlled asthma. ACT assesses the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily life, and overall self-assessment of asthma control.

Total Nasal Symptom Score (TNSS)

It is a type of subjective score. Patient day to day diaries were used to record TNSS by evaluating symptom severity over the 12 hours prior to the recording of the score. Calculated as the sum of 4 nasal symptoms: rhinorrhea, nasal itching, nasal congestion, and sneezing, each of which was rated on a scale of 0 (no signs/symptoms evident) to 3 (signs/symptoms causing significant discomfort that interfered with daily activities)

The primary endpoint was the change from baseline in the mean value of patient- reported TNSS averaged over the 15 days and 1 month treatment period for 3 months

Symptoms score definitions-

Score Grade Guidelines

0- None No sign/symptom is evident

1- Mild Sign/symptom clearly present, but minimal awareness; can be easily tolerated.

2- Moderate definite awareness of sign/symptom that can be bothersome, but tolerable.

3- Severe Sign/symptom that is hard to tolerate causes interference with activities during the challenge session

Visual Analogue Score (VAS)

A Visual Analogue Score (VAS) is a type of measurement instrument (10 cm long) that tries to measure a Characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured.

Scores on the VAS ranges from 0 (absence of symptoms) to 10 (very severe symptoms). The VAS score might become a very simple and precise measurement that could be a primary outcome in clinical trials, as well as an important measurement in clinical practice.

The characteristic curve results showed that patients with a VAS of under 5 cm could be classified as mild rhinitis (negative predictive value: 93.5%) and those with a VAS of over 6 cm as moderate/severe rhinitis (positive predictive value: 73.6%). Visual analog scale were significantly correlated ($P < 0.0001$).

Observations And Results

Sex distribution- The total no of males was 61 and females 39. Group 1 consisted of 27 males and 23 females. Group 2 consisted of 34 males and 16 females as shown in table 1.

Age wise distribution- The youngest patient included in the study was of 12 years and the eldest patient was of 60 years, with a mean age of 24.5±1.54 years. The maximum number of patients in group 1 were between 21-30 years (40%) and in group 2 between 11-20 years (38%) as depicted in table 2.

Chi square test was applied to the above data and it was found that the groups were not significantly different in terms of age and sex distribution of the patients.

Effect of treatment of allergic rhinitis on bronchial asthma

PFT – FEV1/FVC value of most patients improved during monthly follow up for 12 weeks. One patient however showed worsening of asthma symptoms. The mean value of FEV1/FVC increased from pretreatment value of 63.44 to 68.056, as shown in figure1.

Kolmogorov-Smirnov (KS) test was applied to compare the pretreatment and post treatment mean scores and it was found to be statistically significant (p value <0.05) (h=1, p=0.039 from KS-test).

Asthma control test-ACT questionnaire were given to all group 1 patients and follow up was done upto 12 weeks.

The mean ACT score increased from pretreatment score of 16.67 to 19.78 after 12 week (figure 2). However, one patient showed decrease in score.

Kolmogorov-Smirnov (KS) test was applied to compare the pretreatment and post treatment mean scores for 3 months and it was found to be statistically significant. (p value <0.05) (h=1, p=0.00006 from KS-test).

Effect of treatment of bronchial asthma on allergic rhinitis

Total nasal symptom score-TNSS questionnaire was given to all patients and were assessed from pre to post 12 weeks of treatment. The mean value of TNSS decreased from 8.818 to 2.939, as shown in figure 3.

Table 1: Group wise sex distribution.

SEX	GROUP 1		GROUP 2	
	No of Patients	Percentage	No of Patients	Percentage
MALE	27	54%	34	68%
FEMALE	23	46%	16	32%
TOTAL	50	100%	50	100%

Table 2: Age wise distribution of group 1 and group 2 patients.

