ID: JCDR/2012/3457:1846

Original Article

ENT Section

Efficacy of Fluticasone and Oxymetazoline as the Treatment for Allergic Rhinitis

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ABSTRACT

Background: The intranasal steroids remain the most effective treatment as all major symptoms of allergic rhinitis are effectively attenuated. However, addition of decongestant increases the response obtained along with intranasal steroids. The data on effect of addition of Oxymetazoline to fluticasone is limited. Hence, this study was done to compare the efficacy of fluticasone combined with oxymetazoline and fluticasone alone for a 4-week treatment course of allergic rhinitis.

Methodology: In this randomized, open, parallel study, out of 123 patients randomly assigned to receive fluticasone with oxymetazoline (Group 1) or fluticasone alone (Group 2), 91 patients completed the entire 4 weeks of study. The primary outcome measure was mean change of the daytime nasal symptom score (PDTS) and secondary outcome measure was mean change of nighttime nasal symptom score (PNTS) and composite symptom score (PCS).

Results: The change in total daytime nasal symptom, composite symptom, nightime nasal symptom score was significantly ($p<0.05$) greater in Group 1 as compared to Group 2. Sub-group analysis showed a significantly ($p<0.05$) greater improvement in congestion score from 2nd week onwards in Group 1.

Conclusion: Oxymetazoline combined with fluticasone was effective in reducing daytime, night time, and composite symptom score as compared to fluticasone alone.

Key Words: Allergic rhinitis, Oxymetazoline, Fluticasone, Congestion

INTRODUCTION

Allergic rhinitis is a highly prevalent chronic condition which presents an enormous global health burden. It has been estimated that at least 500 million individuals have allergic rhinitis (AR) and it is one of the most common reasons for the appointment with a primary care practitioner [1, 2].

According to the Allergic Rhinitis and its Impact on Asthma (ARIA) document, it is classified by severity, which is based on the duration of the symptoms (i.e. intermittent versus persistent) and the quality of life (mild, or moderate/ severe) [2-4]. The terms “seasonal” and “perennial” allergic rhinitis were previously categorized as allergic rhinitis on the basis of the clinically significant aeroallergens. Perennial allergic rhinitis is associated with the all year round and indoor allergens which includes mould spores, cockroaches, dust mite faecal particles, animal dander, and occupational exposure. Seasonal allergic rhinitis is commonly referred to as “hay fever”, which develops during a defined pollen season and is usually intermittent as a result of allergic reactions to outdoor aeroallergens, which includes mould spores and pollens of trees, grasses, and weeds which depend on the wind for cross-pollination. Commonly, there is an overlap of the “perennial” and “seasonal” symptoms in some geographical regions, which has resulted in the decreased use of and confusion regarding these terms [3, 4].

Apart from infections, allergic disorders affect the nasal mucosa. The inflammatory response of the nasal mucosa involves the engorgement of the venous sinusoids, and the obstruction of the nasal airflow to a variable degree, leading to a significant impairment of the daily living activities e.g. mouth breathing through a dry mouth, stuffy nose feeling, and headache [5]. On physical examination, the patients classically can have a pale nasal mucosa, with swollen, oedematous turbinates and clear nasal secretions (rhinorrhoea) [3].

The drug therapy for allergic rhinitis should be guided by the type and the severity of the individual patient’s symptoms and it should reduce nasal congestion, sneezing, and rhinorrhoea over the course of the entire day and night and the physician preferences [4, 6]. Oral and intranasal antihistamines, mast cell stabilizers, leukotriene inhibitors, decongestants and intranasal anticholinergics, in addition to intranasal steroids (INS), are all established evidence-based therapeutic interventions for AR [1]. The intranasal steroids are significantly more effective than the oral or intranasal antihistamines and the anti-leukotrienes and are equal to the combination of anti-histamine plus anti-leukotriene [2, 7-9]. For a mild disease, either a second-generation antihistamine or a topical nasal corticosteroid (INS) is recommended [1, 2, 10]. For a moderate to severe disease or when the nasal congestion is predominant, INSs are the first line of treatment [2, 11, 12]. For a majority of the patients with allergic rhinoconjunctivitis, intranasal steroids remain the most effective treatment, since all the major symptoms which are associated with AR are effectively attenuated after their administration [2].

