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Comparative study of intranasal corticosteroids and Antihistamine versus effects of monotherapy with intranasal corticosteroids alone in allergic rhinitis

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Introduction

Allergic rhinitis (AR) that affects up to 20% of the population with increasing prevalence is a disease triggered by IgE-dependent chronic allergic inflammation of nasal mucous membranes in response to environmental allergens [1]. Mediators released from immune cells of allergic inflammation including mast cells and eosinophils lead to vasodilatation, hypersecretion and inflammatory edema in nasal mucosa [1,2]. Symptoms include rhinorrhea, sneezing, nasal obstruction and itching due to this inflammation. It leads to significant impairment in quality of life, mental and psychomotor performance compared to the healthy people and also affects school learning performance especially in adolescents [3–5]. The main treatment of AR includes nasal topical corticosteroids [2]. The efficacy of topical nasal corticosteroids depends on compliance, and maximum efficacy is usually apparent after 1–2 weeks [6]. Oral antihistamines, although accepted as standard therapy for AR, have a lesser impact on nasal congestion and inflammation [7,8]. Leukotriene receptor antagonists that were recently introduced in the treatment of allergic rhinitis also have beneficial effects in management. The role of leukotriene receptor antagonist in treating asthma and AR is thought to be related to its impact on the leukotriene pathway of allergic inflammatory cascade [9]. Nasal obstruction secondary to vasodilatation and mucosal inflammatory edema is the major symptom of AR and nasal airway resistance is increased in these patients compared to that in nonallergic patients [1,2]. Nasal airway resistance can be measured using rhinomanometry, but this requires a nonportable equipment and staff. Portable nasal inspiratory peak flow meter (IPFM) was developed and has been shown to correlate with the results of rhinomanometry [10–12]. It has the advantages of simplicity, portability and economy.

Health-related quality of life questionnaires (HRQLQ) can be generic or disease specific. Generic HRQLQ are designed to be used in all disease and measure the burden of illness. Sickness impact profile (SIP) and the SF-36 (medical outcomes survey short form 36) are the well-known examples [13,14]. Disease-specific questionnaires are much more sensitive to important changes in quality of life than the generic instruments

are. In order to overcome this shortcoming, the rhinoconjunctivitis quality of life questionnaire (RQLQ) is frequently used [15].

Aim

This study was to compare the effects of monotherapy with topical steroid and combined therapy with topical steroid plus oral desloratadine or montelukast, on the basis of nasal symptom scores, rhinoconjunctivitis quality of life and nasal inspiratory peak flow in allergic rhinitis patients.

Methods

Ninety-five patients (42 male, 53 female) with seasonal symptoms aged between 15 and 48 years (mean 34 years), who were diagnosed to have pollen-induced intermittent AR (IAR) in the out-patient department, of ENT, Sri Siddhartha medical college and research centre,Tumkur were included in this study between October 2019 and October 2020 . All subjects were sensitive to grass or tree pollen allergens proven by the induration more than 3 mm from saline control in the positive allergen prick test [2]. They have had symptoms of IAR longer than 2 years and no one had had any oral or intranasal antihistamines or topical corticosteroids in the last 8 weeks. Subjects with any other nasal disorders such as nasal polyp, vasomotor rhinitis, septum deviation, etc., lower airway disorders such as asthma, bronchiectasis, COPD, etc., and also systemic disorders such as uncontrolled diabetes, cardiovascular disorders and also those who did not want to participate in the study were not included. Approval of the study was obtained by institutional board review and all the patients gave oral and also written informed consent.

Study design : Subjects were divided into four groups according to the date of the application to our out-patient clinic. This study was a open study and not a randomized study and nor single blind test. Three groups of 25 AR patients assigned to different treatment protocols and one group of 20 AR patients as control. Group-1 received intranasal steroid spray (mometasone furoate 100 mcg for each nostril one per day). Group-2 received a combination of the same dose of intranasal steroid spray and an oral antihistamine (mometasone furoate 200 mcg plus desloratadine 5 mg one morning dose per day). Group-3 received a combination of same dose intranasal steroid spray and a leukotriene receptor antagonist (mometosone furoate 200 mcg plus montelukast, Singulair 10 mg tablet; MSD Co., USA, 10 mg one dose per day). Group-4 was the control group composed of AR patients who received only intranasal serum physiologic spray. All the patients were evaluated at baseline, at the end of the 1st and 2nd weeks and 1st and 3rd months of treatment. Evaluation consisted of total nasal symptom scores, quality of life scores and maximal inspiratory flow rates for all patients.

Skin prick test protocol : Patients were given a skin test conducted by prick method and using 17 prick test solution (Allergopharma Allergy Diagnosis Kit, Germany) containing the most common inhaled allergens including Dermatophagoides, Molds, Animal danders, Tree pollen and Grass pollen. During skin prick tests, physiologic saline was used as the negative control while 10 mg/ml, 1 mg/ml histamine solution was used as positive control. Twenty minutes were allowed for reactions to ensue. An induration more than or equal to 3 mm higher than control was considered as a positive test. Patients that are only sensitive to grasses and/or tree pollens were included in the study.