AGE	GROUP 1		GROUP2	
	No of Patients	Percentage	No of Patients	Percentage
11-20	15	30%	19	38%
21-30	20	40%	15	30%
31-40	10	20%	7	14%
41-50	4	8%	6	12%
>50	1	2%	3	6%
TOTAL	50	100%	50	100%

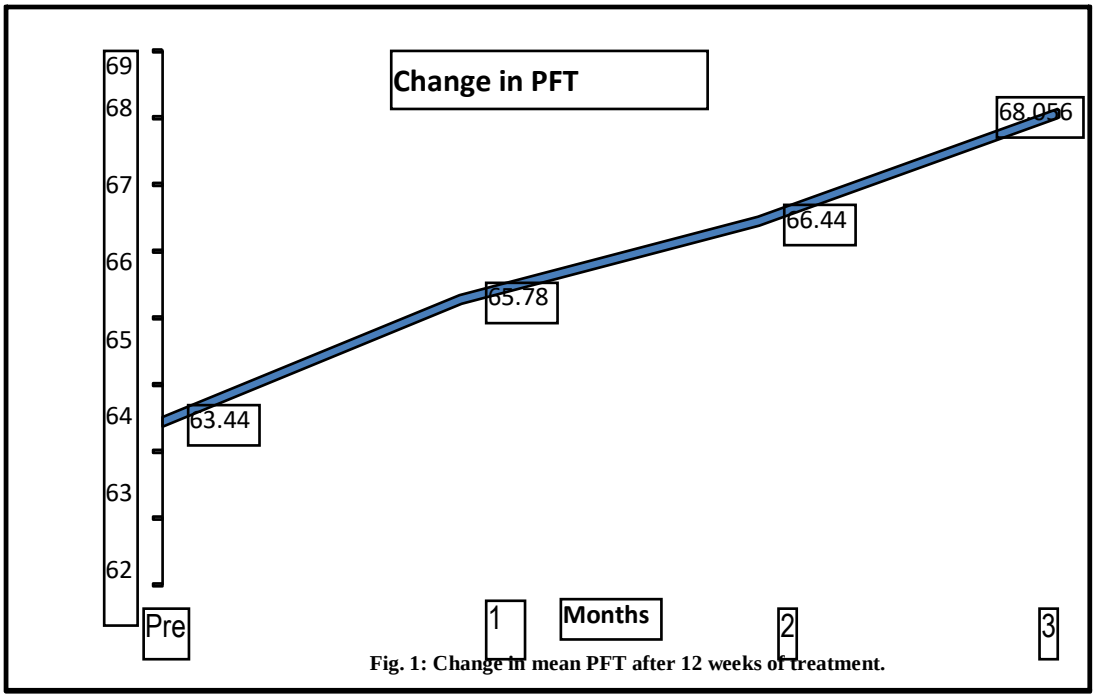

Fig. 1: Change in mean PFT after 12 weeks of treatment.

Table 3: Mean values of FEV1/FVC (PFT) and their standard deviation(SD) at the start and end of 4,8 and 12 weeks of treatment.

Mean PFT	Pre	4 weeks	8 weeks	12 weeks
	63.44444	65.7778	66.44444	68.05556
S.D.	3.17647	4.932552	5.564829	6.530221

