



A Comparative Study of Intranasal Steroids with Intranasal Antihistamines Sprays v/s Intranasal Steroids Sprays Alone in Management of Allergic Rhinitis

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Abstract

Background: Allergic rhinitis is the most common form of rhinitis, worldwide, affecting close to 10% to 30% of the global population. Heredity and environmental exposures may contribute to a predisposition to allergies. Pharmacotherapy along with effective allergen avoidance measures forms the mainstay of management of Allergic Rhinitis. The evidence indicates that intranasal corticosteroids are more efficacious than are antihistamines in the control of Allergic Rhinitis symptoms. This "superiority" is principally related to their effect on nasal obstruction. The numbers of studies done to know the efficacy of combination sprays over steroidal sprays alone are very few and provide insufficient insight.

Objectives: The purpose of this study was to ascertain whether the combination nasal sprays should be prescribed as a standard medical management for allergic rhinitis or not, as to achieve better quality of life after treatment with maximum improvement in Total Nasal Symptom Score (TNSS).

Methods: 100 subjects were taken up for this study, 50 in each group after fulfilling the inclusion and exclusion criteria. Subjects were allocated in two groups according to consultant's preference. Subjects were evaluated for Total Nasal Symptom Score (TNSS) and score of Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) before and after the treatment initiation.

The study was conducted in two groups based on drug given and both the groups were evaluated after 2 weeks and 4 weeks of medication on the basis of TNSS and MiniRQLQ score.

Results: Allergic Rhinitis was found to be more common in younger age group. Both the drugs were effective in reducing the Total nasal symptom scores (TNSS) and score of MiniRQLQ significantly ($p < 0.001$). However, Combination Nasal Sprays (Intra-nasal corticosteroids with intranasal antihistamines) were found to be statistically superior when compared to only intranasal steroid sprays.

Interpretation and Conclusion: Combination Nasal Sprays are highly efficacious and statistically better to steroid nasal sprays hence this study confirms the superiority of combination nasal sprays and recommends combination nasal sprays as first line of treatment for allergic rhinitis.

Keywords: Allergic Rhinitis; Total Nasal Symptom Score; Intranasal Corticosteroids; Intranasal Corticosteroids with Intranasal Histamines; MiniRQLQ; Quality of Life

Introduction

Every organ system in the human body is capable of immunologic response and therefore, is capable of developing allergic dysfunction and clinical disease.

Allergic rhinitis is a clinical hypersensitivity of the nasal mucosa to foreign substances mediated through IgE antibodies. It has a prevalence of between 10% and 20% and affects 20 to 40 million individuals in the United States annually [1-3]. Traditionally, AR is classified as seasonal or perennial and as either mild, moderate, or severe. Mild AR involves no sleep interruption, no impairment of daily activities, and no troublesome symptoms. Moderate-to-severe AR involves one or more of those factors. A newer classification system specifies that AR be characterized as intermittent or persistent. Intermittent disease involves symptoms for fewer than 4 days per week or for a duration of fewer than 4 weeks. Persistent disease involves symptoms that occur more than 4 days per week and are present for longer than 4 weeks [4-11].

Numerous types of drugs are available for this purpose and each has unique characteristics. The physician must tailor the regimen according to the patient symptoms and circumstances. Even today, despite the advances in the understanding of the numerous chemical mediators of allergy, only two major categories of drugs are in common use for the management, namely, Antihistamines and Corticosteroids. Gluco-corticosteroids are currently the most potent medications available for the treatment of AR [12-15]. Intranasal preparations eliminate the systemic side effects and equal or exceed the efficacy of their oral counterparts. Hence, the subject of comparative treatment for AR was chosen to know the efficacy of Combination Nasal Sprays over Steroid Nasal sprays in the treatment of this disease.

Aims and Objectives

- To compare the effectiveness of intranasal corticosteroids alone or with the combination of intranasal antihistamines.
- To compare the improvement in quality of life.

