Comparative Study of Apo-Cetirizine Single Therapy and Intermittent Sequential Therapy with Cetirizine, Loratadine and Chlorpheniramine in Allergic Rhinitis

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Abstract There are limited numbers of articles, studying combined use of antihistamines. In this study, we compare single therapy of Apo-Cetirizine with a new regimen of intermittent sequential therapy with cetirizine, loratadine and chlorpheniramine in treatment of seasonal allergic rhinitis. This randomized clinical trial was performed between April and September at the peak prevalence of seasonal allergic rhinitis. Fifty-four eligible patients diagnosed clinically to have seasonal allergic rhinitis were randomized in two groups: 24 cases in single therapy arm, received Apo-Cetirizine 10 mg tablet daily and in other arm, 30 patients received sequential regimen of cetirizine 10 mg tablet, loratadine 10 mg tablet and chlorpheniramine 4 mg tablet, one tablet each day. Major Symptom Complex Score (MSCS) and Total Symptom Complex Score (TSCS) of patients were recorded before treatment and after 30 days of treatment in two groups. The average post-treatment MSCS and TSCS in combination therapy group showed better improvement than single therapy group but difference was not statistically significant

(p value = 0.053 and p value = 0.104 respectively). Combination therapy regimen was better in improvement of nasal congestion (p value = 0.006). There were no significant difference between two groups in efficacy, side effects and patient's satisfaction. Combination therapy would be effective on a wide spectrum of symptoms with lower price and theoretically offers lower chance of tolerance and re-appearance of complaints.

Keywords Allergic rhinitis · Antihistamines · Combination therapy · Side effects

Introduction

Allergic rhinitis is a common disease involving many people in Iran and other countries. The reported prevalence is 10–30 % [1–4]. The disease impairs the quality of life [5, 6] and is associated with recurrent sinusitis, otitis media and recurrent respiratory infections. Allergic rhinitis results in high direct (physician's visit and drug cost) and indirect (absence from work) costs [7, 8].

Rhinitis is defined based on the presence of two or more of these nasal symptoms: sneezing, rhinorrhea (anterior or posterior), nasal congestion and itching [9]. Allergic rhinitis is one of rhinitis syndromes characterized by a combination of these symptoms especially sneezing and itching of eyes, nose and palate [10]. IgE molecule has a prominent role in pathogenesis of allergic rhinitis. IgE adheres to especial receptors on the surface of mast cells and basophils. Connection of allergen molecule and IgE on the surface of these cells results in degranulation and release of multiple mediators [11]. Histamine is one of these mediators that causes acute symptoms of allergy. Histamine induces mucosal secretion, vascular dilation, increased

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vascular permeability, tissue edema, itching and sneezing. In some patients, delayed symptoms present 2–6 h after allergen exposure and acute symptoms [12].

Treatment of allergic rhinitis consists of allergen avoidance and medical therapy. Intranasal corticosteroids, systemic or intranasal antihistamines, mast cell stabilizers and drugs active on leukotrienes are in use in the treatment of allergic rhinitis [13].

Evaluation of efficacy of new drugs in the treatment of allergic rhinitis may be performed in two different settings: in a naturalistic environment similar to normal life and condition of patient or in a completely controlled or artificial condition [14].

Oral antihistamines frequently are used as OTC, therefore it is important the physician should be sure the patient receives correct drug in enough dose with minimal side effects.

Antihistamines have been used as single therapy or in combination with intranasal corticosteroids or other oral agents such as decongestants or montelukast in treatment of allergic rhinitis [15–17]. There are a few reports in literature about combined use of antihistamines with each other or especially sequential use of different antihistamines [18]. In this study we evaluate efficacy, side effects and satisfaction of patients and costs of two different antihistamines regimens in treatment of allergic rhinitis. We compare single therapy of antihistamines and a new combined therapy regimen of different antihistamines. We think this new regimen may have lower rates of drug tolerance, unwanted effects and lower cost.

Materials and Methods

This study was performed as a randomized clinical trial and investigator blinded. We evaluated outpatients referred to otolaryngology clinic of National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of medical sciences, Tehran, Iran that complained of nasal symptoms from April 2008 to September 2008 at the peak of the prevalence of seasonal allergic rhinitis. We selected cases of allergic rhinitis based on history and physical examination. Patients were between 16 and 60 years of age and had rhinitis history compatible with seasonal allergic rhinitis at least for 2 years. Presence of two or more of these symptoms at least for 3 weeks was mandatory for diagnosis of allergic rhinitis: sneezing, rhinorrhea, nasal congestion and itching of nose and eyes. Patients at least should have one of two symptoms of sneezing or itching. Exclusion criteria were: present smoking, any significant anatomical abnormality on physical examination as nasal septal deviation obstructing more than 50 % of cross sectional area, polyp,

purulent discharge, history of recurrent epistaxis, history of sinonasal surgery during past 3 months, respiratory infection in past 4 weeks, treatment by intranasal or systemic corticosteroids in past 8 weeks, antihistamines in past 4 weeks, anti-inflammatory drugs in past 2 weeks, systemic or topical decongestants during recent 2 weeks and severe comorbidity such as heart, kidney or liver disease. Breast-feeding, pregnancy or uncertain contraception was additional exclusion criteria in women.