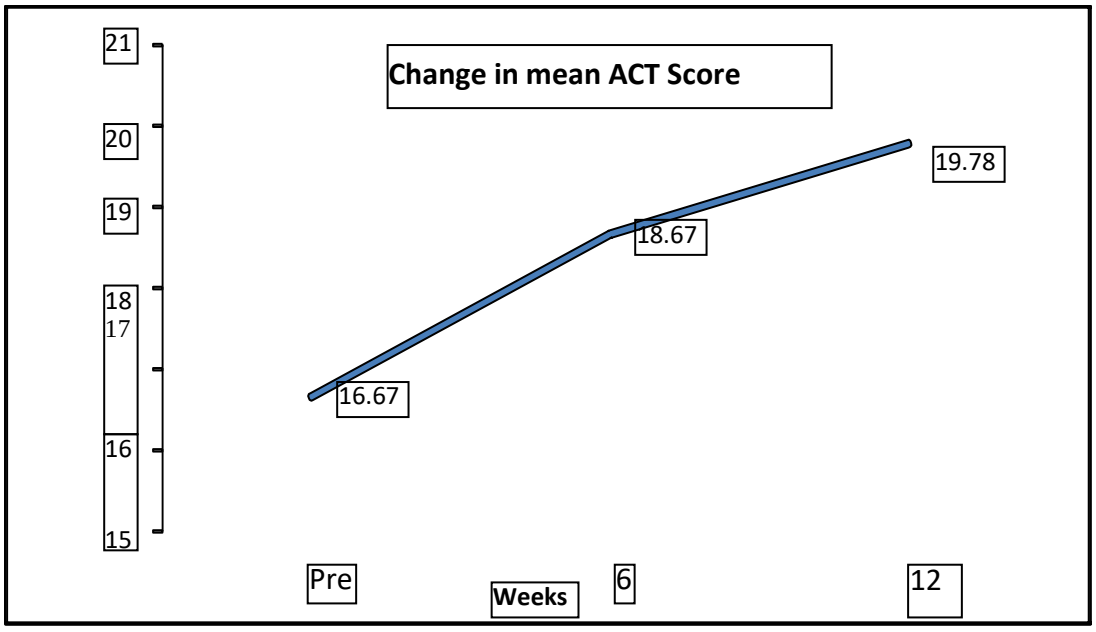

Fig. 2.: Change in mean ACT score after 6 and 12 weeks of treatment

Table 4: Mean ACT score and their standard deviation (SD) at the start and at the end of 6 and 12 weeks of treatment.

	Pre t/t	6-week	12-week
Mean ACT	16.66667	18.66667	19.77778

S.D	1.137593	1.782266	2.073802

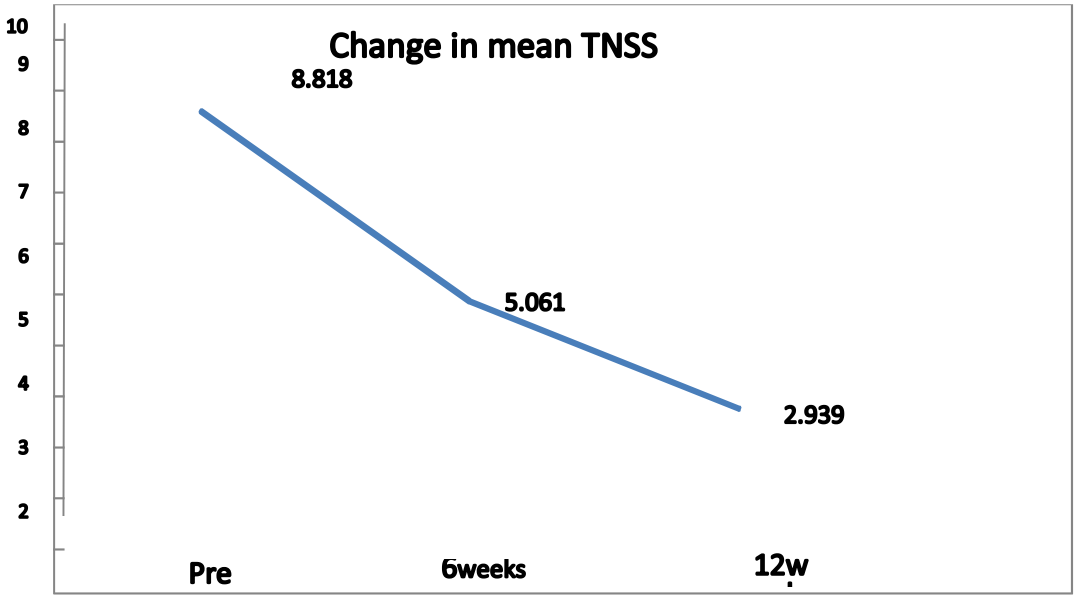

Fig. 3: Change in mean TNSS after 6 and 12 weeks of treatment

Table 5: Mean TNSS and their standard deviation (SD) at start and the end of 6 and 12 weeks of treatment.