Parameters for fulfillment of objectives

- To compare effectiveness: Improvement in Total Nasal Symptom Score (TNSS) after treatment with intranasal sprays in management of allergic rhinitis.

- To compare the improvement in quality of life: assessment of self-administered Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) after treatment with intranasal sprays in case of allergic rhinitis.

Materials and Methods

Data for the study was collected from the patients in the Department of Otorhinolaryngology at Manipal Hospital, Bangalore, Karnataka. This was a comparative prospective non randomized two groups study which was performed between August 2014 to January 2016. This is a 650 bedded multispecialty hospital comprising of intensive care units, outpatient departments, Adult and pediatric emergency units and Health Check department. Approximately 150-200 patients visit the ENT OPD every day.

Study population

This prospective study was conducted on 100 patients (males and females of 18-45 years of age group) with allergic rhinitis diagnosed clinically attending the ENT out patient clinic. The patients were allocated in to the two study groups based on physician's preference considering the inclusion and exclusion criterion. All cases were taken as per the case proforma prepared for the study.

Prognosis

Assessment was based on the general and local improvement of the patient as per the TNSS and self-administered Mini RQLQ questionnaire asked to the participants.

Sample size

Based on outcome variable for comparative prospective two groups study on outcome variable of Symptom score, with 90% statistical power and 5% level of significance sample size was estimated to be 100, 50 in each group.

Justification of sample size

Considering the alpha error to be 5% and power of study to be 80% using the data from previous study the difference in relative outcome, the sample size was found to be 50 subjects in each group. The sample size was calculated using POWER and SAMPLE SIZE calculator PS Vs 3.1.2.

Study design

A time bound, hospital based, prospective, non-randomized, observational and longitudinal study design with the aim of evaluating treatment response in patients with Allergic Rhinitis in terms of changes in TNSS and MiniRQLQ.

Study duration

August, 2014 to January, 2016.

Methods of measurements of outcome of interest

Patients were evaluated for TNSS and MiniRQLQ before and after the treatment initiation. Two types of drugs were chosen for comparison

Combination nasal sprays (Intranasal steroid with intranasal antihistamine)

The combination nasal sprays consist of azelastine hydrochloride, which is a second-generation H₁ receptor-antagonist with potent topical activity, and fluticasone propionate, a synthetic corticosteroid with anti-inflammatory properties.

Intranasal steroid sprays

It contains fluticasone propionate, a synthetic corticosteroid with anti-inflammatory properties.

The study was conducted in following two groups based on drug given;

Group A

In this group, patients were asked to administer the dose of 2 sprays (50 mcg of fluticasone propionate in each spray) in each nostril once daily (total daily dose, 200 mcg) in the morning. This drug was given for a period of 4 weeks.

Group B

In this group Patients were asked to administer 1 spray (Azelastine Hydrochloride 140 mcg, Fluticasone Propionate 50 mcg in each nasal spray) in each nostril twice daily (total daily dose 560 mcg of Azelastine hydrochloride and 200 mcg of fluticasone propionate) in the morning and evening. This drug was given for a period of 4 weeks.

Instruction on proper technique for administering the nasal sprays was given before starting the treatment. Patients were

explained in detail about the procedure and informed written consent was taken from all patients.

Observation on parameters was done on 2nd and 4th week of the treatment. Analysis of symptoms was done statistically on the basis of improvement of TNSS and MiniRQLQ in case of allergic rhinitis.

The purpose of this study was to determine if greater efficacy could be achieved with the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray compared with the efficacy of fluticasone propionate nasal spray alone and also to ascertain whether the combination nasal sprays should be prescribed as a standard medical management for allergic rhinitis or not, as to achieve better quality of life after treatment with maximum improvement in TNSS.

Inclusion criteria

- Patients complaining of sneezing, running nose or blocked nose and itching sensation in the nose which are hallmark symptoms of allergic rhinitis with moderate or severe grade of symptoms, having more than 5 TNSS were included in the study.
- 18 - 45 years old Patients irrespective of sex, religion and economical status
- All types of Allergic Rhinitis i.e., Seasonal, Perennial or Intermittent/Persistent.
- Able to provide written informed consent.