60 % of the subjects reported an excellent response to the intranasal steroids. Steroids work by penetrating the plasma membrane and binding to the cytosolic glucocorticoid receptor (GR). Upon GR binding, the steroid-GR complex translocates into the nucleus and binds the DNA at the glucocorticoid response elements (GRE) in the 5′-upstream region of the steroid responsive genes. The transcriptional activation of the anti-inflammatory genes or the repression of the pro-inflammatory and other mechanisms which regulate inflammation like via protein–protein sequestration via binding to other pro-inflammatory transcription factors such as the

activator protein (AP-1), lead to the inhibition of the transcription of the inflammatory genes [2]. On the other hand, oxymetazoline has a predominant α-2 adrenergic activity and an α-1 adrenergic activity at higher concentrations. Both the effects result in vasoconstriction and if oxymetazoline is applied topically to the nasal mucosa, it results in decongestion, facilitates the drainage of the paranasal sinuses and leads to an improved quality of life [5]. Few studies have reported a significant increase in the response to the add-on therapy of fluticasone with oxymetazoline as compared to either of the drugs given alone; there was also a better mucociliary clearance in patients who received a combination of both the drugs [13, 14]. Since data on the Indian population is lacking, we considered it worthwhile to assess the efficacy of fluticasone furoate with oxymetazoline in the Indian population.

METHODS

Study Design

This prospective, randomized, open, parallel group study (with a 4 week treatment period) was conducted in the Outpatients Department of the Gian Sagar Medical College and Hospital, Patiala District from December 2010 to May 2011. The study protocol and informed consent were reviewed and approved by the Institutional Ethics Committee of Gian Sagar Medical College and Hospital before the initiation of the study and a written informed consent was obtained from each subject prior to his/her enrollment in the study. This study was conducted in accordance with the ICH-GCP guidelines.

Patient Selection

Patients with allergic rhinitis, of both sexes, in the age group of 18 to 55 years, were recruited for the study. The exclusion criteria included the following: pregnancy and/or lactation; physical signs and symptoms which were suggestive of renal, hepatic or cardiovascular disease; subjects who were treated with systemic steroids or topical steroids during the previous 30 days; subjects who were treated with oral/ topical anti-histamines/decongestants during the past 7 days; subjects with polyps in the nose or a significantly displaced septum; and subjects with upper respiratory tract infection within 14 days of the start of the study.

Procedure

The subjects who fulfilled the inclusion and exclusion criteria and who were willing to give an informed consent were recruited for the study. Their clinic visits were scheduled at screening (visit 1), and after every 2 weeks of treatment according to the randomization for 4 weeks (visit 2 and 3). The subjects were randomized into two groups by using a random number table. Group 1 received Oxymetazoline (0.05%) nasal drop for 1 week, 2 puffs of Fluticasone furoate nasal spray (100µg/ day) in each nostril every evening and early morning daily for 4 weeks, whereas Group 2 received only Fluticasone furoate nasal spray (100µg/day) early morning daily for 4 weeks. A physical examination for nasal secretion and turbinate swelling was also done at each visit.

Outcome Measurements

The primary outcome measure was the mean change of the total daytime nasal symptom scores (PDTS), which was defined as the average score of four daytime nasal symptoms.

The secondary outcomes were the mean changes of the night time nasal symptom scores (PNTS), and the composite symptom scores (PCS) (average score of day and night time nasal symptom score). The same observer examined all the patients and at various intervals of time. The credibility of the nasal examinations of the subjects was markedly enhanced by the single-observer design of this trial for every patient, which eliminated the inter-observer reliability issue.

Daily Rhinitis Diary Card

As was recorded on the daily diary card, the allergic rhinitis and conjunctivitis symptoms were assessed on a 4-point scale (0 to 3) for both the day time (diary card completed in the evening) and the night time (diary card completed on awakening). The daytime nasal (rhinorrhoea, sneezing, itching, and congestion) and the night time nasal (nasal congestion upon awakening, difficulty in going to sleep, and night time awakening) symptoms and their rating were described to every patient by the same technician. The ratings of the symptoms were: 0 = not noticeable, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms. The rating had to be performed by the patients themselves to increase the creditability of the subjective scale. The safety evaluation included spontaneously reported adverse events throughout the study.

Statistical Analysis

The data was tabulated as mean ± standard deviation (SD). The results were analyzed by using non-parametric tests (the Chi-Square Test, the Wilcoxon Sign Ranked Test and the Mann Whitney U Test) and parametric tests (two tailed student t-test). A p value of < 0.05 was considered as statistically significant.