Written informed consent was obtained from eligible patients or parents. Based on a computer generated randomized codes, patients were divided in two groups. In one group, patients received Apo-Cetirizine tablet of APOTEX Company, Canada, 10 mg daily for 30 days. Patients of other group treated with our protocol of a sequential intermittent regimen of Cetirizine-ABIDI 10 mg tablet, Loratadine OSVAH 10 mg tablet and Chlorpheniramine PURSINA 4 mg tablet, one tablet each day, in this order. Dosage of chlorpheniramine that we used in this study was less than its usual dose.

Our study was done in a naturalistic environment. Before treatment, Major Symptom Complex Score (MSCS) and Total Symptom Complex Score (TSCS) of patients were recorded. These parameters were recorded again after treatment. MSCS, a predetermined composite variable, was defined as a sum of the scores of six symptoms: runny nose (average of left and right), sniffles, itchy nose (average of left and right), nose blows, sneezes and watery eyes. The TSCS was composed of the MSC symptoms plus four additional symptoms (itchy eyes/ears, itchy throat, cough and post-nasal drip). Symptoms were rated on a scale ranging from 0 (none = no symptoms whatsoever) to 5 (very severe symptoms = very bothersome and disabling) [19].

Clinician blind to therapeutic regimen performed evaluation of symptoms of patients before and after treatment. Side effects were recorded separately.

We recommended patients to come back in the case of severe or intolerable drug side effects. In this clinical trial, we treated patients with drugs commonly used in allergic rhinitis control, so there was no ethical challenge in performing this study.

Data analyzed by SPSS version 15. Quantitative variables were compared by *T* test and qualitative variables by χ^2 test and $p < 0.05$ considered significant.

Results

Fifty-four patients had clinical criteria of allergic rhinitis to include in this study. They were 29 male and 25 female. Randomly 24 patients treated in single therapy group of Apo-Cetirizine with mean age of 32.4 ± 9.7 years and 30

Table 1 Gender distribution between two treatment groups

Gender	Combination therapy	Apo-Cetirizine	Total	<i>p</i> value
Male	16	13	29	0.993
Female	14	11	25	
	30	24	54	

There was no difference between groups in gender

Table 2 Age distribution between two treatment groups

Age	Combination therapy	Apo-Cetirizine	Total	<i>p</i> value
16–25	7	6	13	0.628
26–35	7	10	17	
36–45	10	6	16	
46–55	5	1	6	
56–60	1	1	2	
	30	24	54	

Age distribution was similar in two treatment groups, without significant difference between them

patients treated in combined therapy group that their mean age was 36.3 ± 12 . There was no significant difference between two groups in gender, age and education level (Tables 1, 2).

The most common symptoms in single therapy group were: PND (21 cases, 87 %), sneezing (21 cases, 87 %), rhinorrhea (20 cases, 83 %) and aural itching (19 cases, 79 %). The most common symptoms in combination therapy group were: PND (26 cases, 92 %), nasal obstruction (24 cases, 85 %), sneezing (22 cases, 78 %).

The average pre-treatment MSCS was 9 ± 4.1 in single therapy group and 8.5 ± 4.1 in combination therapy group. Difference between two groups was not significant (p value = 0.71).

The average pre-treatment TSCS was 30 ± 12.9 in single therapy group with Apo-Cetirizine and 27.7 ± 15.4 in combination therapy group without significant difference between two (p value = 0.501).

The average post-treatment MSCS was 5.08 ± 4.2 in single therapy group. The difference between pre- and post-treatment average of MSCS in this group was significant (p value = 0.036). The average post-treatment MSCS in combination group was 3.21 ± 2.45 , showing significant difference with pre-treatment average (p value = 0.001) (Fig. 1).

The average TSCS after treatment in single and combination therapy groups was 16.75 ± 12.2 and 11.82 ± 9.25 respectively. Difference with pre-treatment values was significant in both groups (p value = 0.03 and p value = 0.019 respectively) (Fig. 2).

Fig. 1 MSCS before and after treatment in two groups. MSCS in both groups decreased significantly after treatment **Fig. 2** TSCS before and after treatment in two groups. TSCS in both groups decreased significantly after treatment

The average post-treatment MSCS in combination therapy group showed better improvement than single therapy group but this difference was not statistically significant (p value = 0.053).