Exclusion criteria

- Age more than 45 years.
- Patients complaining of symptoms due to structural abnormalities i.e., grossly deviated nasal septum, nasal polyps or nasal tumors.
- Use of systemic/oral corticosteroids within 30 days of first visit
- Hypersensitivity to Antihistamines or Corticosteroids.
- Significant medical (i.e. asthma, chronic sinusitis, tuberculosis, carcinoma of lung, pneumonia and upper respiratory tract infections), surgical or psychiatric disease which can affect participant's safety or influence the study outcome
- Patients with history of blood disorders like non-allergic eosinophilic syndrome, tropical eosinophilia syndrome.

- Patients with mild symptoms of AR with TNSS less than 5 were excluded from this study.

Data collection techniques and tools

Patients presenting with sneezing, watery nasal discharge, nasal obstruction and itching sensation in the nose were carefully evaluated by means of a predesigned proforma, used to record the relevant information like Patient's data, Clinical findings and TNSS (Total Nasal Symptom Score) from the individual patient shortlisted with inclusion and exclusion criteria.

TNSS

Intensity of nasal symptoms (rhinorrhea, nasal itching, nasal obstruction and sneezing) using a 4-point Likert scale from 0 to 3 (0 = no symptom, 1 = mild, 2 = moderate, 3 = severe). The TNSS was obtained from the sum of all 4 individual symptom scores, with a total possible score ranging from 0 (no symptoms) to 12 (maximum symptom intensity). Patients with a TNSS of 5 or higher, not treated with antihistamines in the previous week or with topical corticosteroids in the previous 2 weeks, was included in the study.

MiniRQLQ

Disease-specific questionnaires are the instruments most widely used in order to "measure the quality of life", because they more accurately describe the problems associated with the disease and are more responsive to possible alterations in the quality of life, when compared with generic questionnaires. In the case of allergic rhinitis, the disease-specific questionnaire most commonly used is the Mini Rhino-conjunctivitis Quality of Life Questionnaire (Mini-RQLQ) [75].

Mini rhino-conjunctivitis quality of life questionnaire

This self-administered, 14-item questionnaire has been validated to measure the functional impact of rhino-conjunctivitis in five domains (activity limitation, practical problems, nose symptoms, eye symptoms and other symptoms).

Patients score their experiences during the previous week on a 7-point scale (0 = not troubled, 6 = extremely troubled) with total possible score ranging from 0 to 84.

Analysis of data

A database was created which includes the Patient's Name, Age, Sex, Hospital Number, Parameters of TNSS and Mini RQLQ scores before and after the treatment.

Statistical methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean \pm SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Kolmogorov smirnov analysis was used to assess the distribution of data. Student's t test in case of parametric data and Mann whitney U test for non-parametric data was used to compare the significance of difference between two variables. ANOVA followed by post hoc Tukey's HSD test was used to assess the significance of difference between more than two groups in case of parametric data and Kruskal Wallis test followed by post hoc Dunn test or Friedman test followed by Post hoc Benferroni's test was used to assess the significance of difference between more than 2 groups in case of non-parametric data. Significance of difference of frequency distribution was assessed by chi square analysis. $P < 0.05$ was considered to be statistically significant.

Results

This study included total 100 subjects, 50 in each group and were evaluated for TNSS and MiniRQLQ before and after the treatment initiation. Demographic characteristics of study subjects were assessed. Maximum subjects were found to be in 27-35 years of age (51 subjects (51%), 16 male (16%) 35 female (35%)) The subjects were further divided in two groups, 50 subjects who received steroid therapy and 50 subjects received combination therapy. Two groups were found to be age matched ($p = 0.4$) Sex distribution of study groups was studied and it was noted that both groups were matched for sex distribution ($p = 0.4$) Two study groups those on treatment with steroid therapy and on combination therapy were compared for various components of TNSS score using student's t test.