The nominal variables were compared by using Chi-square analysis. The Student's t-test was used for the comparison of the group means for the normally distributed data and the Mann-Whitney U test/Wilcoxon Sign Rank Test was used for the non-normally distributed data.

RESULTS

Patients

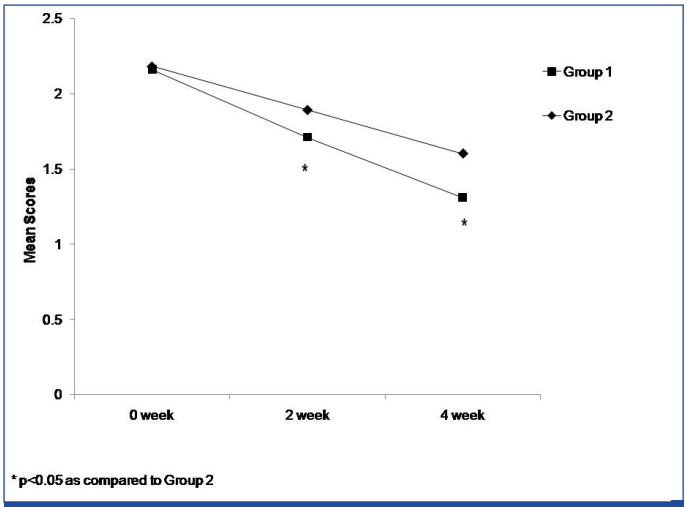
A total of 155 patients with allergic rhinitis were screened for the study. Out of the 155 screened patients, 123 were eligible for the study. All the eligible patients were invited to participate in the study. 11 patients in group 1 and 12 patients in group 2 were excluded from the study due to the withdrawal of their written informed consent for participation in the study. 9 patients did not complete the entire 4 weeks of follow-up and hence, were excluded from the study. 4 patients (1 in group 1 and 3 in group 2) did not report for follow-up after 2 weeks of therapy and 5 patients (3 in group 1 and 2 in group 2) did not report for follow-up after 4 weeks of therapy. 91 patients completed the entire 4 weeks of follow-up of the study.

Efficacy

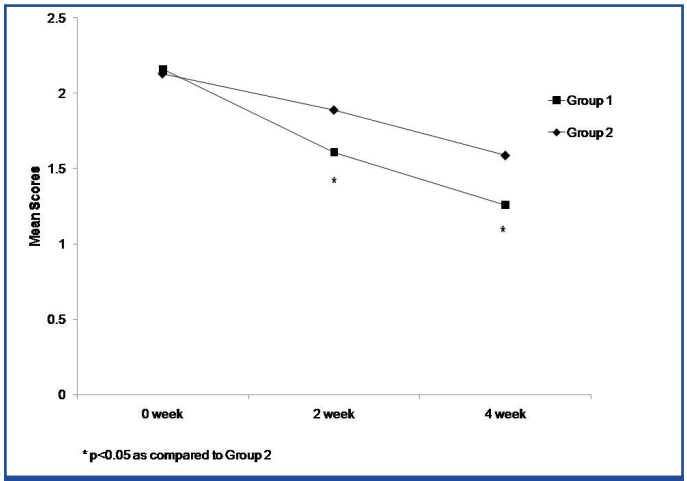
The patients in both the groups had comparable demographic and clinical profiles, as shown in [Table/Fig-1]. The PDTS, PNTS, and the PCS scores were found to be reduced significantly as compared to the baseline in both the groups. The PDTS score (mean ± SD) at baseline was 2.16 ± 0.32, which reduced significantly to 1.31 ± 0.27 at the end of 4 weeks in group 1. Similarly, the PDTS score was found to be reduced significantly from 2.18 ± 0.35 to 1.60 ± 0.26 at the end of 4 weeks in group 2 [Table/Fig-2]. The PNTS score (mean ± SD) was found to be decreased significantly from 2.15 ± 0.34 to 1.26 ± 0.30 in group 1 and from 2.13 ± 0.38

Characteristic	Group 1 (n=46)	Group 2 (n=45)	p value
Age (Years) (Mean±SD)	36.59±10.43	35.56±9.75	p=0.627*
Sex (M:F)	26:20	23:22	p=0.676#
Mean Daytime Nasal Symptom Score (PDTS) (Mean±SD)	2.16±0.32	2.18±0.35	p=0.858∞
Mean Nighttime Nasal Symptom Score (PNTS) (Mean±SD)	2.15±0.34	2.13±0.38	p=0.689∞
Mean Composite Symptom Score (PCS) (Mean±SD)	2.16±0.22	2.15±0.26	p=0.883∞