	Pre	6-week	12-week
Mean TNSS	**8.818**	**5.061**	**2.939**
S.D.	**0.727**	**1.142**	**1.349**

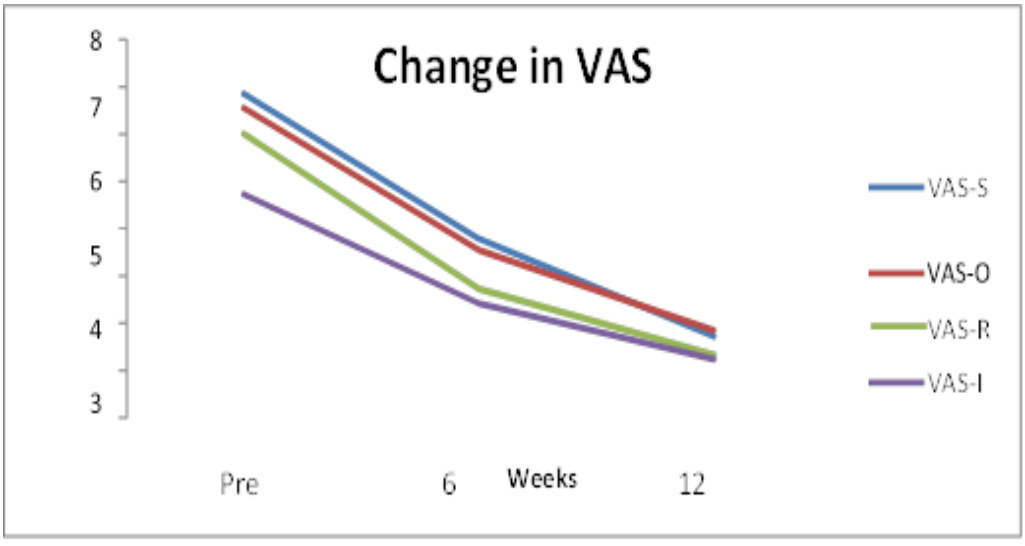

Fig. 4: Change in mean VAS (all four symptoms) after 6 and 12 weeks of treatment

Table 6: Mean VAS score (all four symptoms) and their standard deviation (SD) at the start and the end of 6 and 12 weeks of treatment.

VAS	VAS-Sneezing			VAS-nasal obstruction			VAS-Rhinorrea			VAS-Nasal itching		
	Pre	6-week	12 wk	Pre	6 week	12 Wk	Pre	6 Week	12 Wk	Pre	6 Week	12 Wk
Mean	**6.84**	**3.78**	**1.72**	**6.54**	**3.54**	**1.84**	**6**	**2.73**	**1.33**	**4.72**	**2.42**	**1.24**
S.D.	**0.74**	**0.76**	**0.66**	**0.78**	**0.6**	**0.56**	**0.65**	**0.51**	**0.47**	**0.66**	**0.55**	**0.42**

Discussion

Recently a meta-analysis done by Lohia R et al[9] identified a total of 23 trials assessing the efficacy of intranasal corticosteroids medications in patients with allergic rhinitis and asthma. Of the 23 trials, adequate data Allergic rhinitis and Bronchial asthma are a common health problem accounting for a large number of cases in otorhinolaryngology OPDs. Many different studies have been done to study the relationship of both diseases in terms of clinical and pathophysiological and therapeutic aspects.

Allergic rhinitis and bronchial asthma frequently exist in same patient. Yawn. BP and Yunginger JW et al[3] found that bronchial asthma was found to be present in 20-40 % of patients of allergic rhinitis. Coren J et al[4] found that approx. 80% of bronchial asthma patients had nasal symptoms also. In another study done by Sawako Masuda et al[5] in children they found that persistent nasal symptoms were present in 83.8% of the asthmatic children.

The high coincidence of both the diseases can be explained by various anatomical physiological and pathological basis. The respiratory tract can be considered as a single morpho-functional unit. It is entirely covered until the smaller bronchi, by ciliated epithelium and mucinous glands and an extensive vasculature and innervation (similar innervation in the upper and lower airways[6].