The total score was found to be matched $p = 0.3$. TNSS after two weeks of therapy was compared in study groups using Mann Whitney U test as their distribution was found to be non-parametric. The difference in total score of two groups was found to be statistically significant ($p < 0.001$). TNSS after four weeks of therapy was compared in study groups using Mann Whitney U test as their distribution was found to be non-parametric. The difference in total score of two groups was found to be statistically significant ($p < 0.001$).

Characteristics Before treatment		In subjects treated with combination therapy			p Value
		After 2 Weeks of Treatment	After 4 Weeks of treatment		
TNSS in (Mean ± S.D)	Rhinorrhea	2.28 ± 0.64	0.38 ± 0.49 ^a	0.1 ± 0.30 ^{a,b}	<0.0001
	Itching	2.08 ± 0.72	1.08 ± 0.72 ^a	0.3 ± 0.46 ^{a,b}	<0.0001
	Nasal Obstruction	1.42 ± 0.85	0.58 ± 0.64 ^a	0.08 ± 0.27 ^{a,b}	<0.0001
	Sneezing	2.64 ± 0.52	0.68 ± 0.51 ^a	0.02 ± 0.14 ^{a,b}	<0.0001
	Total Score	8.42 ± 1.27	2.72 ± 1.06 ^a	0.5 ± 0.61 ^{a,b}	<0.0001

Table 1: Comparison of TNSS values at different interval of treatment with combination therapy.

a = p < 0.01 compared to before treatment group.

b = p < 0.01 compared to After 2 weeks group.

All the parameters of TNSS before treatment, after 2 weeks of treatment and after 4 weeks of treatment were analysed using ANOVA test (as it was found to be parametric in distribution) in the subjects treated with combination therapy and it was noted that statistically significant difference was found in all the parameters of all three groups (p < 0.0001).

Percentage improvement in TNSS

Two study groups those on treatment with steroid therapy and on combination therapy were compared for various components of Mini RQLQ using student’s t test.

The total score was found to be matched in both groups (p = 0.3, mean = 55.4 ± 6.72 in steroid therapy v/s mean = 54.76 ± 7.04) in combination therapy.

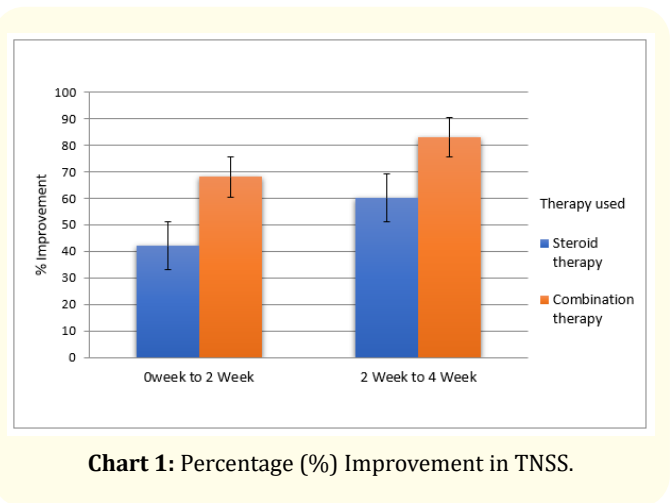


Chart 1: Percentage (%) Improvement in TNSS.

Characteristics Before treatment		In subjects treated with steroids alone			p Value
		After 2 Weeks of Treatment	After 4 Weeks of treatment		
Mini RQLQ (Mean ± S.D)	Activities	11.48 ± 2.77	10.48 ± 2.75 ^a	09.90 ± 3.77 ^a	<0.01
	Practical Problems	9.28 ± 2.2	7.28 ± 2.24 ^a	6.2 ± 2.24 ^a	<0.001
	Nose Symptoms	11.48 ± 3.17	9.48 ± 3.17 ^a	9.32 ± 3.2 ^a	<0.01
	Eye Symptoms	11.04 ± 2.57	10.04 ± 1.48 ^a	9.04 ± 2.57 ^{a,b}	<0.01
	Other Symptoms	12.12 ± 3.15	10.12 ± 3.15 ^a	9.84 ± 2.45 ^{a,b}	<0.01
	Total	55.4 ± 6.72	47.4 ± 6.72 ^a	45.4 ± 6.7 ^{a,b}	<0.001

Table 2: Comparison of MiniRQLQ Values at Different Interval of Treatment with Steroids Alone.

a = p < 0.01 compared to before treatment group.

b = p < 0.01 compared to After 2 weeks group.