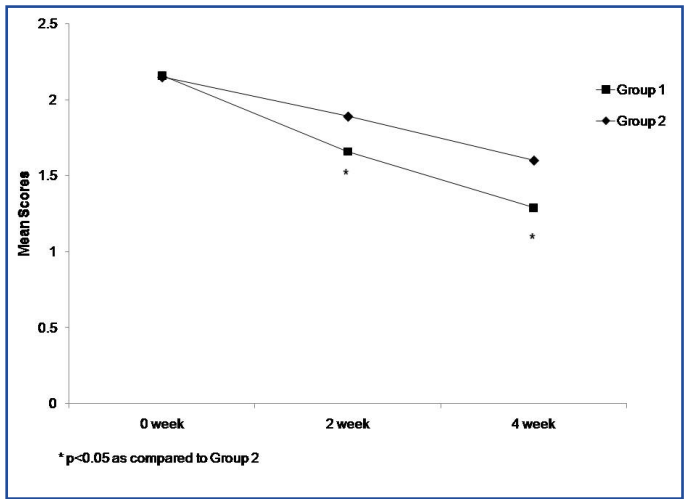
[Table/Fig-1]: Baseline characteristics of the study group
* Using unpaired student 't' test; # Using Chi-square test; ∞ Using Mann-Whitney U test



[Table/Fig-2]: Mean Daytime Nasal Symptom Scores (PDTS) in both groups



[Table/Fig-3]: Mean Nighttime Nasal Symptom Scores (PNTS) in both groups



[Table/Fig-4]: Mean Composite Symptom Scores (PCS) in both groups

to 1.59±0.33 in group 2 at the end of 4 weeks [Table/Fig-3]. The PCS score (mean±SD) was found to be decreased significantly from 2.16±0.22 to 1.29±0.18 in group 1 and from 2.15±0.26 to1.60±0.24 in group 2 at the end of 6 weeks [Table/Fig-4]. The improvement in group 1 was significantly ($p<0.05$) more as compared to that in group 2 from the 2nd week onwards in the PDTS score (1.71±0.24 Vs 1.89±0.21), the PCS scores (1.66±0.28 Vs 1.89±0.17), and the PNTS score (1.61±0.28 Vs 1.89±0.24).

The sub-group analysis showed a significant ($p<0.05$) improvement in the congestion scores in group 1 from the second week onwards and a significant ($p<0.05$) improvement in itching, sneezing, rhinorrhoea, difficulty in going to sleep and the night time awakening scores in group 1 from the fourth week onwards, as compared to group 2.

Safety

No serious adverse event was reported in both the groups. The incidence of adverse events which were reported in group 1 was more as compared to that in group 2, but none of the adverse events which were reported were so severe that the termination of the treatment was required. The adverse events which were reported in both the groups did not require a reduction in the dose or any therapy for their treatment. The patients complained about watering of the eyes, burning and stinging sensations and bad taste or sneezing. Two patients in group 1 complained of watering of the eyes, whereas one patient in group 1 reported of a bad taste, sneezing and a stinging and burning sensation. There was no prolongation of hospitalization in any patient.

DISCUSSION

There are a number of therapeutic choices which are available for the treatment of allergic rhinitis, which include oral and intranasal H_1 anti-histamines, intranasal corticosteroids, oral and intranasal decongestants, intranasal anticholinergics and intranasal cromolyn and leukotriene receptor antagonists [3, 4, 15]. Intranasal steroids are more effective as compared to a combination of anti-histamine plus anti-leukotriene. For a moderate to severe disease or when the nasal congestion is predominant, intranasal steroids are very effective, as all the major symptoms which are associated with allergic rhinitis are attenuated after their administration [2].

The addition of oxymetazoline to fluticasone furoate adds to the efficacy in the treatment of allergic rhinitis [13]. In the present study, a combination of oxymetazoline and fluticasone furoate was effective in improving the PDTS, PNTS and the PCS scores in patients with allergic rhinitis. The therapy of oxymetazoline with fluticasone furoate significantly improved these scores as compared to fluticasone furoate alone.

