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Original Research Article

Comparative Research on the Effectiveness and Safety of Long-Acting Antihistamines in Allergic Conjunctivitis in Indian Patients: An RCT Trial

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Abstract

Aim: The aim of the present study was to compare the safety and efficacy of Alcaftadine 0.25%, Olopatadine hydrochloride 0.2% and Bepotastine besilate 1.5% in allergic conjunctivitis. **Methods:** A total of 90 patients with mild or moderate allergic conjunctivitis were randomized into three groups with an allocation ratio of 1:1:1 using computer-generated random number sequence to receive topical anti-allergic medication for 14 days as Group 1: Topical 0.25% Alcaftadine eye drops OD, Group 2: Topical 0.2% Olopatadine eye drops OD and Group 3: Topical 1.5% Bepotastine besilate eye drops BID. Patients were examined and their baseline symptoms and signs (TOSS) were recorded. **Results:** The 4 major complaints recorded by patients were itching (30 patients, 100%), redness (22 patients, 73.33%), tearing (25 patients, 83.33%), and swelling (13 patients, 43.33%). The total ocular symptom score (TOSS) showed a consistent decrease in subsequent visit in all the Groups and it was statistically significant, when compared from baseline to 14th day in all the groups ($p=0.0008$). The difference in mean TOSS between (Group A) Alcaftadine and (Group C) bepotastine treatment groups was observed at the third day of follow-up. This showed early relief of allergic conjunctivitis symptoms by bepotastine (5.57 ± 1.26) compared to Alcaftadine (mean (6.31 ± 1.47) and olopatadine (6.31 ± 1.47) but this was not statistically significant. Total ocular symptom score at 14th day visit with post hoc Tukey HSD test showed mean of Alcaftadine group vs mean of olopatadine group – $p < 0.05$, mean of olopatadine group vs mean of bepotastine group – $p<0.01$, which were statistically significant whereas mean of Alcaftadine group vs mean of bepotastine group showed no significant difference. Alcaftadine was found to be better than olopatadine in reducing the Allergic Conjunctivitis symptoms using TOSS score at 14th day visit ($p < 0.5$). Although there is no significant difference between bepotastine and Alcaftadine groups, bepotastine showed a better reduction of symptoms compared to Olopatadine group using TOSS score at 14th day visit ($p<0.1$). Conjunctival hyperaemia had reduced in all the treatment groups but there was a significant reduction in Alcaftadine and Bepotastine treatment groups at 14th day compared to olopatadine group ($p = 0.0023$). **Conclusion:** All three topical ophthalmic medications used in the study are safe and effective in the treatment of allergic conjunctivitis. However, Bepotastine and Alcaftadine appear to outweigh Olopatadine in resolving the symptoms of allergic conjunctivitis.

Keywords: Alcaftadine, allergic conjunctivitis, Bepotastine besilate, hyperaemia scale, olopatadine, Total ocular symptom score (TOSS)

Introduction

The conjunctiva of the eye is continually exposed to a variety of airborne antigens that can lead to inflammation, termed allergic conjunctivitis,[1] which is an ocular surface inflammatory disease that affects approximately 40% of the global population.[2] It is predominantly IgE mediated Type I hypersensitivity reaction where allergen binds to specific IgE molecules, triggers mast cell degranulation and subsequent increase in histamine leading to activation of both H_1 and H_2 types of histamine receptors.[3]Allergic conjunctivitis includes persistent allergic conjunctivitis, seasonal allergic conjunctivitis (SAC), vernal kerato conjunctivitis (VKC), and atopic keratoconjunctivitis. SAC is about 25%–50% of cases.[4] Number of causes have been considered for this increase such as genetics, air pollution, pets, etc.[5] Various forms of conjunctivitis such as seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis, and giant papillary conjunctivitis are included in ocular allergy, sharing some common markers of allergy.[6] Seasonal and perennial conjunctivitis are in response to exposure to specific allergans and are predominantly mediated by IgE antibodies activating the mast cells.[7,8] VKC is in response to non-specific allergans and is mediated mainly by Th2 cells, but mast cells and eosinophils also play a majorrole.[9,10] Atopic conjunctivitis occurs in patients predisposed to atopy. It is mediated by both Th2 response and mast cells.[11] Avoidance of allergans and lubricants plays a key role in the management of allergic conjunctivitis. Addition of anti-histaminics such as levocarbastine reduce inflammation, whereas mast cell stabilizers prevent mast cell degranulation on exposure to allergans.[12,13] Topical corticosteroids are the most potent agents to control inflammatory symptoms, but their use is not devoid of side-effects.[14,15] Recently, introduced topical agents have both anti-histaminic and mast cell stabilization action.[16] Their use can control acute symptoms and prevent relapses as well. These agents (such as olopatadine, bepotastine, and alcaftadine) are FDA approved for use in allergic conjunctivitis, but there is not much literature comparing these three agents directly. Being a chronic condition, prudent use of medicament is needed because drug treatment is prolonged and frequent. There were only minimal research studies done in VKC by comparing efficacy and safety of 0.1% olopatadine and 1.5% bepotastine in India. Considering the paucity of comparative studies between long-acting anti-histamines, Alcaftadine 0.25% and Olopatadine hydrochloride 0.2% and Bepotastine besilate 1.5% in Allergic conjunctivitis with regard to efficacy and safety amongst Indian patients, this study was undertaken.