Nasal symptoms scoring: Patients were instructed to record their daily nasal symptoms including nasal obstruction, nasal discharge, sneezing and itching. Each

symptom was evaluated individually and the total symptom score was calculated as the sum of four nasal symptoms. Symptom were scored as follows: 0 = no symptom; 1 = mild (symptom present but not troublesome); 2 = moderate (symptom is frequently troublesome but does not interfere daily activity or sleep); 3 = severe (symptoms that interfered with daily activity and sleep).

Rhinoconjunctivitis quality of life: Patients were administered the rhinoconjunctivitis quality of life questionnaire (RQLQ), originally developed by Juniper [15]. This questionnaire has 28-item questions related to the symptoms in seven domains (sleep, non-hay fever symptoms, practical problems, nasal problems, eye symptoms, activities and emotional function). Patients are asked to give their responses on a 7-point scale (0 = no impairment, 6 = severe impairment). Overall mean score for all 28 questions was detected. . High score corresponds to low quality of life.

Nasal peak inspiratory flow rate: Peak inspiratory flow rate was measured using an incheck flow meter (Clement Clarke International Ltd., Harlow, UK). Measurements were taken at the same time of day on each evaluation throughout the study. All measurements were done in a sitting position, with a good seal around the facemask and patients inspired forcefully through their nose with mouth-closed. Results of three measurements were recorded as L/min and the highest value was recorded as the patient's final score.

Statistical analysis

Kruskal–Wallis test was used for independent group comparisons and Friedman test was used for dependent group comparisons. Variables were summarized as median S.D. All the analyses were conducted using SPSS 10.0 statistical analysis program for Windows with a 95% confidence interval. p values less than 0.05 were considered significant.

Results

Total nasal symptom score (TNSS): Within the individual group evaluations, total nasal symptom scores decreased significantly at each evaluation when compared to the baseline scores ($p < 0.05$) (Table 1). There was a significant difference between the groups at the 2nd week, and 1st and 3rd month evaluations ($p < 0.05$). All the groups that received treatment showed improvement when compared to the control group. Most significant improvement was first observed in group-2 at the 2nd week. However, at the 1st month evaluation, TNSS of group-3 was significantly lower than that of group-2. Both group-2 and -3 had significantly lower TNSS than that in group-1.

Rhinoconjunctivitis quality of life questionnaire: In the groups that received treatment, quality of life scores improved significantly when compared to the baseline scores ($p < 0.05$) (Table 2). There was a significant difference between the groups was observed at the 1st and 2nd week, 1st and 3rd month ($p < 0.05$). The most significant improvement was first observed in group-2 at the end of 1st week. However, at the 1st month evaluation, QOL score of group-3 was equal to group-2, but significantly lower than group-1.

Nasal inspiratory peak flow rates: No significant difference was observed in IPFR between baseline levels of groups at the beginning of the study ($p > 0.05$) (Table 3). Additionally, differences among the groups were statistically insignificant at repeated evaluations ($p > 0.05$) (Table 3). However, IPFR improved significantly in all groups during the study ($p < 0.05$).

Table 1
Total nasal symptom scores of study and control groups at the given periods

	Group-1	Group-2	Group-3	Group-4	*p* value
TNSS baseline	7.0±2.56	9.0±1.83	9.0±1.78	9.0±2.09	0.245
TNSS 1.weeks	4.0±2.5	4.0±3.02	4.0±2.17	6.0±2.50	0.097
TNSS 2.weeks	4.0±3.37	2.0±3.19	3.0±1.68	4.0±2.69	**0.014***
TNSS 1.months	3.0±3.19	2.0±1.90	1.0±1.28	4.0±2.84	**0.001***
TNSS 3.months	1±1.93	1±1.24	1±1.18	3.5±3.53	**0.011***
p value	**0.000†**	**0.000†**	**0.000†**	**0.000†**	

*Kruskal–Wallis; †Friedman test.
Bold values are statistically significant ($P < 0.05$).

Table 2
Quality of life scores of study and control groups at the given periods

	Group-1	Group-2	Group-3	Group-4	*p* value
QOL baseline	76.0±35.56	93.0±23.89	86.0±29.98	65.5±21.64	0.216
QOL 1.weeks	39.0±27.89	18.0±34.39	35.0±26.91	63.0±21.80	**0.041***
QOL 2.weeks	25.0±36.99	7.0±36.6	19.0±22.57	57.5±25.39	**0.033***
QOL 1.months	15.0±30.53	5.0±29.92	7.0±21.39	50.0±28.87	**0.009***
QOL3. months	3.0±22.49	2.5±12.0	3.0±16.89	42.0±28.93	**0.004***
p value	**0.000†**	**0.000†**	**0.000†**	**0.001†**	

*Kruskal–Wallis; †Friedman test.
Bold values are statistically significant ($P < 0.05$).