These results are in agreement with those of earlier studies, which have demonstrated a significant improvement in the nasal symptom

scores of the patients who were on a combination of oxymetazoline and fluticasone furoate, who were suffering from allergic rhinitis [13, 14]. The sub-group analysis demonstrated a significantly greater improvement in the congestions score in patients who received oxymetazoline with fluticasone furoate.

The adverse effects which were reported in our study were similar to those which were reported in earlier studies [13, 14]. The adverse events which were reported were mainly watering of the eyes, sneezing and/or a burning and stinging sensation. There was no report of any clinically significant effect on the HPA-axis, bone growth, or cataract formation/glaucoma after the use of steroid therapy. This reflection was due to the low systemic bioavailability following the intranasal administration of steroids [2].

Our results confirm and extend those of earlier studies, that oxymetazoline withfluticasone furoate is effective and safe in Indian patients with allergic rhinitis and that this combination may be of more clinical utility for the alleviation of the residual symptoms and for an improvement in the quality of life which is associated with allergic rhinitis [2, 5, 13, 14].

The limitations of our study were that firstly the sample size was so small that the number of adverse events which were reported was not significantly more as compared to that which was related to the use of fluticasone furoate alone. May be a larger sample size may show a significant difference. Secondly, the duration of the study which was 4 weeks, which was small. May be a longer duration of the study would show variable results. Thirdly, this was an open label study, with the limitations of funds. A double-blind study would have been ideal.

To conclude, the patients in both the groups tolerated the treatment well and showed a significant improvement from the baseline. There was a significant improvement in the PDTS, PNTS and the PCS scores in the patients who received oxymetazoline with fluticasone furoate versus fluticasone furoate alone at all intervals of time. The subgroup analysis showed a significant improvement in the congestions score.

ABBREVIATIONS

PDTS: Daytime Nasal Symptom Score
PNTS: Nighttime Nasal Symptom Score
PCS: Composite Symptom Score
INS: Intranasal Steroids
AR: Allergic rhinitis

REFERENCES

[1] Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA²LEN and AllerGen). *Allergy* 2008; 63 (Suppl 86): 8–160.
[2] Kariyawasam HH, Scadding GK. Seasonal allergic rhinitis: fluticasone propionate and fluticasone furoate therapy evaluated. *Journal of Asthma and Allergy* 2010; 3: 19–28.
[3] Bousquet J, Lund VJ, van Cauwenberge P, et al. Implementation of the guidelines for seasonal allergic rhinitis: a randomized controlled trial. *Allergy* 2003; 58: 733-41.
[4] Lagos JA, Marshall GD. Montelukast in the management of allergic rhinitis. *Ther Clin Risk Manag* 2007; 3: 327-32.
[5] Grigoleit HG. Oxymetazoline in allergic rhinitis: A review of controlled clinical trials. *Journal of Chinese Clinical Medicine* 2006; 1: 411-7.
[6] Storms W. Allergic rhinitis-induced nasal congestion: its impact on the sleep quality. *Prim Care Res J* 2008; 17: 7-18.
[7] Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: a systematic review of randomised controlled trials. *BMJ* 1998; 317: 1624–9.
[8] Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2002; 89: 479–84.
[9] Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004; 116: 338–44.
[10] Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on the practice parameters in allergy, asthma and immunology. American Academy of Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol* 1998; 81: 478–518.
[11] Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008; 122: S1–84.
[12] Scadding GK, Durham SR, Mirakian R, et al. The BSACI guidelines for the management of allergic and non – allergic rhinitis. *Clin Exp Allergy* 2008; 38: 19–42.
[13] Baroody FM, Brown D, Gavanescu L, Detineo M, Naclerio RM. Oxymetazoline adds to the efficacy of fluticasone furoate in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol* 2011; 127: 927-34.
[14] Nanl S, Öztürk Ö, Korkmaz M, Tutkun A, Batman Ç. The effects of the topical agents of fluticasone propionate, oxymetazoline, and 3% and 0.9% sodium chloride solutions on mucociliary clearance in the therapy of acute bacterial rhinosinusitis in vivo. *The Laryngoscope* 2002; 112: 320–5.
[15] Gonyeau MJ, Partisano AM. A clinical review of montelukast in the treatment of seasonal allergic rhinitis. *Formulary* 2003; 38: 368-78.

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FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Submission: **Sep 13, 2011**
Date of Peer Review: **Oct 17, 2011**
Date of Acceptance: **Dec 10, 2011**
Date of Publishing: **Feb 15, 2012**