Material and methods

This randomized, prospective, parallel-group study was done the Department of Ophthalmology, Anugrah Narayan Magadh Medical College Hospital (ANMMCH), Gaya, Bihar, India for 11 months, after taking the approval of the protocol review committee and institutional ethics committee. After taking informed consent detailed history was taken from the patient or relatives.

Patients with severe allergic conjunctivitis, need for topical steroids or topical immunosuppressive, contact lens wearers, patients with an intra-ocular pressure of more than 21 mm Hg in either eye or any

type of glaucoma, history of hypersensitivity to the study medications or their components (including benzalkonium chloride), history of an ocular herpetic infection, an active ocular infection, or any significant illness, taking systemic steroids or antihistamines currently or within 7 days prior to enrolment, pregnant, planning pregnancy, or nursing/lactating and use of any other topical ocular medications were excluded from the study. A total of 90 patients with mild or moderate allergic conjunctivitis were randomized into three groups with an allocation ratio of 1:1:1 using computer-generated random number sequence to receive topical anti-allergic medication for 14 days as follows:

Group 1: Topical 0.25% Alcaftadine eye drops OD
Group 2: Topical 0.2% Olopatadine eye drops OD
Group 3: Topical 1.5% Bepotastine besilate eye drops BID.

Complete general, physical, and ophthalmologic examination was done. Patients were examined and their baseline symptoms and signs (TOSS) were recorded. Demographic data, ocular and medical histories, concomitant medications, physical examination, clinical examination, including recording of vital signs, Ophthalmological examination and details of drug prescribed by the treating ophthalmologist were recorded in the study pro forma at baseline visit (visit 1). Follow-up visits were on day 3 (visit 2), day 7 (visit 3) and day 14 (visit 4) after administering the study drugs. At each follow-up visit data on concomitant medications, ocular symptoms and ocular signs using hyperaemia score (Table 1)[17] graded by slit-lamp examination by the investigator and adverse events (AEs) were collected. In case of relapse, the patient was asked to visit OPD on Day 21. Medication compliance was assessed with the help of a medication compliance card. Safety of study medications was assessed by ADRs.

Statistical analysis

The sample size was calculated at a confidence level of 95%, the sample size determined was 50subjects in each treatment group. All data were analyzed by Microsoft Excel and Statistical Package for Social Sciences (SPSS version 23.0). Continuous variables are presented as mean ± standard deviations (SD's) and the categorical variables as percentages. Comparison of TOSS and adverse effect scores between and within group at different time points (baseline, days 1, 3, 7 and 14) was performed by ANOVA with repeated measure analysis and with Bonferroni corrections. The value of $p < 0.05$ were considered to be statistically significant.

Table 1: TOSS and hyperaemia score grading

0	Indicating no symptoms
1+	Mild symptoms of discomfort which were just noticeable
2+	Moderate discomfort noticed most of the day but did not interfere with daily activities
3+	Severe symptoms interfering with daily activities

Table 2: Hyperaemia score Grading of signs

0 -No	Normal
0.5 -Trace	Inconsistent rose red hyperaemia
1-Mild	Reddish color
2-Moderate	Bright red color
3-Severe	Bright and intense diffuse hyperaemia

Results

A total of 105 patients were screened for the study of which 90 patients with mild or moderate allergic conjunctivitis, who met the required inclusion and exclusion criteria were included in the study. Age, gender, and TOSS and hyperaemia scores were matched at baseline [Table 2]. Table 2 represents the demographic profile of the patients included in the study. Both the treatment groups were matched with respect to baseline demographic characteristics.

The 4 major complaints recorded by patients were itching (30 patients, 100%), redness (22 patients, 73.33%), tearing (25 patients, 83.33%), and swelling (13 patients, 43.33%). The total ocular symptom score (TOSS) showed a consistent decrease in subsequent visit in all the Groups and it was statistically significant, when compared from baseline to 14th day in all the groups (p = 0.0008) (Table 3) The difference in mean TOSS between (Group A) Alcaftadine and (Group C) bepotastine treatment groups was observed at the third day of follow-up. This showed early relief of allergic conjunctivitis symptoms by bepotastine (5.57 ± 1.26) compared to Alcaftadine (mean (6.31 ± 1.47) and olopatadine (6.31 ± 1.47) but this was not statistically significant.