More improvement of the average post-treatment TSCS was seen in combination therapy group but there was not statistically significant difference between two regimens (p value = 0.104).

Fig. 3 Side effects of treatment in two groups. There was no significant difference between groups in frequency of important side effects

Fatigue was the most common side effect of treatment in combination therapy group, we saw in 23 cases or 82.1 % of patients. In single therapy group, 17 cases or 70.8 % of patients complained of this problem. Difference between two groups was insignificant (p value = 0.67). There was also no significant difference between two treatment groups in prevalence of dryness of mouth, dryness of nose and sleepiness (Fig. 3).

In single and combination therapy groups, 13 patients (54.2 %) and 22 patients (78.6 %) respectively were satisfied by their treatment and difference between two regimens was not significant.

Discussion

Currently prevalence of allergic rhinitis is increasing [20, 21]. Choosing correct treatment with minimal side effects still is a challenge for physicians. Besides intranasal corticosteroids, second generation antihistamines have an outstanding role in treatment of allergic rhinitis [22]. They are more effective and have fewer side effects in comparison with first generation antihistamines. Physicians should consider two points in prescribing antihistamines. First, symptoms are not completely similar in all of patients and occurrence and severity of a certain symptom may be different among patients. Second, spectrum of therapeutic and also unwanted effects of antihistamines are different and the physician has a critical role in choosing drug because no H_1 receptor antagonist has important advantage over another [17, 22].

Because of lack of an ideal antihistamine drug covering all symptoms of allergic rhinitis with acceptable side effects, researchers have used these agents in combination with other family of drugs. Combination of these drugs with oral decongestants is an example. Nasal congestion is not completely relieved by most antihistamines so decongestants are suitable candidates for combination therapy [17]. There is also suggestion for combined use of first and second-generation antihistamines for better control of diurnal and nocturnal symptoms [17, 18, 23].

After search of PubMed and MEDLINE databases, we did not find any study similar to our trial of sequential intermittent treatment with first and second-generation antihistamines. We supposed that this regimen would be effective on a wide spectrum of symptoms with lower chance of tolerance, side effects, re-appearance of complaints and lower price. In contrast to usual dose of chlorpheniramine, we prescribed it once a day and sleepiness was not more common in combined therapy group. Because of chronic nature of the disease and dependence of symptoms to drug, patients have to use medications for long times, so economic burden and price of treatment especially in developing countries should be considered. Though tolerance to antihistamines has not been proved, but it may be possible especially in long-term use of these drugs [24]. We think this strategy can lower the chance of probable drug tolerance.

In our study there was no significant difference in efficacy, side effects and patient's satisfaction between single therapy group with Apo-Cetirizine and sequential intermittent combination of cetirizine, loratadine and chlorpheniramine. Price of 1-month course of single Apo-Cetirizine treatment and combination therapy is 60,000 and 8,000 Rials respectively. This difference will be prominent in long-term period. If we imagine a 10 % prevalence of allergic rhinitis in IRAN, nearly 7,000,000 of population may need treatment. On the other hand, constant access to imported drugs may be a problem especially in some areas.

In most studies, antihistamines have had variable effects on nasal congestion and many of them cannot relieve this symptom [17]. In this study, there was no significant difference in nasal congestion prevalence between two arms of therapy before treatment. This was 24 (85 %) in combination group and 18 (75 %) in single therapy group. After 1-month therapy, 15 patients in each group or 53 % of combination treatment and 62.5 % in single therapy still complained of nasal congestion. There was significant difference between groups in nasal congestion (p value = 0.006). So combination therapy was more effective in treating nasal congestion.

Different response of various symptoms of allergic rhinitis to treatment is another interesting issue. In combination treatment group, sneezing and aural fullness showed the best and the worst improvement respectively. In single

therapy group, sneezing and aural itching were more responsive and epiphora and itching of eyes were poor responsive to treatment. So we can conclude every antihistamine regimen is more effective on certain types of symptoms and exclusive recommendation of one drug as the best choice in every case is not correct.

In previous studies, various side effects of antihistamines have been indicated. But nasal dryness, which may have physiological implications, has been forgotten. In this study, 64.3 % of combination therapy group and 62.5 % of patients of single therapy group showed nasal dryness after treatment. There was no significant difference between two groups. This necessitates more research to resolve the problem.

It may seem impractical to use this regimen by patients, but if other studies confirm our results, this problem can be resolved by modification in package of drug to help the patient to receive correct antihistamine in correct day.

Conclusion

Results of our study showed no significant difference between two treatment groups, but because of novelty of combining different types of antihistamines in allergic rhinitis, more studies with more definite diagnostic criteria are required. Though this study with its small sample size, gives a promising prospect in treating seasonal allergic rhinitis with antihistamines.

Conflict of interest Authors declare no conflict of interest.

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