Table 3
Nasal inspiratory peak flow rates scores of study and control groups at the given periods

	Group-1	Group-2	Group-3	Group-4	*p* value
IPF baseline	80.0±39.07	70.0±29.47	80.0±35.29	105.0±45.54	0.501
IPFR 1.weeks	110.0±35.24	100.0±40.46	120.0±41.25	110.0±44.98	0.748
IPFR 2.weeks	130.0±38.28	110.0±37.22	120.0±33.51	105.0±47.25	0.526
IPFR 1.months	110.0±36.29	120.0±33.74	120.0±37.16	110.0±45. 81	0.487
IPFR 3.months	110.0±38.58	140.0±36.80	120.0±36.86	105.0±43.47	0.532
p value	**0.000†**	**0.000†**	**0.000†**	0.082	

†Friedman test.
Bold values are statistically significant ($P < 0.05$).

Discussion

Allergic rhinitis, which is the most frequent atopic disease, affects nearly 10–20% of the population in many developed countries [2]. It has considerable social, clinical and economical outcomes and thus treatment has gained great importance. An effective treatment requires treatment of AR and its comorbidities including asthma and sinusitis [16–18]. The most effective treatment modality for allergic rhinitis is intranasal topical corticosteroids. Topical use of corticosteroids is favoured since systemic use is associated with serious adverse effects [19–21]. Maximal effect of topical steroids is observed in 1–2 weeks. Our results showed that when compared on the basis of TNSS, all groups that received treatment had superior symptomatic relief when compared to the control group that received placebo. Furthermore, this improvement was more significant with combination therapy including topical corticosteroid and antihistamine or MSK. The results of our study suggest that combination of topical mometasone furoate with desloratadine or montelukast in AR treatment may be rational. On the contrary, Di Lorenzo et al. and Meltzer et al. found no substantial advantage of combination therapy with topical steroid and oral antihistamines or montelukast compared to monotherapy with topical steroid on the basis of nasal symptom improvement [22,23].

Leukotriene receptor antagonists (montelukast, zafirlukast) are a novel treatment method in allergic asthma [16]. It has been reported that leukotriene receptor antagonists may also be used in the treatment allergic rhinitis [16,17,22,23]. Grossman et al. found that antileukotrienes are effective in treatment of rhinitis, and that LTRA improves the symptoms by 24% over a 4 weeks treatment when compared to placebo [24]. In an effort to potentialize the effect on AR, LTRA have been combined with other treatment agents. Effective relief of nasal symptoms in AR patients with montelukast in combination with loratadine was documented by Meltzer et al. [25]. On the other hand, Nayak et al. reported that, although the combination of montelukast and loratadine provided some additive effects in improving symptom score and quality of life when compared to either agent in monotherapy, the difference did not reach statistical

significance [26]. In the present study, first improvement in TNSS and QQL was seen in group-2, but group-3 was superior to group-2 based on TNNS at the end of 1st month. Due to montelukast reduces nasal inflammation much more than oral antihistamines, combined therapy with montelukast caused a significant decrease in TNSS compared with combined therapy with antihistamines at the end of the 1st month.

Rhinoconjuctivitis quality of life questionnaire has strong measurement outcomes and evaluative and discriminative properties compared to the other questionnaires about AR [27]. Influence of different treatment modalities on RQLQ was investigated in many previous studies [28–30]. It was reported that montelukast and loratadine, either as single or combination therapy had a significant improvement in quality of life when compared to placebo; however these treatment modalities were not different when compared to each other. In our study, monotherapy with intranasal mometasone furoate as well as its combination with desloratadine and montelukast led to a statistically significant improvement in quality of life in AR patients when compared to control group. The first improvement in RQLQ was observed at the end of the 1st week and then continued until the end of study in all treatment groups. Combination therapy (group-2 and -3) was significantly more effective than monotherapy with topical steroid on the basis of RQLQ.

Nasal peak flow rate measurements

It have been shown to correlate with the results of rhinomanometry previously, allow appropriate measurement of nasal airway during therapeutic approaches [7,12,31]. Maximal inspiratory air flow rate measurement can be a convenient method of objective evaluation of therapeutic response in AR patients [32]. Wilson et al. has shown that monotherapy with topical steroids and its combination with montelukast and cetirizine are effective in AR symptoms. They have also reported that symptoms were associated with domiciliary measurements of nasal flow more than the laboratory measurements of nasal function [33]. Similarly, we found that monotherapy with intranasal mometasone furoate or a combination therapy including desloratadine or montelukast leads to a significant difference in nasal inspiratory peak flow rates from baseline in AR patients; however, the differences between the groups that received either one of the treatment modalities was not statistically significant. Combination of montelukast and intranasal mometasone furoate was found to have no superiority to intranasal mometasone furoate monotherapy or to intranasal mometasone furoate plus desloratadine therapy.

Conclusion

There were no statistically significant superiority between the medication groups in respect of IPFR and RQLQ. First significant improvement was seen in group-2 at the end of the 2nd week based on TNSS, but group3 had better results than group-2, therefore faster development in TNNS and RQLQ could be obtained by the combination therapy that includes montelukast or oral antihistamines. We suggest that montelukast may be used in AR patients to reduce nasal symptoms scores and to improve the quality of life.

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