Responsiveness Of Treatment Of One Disease To Another

In our study we found that treatment of one disease had significant impact on other disease. Patients of allergic rhinitis also having bronchial asthma were treated with intranasal corticosteroid and antihistamine and response of it was seen on asthma symptoms by doing PFT and Asthma control test. Patient of bronchial asthma also having allergic rhinitis were treated with inhaled corticosteroid and SABA/LABA and response of it was seen on allergic rhinitis symptoms by doing TNSS and VAS. We checked the difference in indices with time using two-sample Kolmogorov-Smirnov (KS) test at 5% significance level using MATLAB Toolbox. Pretreatment score and post treatment mean scores were seen at 6 weeks and at 12 weeks. Mean value of FEV1/FVC and Asthma control test scores significantly increased from pretreatment score to post treatment score in 12 weeks period in patients of group 1. Mean TNSS and mean VAS score (for all four symptoms) decreased significantly from pretreatment to post treatment score for 12 weeks period in patients of group 2.

Several other studies with similar results have been done in the past to see the treatment response of one disease to other.

Rafael Stelmach et al[7] in their study compared nasal and pulmonary symptoms, as well as pulmonary function and bronchial hyper reactivity after 4 weeks and 16 weeks of treatment in patients receiving inhaled corticosteroid versus those taking placebo. Patients taking corticosteroid demonstrated a progressive and significant decrease in nasal and pulmonary symptoms, which started after 4 weeks ($p < 0.05$) and continued through the end of treatment ($p < 0.001$). Asthma-related morbidity, evaluated by quantifying absence from routine work, hospital emergency visits, and nighttime awakenings, also decreased in the three groups ($p < 0.05$).

Wade T. A et al[8] in their study found that Intranasal topical corticosteroids significantly reduced global rhinitis symptom scores in all patients ($p = 0.05$). Rhinitis symptom scores of the patients were 3.1±0.3 at baseline. After intranasal beclomethasone administration, rhinitis symptom scores decreased to 1.72 ± 0.2.

Recently a meta-analysis done by Lohia R et al[9] identified a total of 23 trials assessing the efficacy of intranasal corticosteroids medications in patients with allergic rhinitis and asthma. Of the 23 trials, adequate data for analysis were retrieved for analysis were retrieved for 18 studies, including 14 parallel and four cross over randomized, placebo-controlled trials. Studies included a total of 2162 patients, of which 1659 completed the full study and 503 patients did not turn for follow up. Three of the18 studies contributed the largest population of participants: 509 patients from Nathan et al,366 patients from Katial et al. and 236 patients from Dahl et al. The remaining trials enrolled lesser numbers of patients ranging from 16 to 90.

They concluded that Intranasal corticosteroid medications significantly improve some asthma specific outcome measures in patients suffering from both AR and asthma. This effect was most prominent with intranasal corticosteroid sprays when patients were not on daily orally inhaled corticosteroids, or when corticosteroid medications were inhaled through the nose into the lungs. Further research is needed to clarify the role of intranasal corticosteroid sprays as asthma therapy, as well as the role of the nasal inhalation technique as a monotherapy in patients suffering from both asthma and AR.

Crystal-Peters et al[10] in studied 4944 patients with allergic asthma symptom, approximately 73% of whom were treated for their allergic rhinitis. Asthma-related symptoms occurred more often for the untreated group compared with the treated group, 6.6% compared with 1.3%. An incidence related density ratio of 0.49 for the treatment group (P =.001) shows that the risk of an asthma-related event for the treated group was about half that for the untreated group.

Although antihistamines are not a primary treatment for asthma, they may have indirect beneficial effects on asthma symptoms, in those patients who have both rhinitis and asthma. In a placebo-controlled study of 186 patients with seasonal allergic rhinitis and seasonal asthma, cetirizine 10 mg was able to reduce significantly asthma symptoms during pollen season[11]. In another study, the administration of combination of loratadine 5 mg+ pseudoephedrine 120 mg twice daily could significantly improve asthma related events, peak expiratory flow and reduce albuterol intake in patients with seasonal allergic rhinitis and mild asthma[2]. One small study [12] suggested that fexofenadine had an additive effect when combined with inhaled corticosteroids as in our study. Overall, beneficial effects observed with this class of drugs are small and may be most important in patients with mild intermittent asthma and concomitant nasal allergy along with the use of inhaled corticosteroids.