All parameters ANOVA followed by post hoc Tukey’s HSD test.

Characteristics Before treatment		In subjects treated with combination therapy			p Value
		After 2 Weeks of Treatment	After 4 Weeks of treatment		
Mini RQLQ (Mean ± S.D)	Activities	12.32 ± 3.43	10.32 ± 3.43 ^a	9.32 ± 3.43 ^a	<0.0001
	Practical Problems	9.76 ± 2.19	6.76 ± 2.19 ^a	4.76 ± 2.19 ^{a,b}	<0.0001
	Nose Symptoms	12 ± 2.9	8 ± 2.9 ^a	5.04 ± 2.87 ^{a,b}	<0.0001
	Eye Symptoms	8.64 ± 1.98	4.64 ± 1.98 ^a	1.92 ± 1.62 ^{a,b}	<0.0001
	Other Symptoms	12.04 ± 3.2	9.04 ± 3.2 ^a	9.04 ± 3.28 ^a	<0.0001
	Total	54.76 ± 7.04	38.76 ± 7.04 ^a	30.08 ± 6.9 ^{a,b}	<0.0001

Table 3: Comparison of MiniRQLQ Values at Different Interval of Treatment with Combination Therapy.

a = p < 0.01 compared to before treatment group.

b = p < 0.01 compared to after 2 weeks group.

Discussion

Allergic Rhinitis is the most common immunologic disease and is the most common chronic disease experienced by humans. Even today despite the advances in the understanding of the numerous chemical mediators of allergy, only two major categories of drugs are in common use for the management, namely antihistamines and corticosteroids.

AR with its attendant complications is a common condition today, affecting all the age groups with more predilection in the younger ones upto 3rd decade.

Age group wise distribution

The age of patients in our study ranged from 18 to 45 years as per the inclusion criterion. Maximum subjects were found to be in 27-35 years of age (51 subjects (51%), 16 male (16%) 35 female (35%)) Followed by in 18-26 years of age (28 subjects (28%), 14 male (14%) 14 female (14%)). The mean age of subjects who entered this study was 30.17 years. Two groups were found to be age matched (p = 0.4). The incidence of mean age is in accordance with the studies of Charles Freche (2002) 32 years, Robonson (1998) 31 years, Bunnag (1998) 30 years, Vervloet (1998) 29 years, Darnell (1998) 28 years. One reason for this may be the life style and activity in this age group, who are more active compare to older age group which will increase the chances of bringing them in to contact with a wide variety of allergens.

Sex distribution

In this study males constitute 41% and females 59%. Male to female distribution in steroid therapy group was found to be 66%

(20:30) and in combination therapy group was 72% (21:29) but it was noted that both groups were matched for sex distribution (p = 0.4). Sex incidence is according to the studies of C. Bachert (2001) M: 43%, F: 57% and William E Berger (2002) M: 38%, F: 62% respectively. In one study in Finland, the incidence rate for allergic rhinitis in males at age 16–32 was 13.4/per 1000 person-years, slightly greater than that in females with 11.4/per 1000 person-years [16-18]. Among both genders, the highest incidence rate of allergic rhinitis was between 17 and 22 years. In another self-report questionnaire study on adults from Stockholm, Sweden, there were no statistically significant gender differences in the prevalence of either allergic or nonallergic symptoms [19]. However, women reported more severe psychosocial effects such as social embarrassment and depression/irritation in both perennial allergic rhinitis and nonallergic rhinitis [18]. In one study done by Romieu I., *et al.* they found that being a woman was a risk factor for nasal blocking and runny nose. In Vietnam women are responsible for house works, especially for preparing food. The use of solid fuels in poorly ventilated homes results in high levels of indoor air pollution [20]. Randomized controlled trials have shown that women who used biomass stove or chimney woodstove most of the time, compared with those using traditional indoor open fire, were at a lower risk of developing respiratory symptoms [21].