Although not extensive, we also observed a reduction in symptoms such as itchy nose, sneezing, and rhinorrhea with the use of inhaled glucocorticosteroids and SABA/LABA. Greiff et al[13] reported similar results with inhaled budesonide. This observation supports the hypothesis of Bucca et al[14] that extra thoracic receptors stimulated by upper airway inflammatory processes trigger both asthma and rhinitis attacks. The coexistence of extra thoracic hyper responsiveness and BHR in patients with rhinitis asthma, and particularly their improvement in both nasal and pulmonary symptoms after treatment, suggests an allergic-based impairment involving all airway[15].

There role of beta agonist in nasal allergy is uncertain. Studies employing allergen challenges have shown an acute reduction in allergen-induced nasal blockage, sneezing and rhinorrea by high intranasal doses of SABA fenoterol, which most likely is the result of dilation of capacitance vessels [16]. Moreover, this drug has also demonstrated an action on mediator release from mast cells and basophils[17,18]. High dose topical terbutaline (1 mg) repeated before each of several challenge doses of allergen led to significant inhibition of symptoms induced only by the highest allergen dose [19]. Another study has shown that oral salbutamol is effective in seasonal pollen induced allergic rhinitis, reducing symptoms, use of antihistamine and the increase in serum IgE that occurred during seasonal rhinitis[20].

Despite the interesting findings obtained with SABAs, studies are available with LABAs are mostly negative. In a randomized double-blind placebo-controlled crossover trial including 12 asymptomatic individuals with a history of seasonal allergic rhinitis, administration of salmeterol intranasal dose (50 µg for 4 weeks) failed to reduce sneezing and total symptoms score[21]. The lack of efficacy of LABAs in allergic rhinitis has also been observed other study using formeterol[22]. Denburg et al[23] demonstrated a overall systemic effect of the allergic response,

irrespective of the initial target organ. The massive presence of eosinophils in the airways of asthmatics individuals seems to be the result of final systemic response to the persistent recruitment of basophils, eosinophils, and progenitor cells from bone marrow. Braunstahl et al[24] demonstrated a bidirectional relationship between nasal and bronchial inflammation. In an initial study, they observed an increase in the number of eosinophils in the nasal and bronchial mucosa 24 h after allergen bronchoprovocation. In a second study[25], an increase in number of eosinophils both in the nasal and bronchial epithelium after nasal provocation was observed, which was positively correlated with increases in vascular cell adhesion molecule, intracellular adhesion molecule and E-selectins in vessels mainly supplying the nasal and bronchial tissue. Given this bidirectional pathophysiology, we can hypothesize that intranasal corticosteroid may act in the lungs, and inhaled corticosteroid may act in the nasal mucosa. Our finding that asthma and rhinitis could be controlled exclusively by intranasal topical medication in some patients is consistent with such a systemic effect of corticosteroid, despite its local application. However, direct anti-inflammatory action on lungs of the intranasal corticosteroid appears very unlikely, as less than 2% of the nasal medication was delivered to the lungs. The total amount of corticosteroid swallowed and absorbed from the gastrointestinal tract would not be high enough to explain the anti-inflammatory effect. Previous studies of asthma treatment with inhaled corticosteroids have shown that the anti-inflammatory effect of therapy was the result of a direct topical effect in the lungs rather than systemic absorption[26].

The probable neuromechanisms may also explain these results. Nasal mucosa stimulation in anesthetized and awake dogs induced a “nasopulmonary reflex” with a secondary increase in pulmonary airway resistance. Topical corticosteroids may interfere with a similar reflex in humans[27].

Conclusion

Thus from our study we can say that the failure to consider treatment of coexisting rhinitis as essential to the management of asthma may impair clinical control of the latter. Despite relatively fewer number of patients in this study, they were followed up in a close manner for almost 12 weeks. When asthma is considered as an exclusively pulmonary disease, the patient may require higher doses of oral corticosteroids and might demonstrate higher morbidity. Conversely, mild to moderate asthma can be controlled by the exclusive use of allergic rhinitis medication. Overall, we can suggest that management of allergic rhinitis should be considered an integral part of treatment for asthma and vice versa.

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Conflict of Interest: Nil Source of support: Nil