Comparison of MiniRQLQ values before treatment between groups

The two study groups, group A on treatment with steroid therapy only and group B on treatment with combination therapy were compared for various components of MiniRQLQ using

student's t test. It was found that two groups were matched for activities ($p = 0.09$, mean = 11.48 ± 2.77 in steroid therapy v/s mean = 12.32 ± 3.43 in combination therapy), practical problem ($p = 0.1$, mean = 9.28 ± 2.2 in steroid therapy v/s mean = 9.76 ± 2.19 in combination therapy), nose symptoms ($p = 0.1$ mean = 11.48 ± 3.17 in steroid therapy v/s mean = 12 ± 2.9 in combination therapy), other symptoms ($p = 0.4$ mean = 12.12 ± 3.15 in steroid therapy v/s mean = 12.04 ± 3.2 in combination therapy). Eye symptoms were found to be significantly higher in steroid therapy group (mean = 11.04 ± 2.57) compared to combination therapy group (mean = 8.64 ± 1.98) ($p < 0.001$). But total score was found to be matched in both groups ($p = 0.3$, mean = 55.4 ± 6.72 in steroid therapy v/s mean = 54.76 ± 7.04) in combination therapy. steroid therapy group compared to combination therapy group ($p = 0.008$, $p < 0.001$, $p = 0.04$ respectively). Total score was found to be significantly higher in the steroid therapy group compared to combination therapy group ($p < 0.0001$).

Percentage improvement in MiniRQLQ

In this study, mean percentage improvement in MiniRQLQ score was calculated for both Steroid Therapy group and combination therapy group. The improvement was calculated over period of 0 weeks to 2 weeks and then from 2 weeks to 4 weeks of treatment. Respective MiniRQLQ scores for zero week (before the start of treatment), 2 weeks after the start of treatment and 4 weeks after the start of treatment were considered for same. It was observed that in the steroid therapy group, mean percentage improvement was found to be 14% (0 weeks to 2 weeks) and 4% (2 weeks to 4 weeks) whereas for combination therapy group, the same was found to be 29% (0 weeks to 2 weeks) and 23% (2 weeks to 4 weeks).

Limitations of the Study

A sample size of 100 was taken from a population attending our hospital, is less and selection is too difficult to prevent confounding factors. A larger sample size would have made the study more sensitive. The study period was 4 weeks post treatment for each subject, however, a longer duration could have shown more significant response. This study was based on relatively short follow-up period. Therefore, further follow-up studies are needed for a more exhaustive evaluation of longterm improvement of symptoms. Either randomization or inclusion of controls in the study would have more insight into the data obtain. Allocation of

treatment in terms of combination sprays or steroid sprays was sequential and was not grouped or randomized. The side effects of both the drugs were not studied. Age group for the study is 18 years to 45 years. The results of this study are only restricted to same age group and does not apply to patients less than 18 years old and more than 45 years old. The third group treated with topical antihistamines sprays alone could have been included in the study.

Conclusion

The outcome of results of combination nasal sprays were compared with steroid spray alone in treatment of allergic rhinitis. The significant statistical difference was found in total nasal symptom score and MiniRQLQ score. Total Nasal Symptom score improvement after combination nasal spray therapy and steroid nasal spray therapy in allergic rhinitis were comparable. It was noted that rhinorrhea, nasal obstruction and sneezing were significantly improved with combination therapy after 2 weeks as well as after 4 weeks of treatment as compared to improvement shown by steroid therapy alone. Overall, percentage improvement in total nasal symptom score was found to be higher in combination nasal therapy. Overall, percentage improvement in MiniRQLQ Mean value was found to be higher in combination nasal therapy.

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