Total ocular symptom score at 14th day visit with post hoc Tukey HSD test showed mean of Alcaftadine group vs mean of olopatadine group – $p < 0.05$, mean of olopatadine group vs mean of bepotastine group – $p < 0.01$, which were statistically significant whereas mean of Alcaftadine group vs mean of bepotastine group showed non-significant difference. Alcaftadine was found to be better than olopatadine in reducing the Allergic Conjunctivitis symptoms using TOSS score at 14th-day visit ($p < 0.5$). Although there is no significant difference between bepotastine and Alcaftadine groups, bepotastine showed a better reduction of symptoms compared to Olopatadine group using TOSS score at 14th-day visit (p<0.1). Conjunctival hyperaemia had reduced in all the treatment groups but there was a significant reduction in Alcaftadine and Bepotastine treatment groups at 14th day compared to olopatadine group (p = 0.0023) (Table-4) No systemic or ocular serious adverse events were reported. Most common adverse events were burning sensation (4) in Alcaftadine group and taste impairment (4) in bepotastine group, followed by headache (3) in Alcaftadine group, dizziness (3) in olopatadine and mild redness (3) in bepotastine group were noted. No significant difference in the number of adverse events was noted among the three groups.

Table 2: demographic profile of the patients

Parameter	**Group A Alcaftadine (n=30)**	**Group B Olopatadine (n=30)**	**Group C Bepotastine (n=30)**	**P-value**
Age (years) (Mean±SD)	29.78 ±11.63	29.88±9.74	32.23±10.69	0.15
Gender n (%)				0.17
Male	21 (70%)	18(60%)	25 (83.33%)	
Female	9 (30%)	12 (40%)	5 (16.67%)	
Total Ocular Symptom Score (TOSS)	9.03±2.54	9.03±2.75	9.15±2.63	0.59

Table 3: Total ocular symptom score at different visits

Parameter	Group A Alcaftadine	Group B Olopatadine	Group C Bepotastine	P-value
	(n=30) Mean (SD)	(n=30) Mean (SD)	(n=30) Mean (SD)	
Day 1 (Baseline)	8.24 (2.31)	8.24 (2.31)	8.06 (2.24)	0.59
Day 3	6.31 (1.47)	6.31 (1.47)	5.57 (1.26)	0.16
Day 7	2.6(1.23)	2.5 (0.71)	2.4 (1.01)	0.19
Day 14	0.3 (0.43)	0.5 (0.52)	0.2 (0.31)	0.0008

Table 4: Conjunctival hyperaemia score at different visits

Variable	Group A Alcaftadine	Group B Olopatadine	Group C Bepotastine	P-value
	(n=30) Mean (SD)	(n=30) Mean (SD)	(n=30) Mean (SD)	
Day 1 (Baseline)	1.5 (0.70)	1.6 (0.70)	1.6 (0.61)	0.9
Day 3	0.7 (0.52)	0.7 (0.52)	0.7 (0.45)	0.9
Day 7	0.2 (0.17)	0.2 (0.17)	0.2 (0.17)	0.8
Day 14	0.006 (0.08)	0.05 (0.12)	0.005 (0.07)	0.0023

Discussion

Most of the earlier studies comparing the efficacy of anti-allergic medications were according to conjunctival allergen challenge. In this model, antigens are instilled in both eyes of subjects, and then, the efficacy of anti-allergic medications to reduce symptoms is evaluated. This model can mimic acute allergic response in a normal subject but not exactly similar to acute response in a patient with chronic allergic conjunctivitis or an acute response in a patient prone to allergic conjunctivitis. Ocular allergy is a commonly encountered pathology in clinical practice, with an increase in the number of patients noticed in the last decade with a prevalence of approximately 40% of the population globally. Avoidance of allergens plays a key role in the prevention of allergic conjunctivitis. Addition of anti-histamine reduces inflammation, whereas mast cell stabilizers prevent mast cell degranulation on an exposure to allergens. Topical corticosteroids are the most potent agents to control inflammatory symptoms of allergic conjunctivitis but there is a risk of many side effects. Newer topical agents have both anti-histamine and mast cell stabilization action. Their use can control acute symptoms and prevent relapses.[18] A comparative study done by Dudeja I, et al. concluded Alcaftadine 0.25%, olopatadine 0.2%, and bepotastine 1.5% eye drops have been proved to be safe and well-tolerated topical medication for allergic conjunctivitis.[17] This study resounded the same, and the medications were found to be safe, with minimal transient side effects of burning sensation and taste impairment noticed by a few patients (more in group 1 and group 3, respectively). Most patients responded to treatment and were willing to continue the eye drop, if indicated.

The efficacy of these anti-allergic medications over placebo has been proven in a study conducted by Donshik et al. All three medications showed significant relief in symptoms of redness and itching, which was proved statistically.[19] This study showed that all three study medications provide significant relief in symptoms from baseline to 14 days.

A study done by Ackerman S, et al. compared 0.25% Alcaftadine and 0.2% olopatadine using conjunctival allergen challenge found Alcaftadine superior to olopatadine at the earliest time point (3 min post-challenge). Alcaftadine showed

significant relief in chemosis at 16 and 24 h post-instillation.[20] Another study done by McLaurin EB, et al., with 284 subjects found that subjects treated with Alcaftadine had a lower overall mean itch score of 3, 5, and 7 min than those treated with olopatadine.[21] This study results also showed Alcaftadine is better in reducing the Allergic conjunctivitis symptoms compared to Olopatadine at 14th day, which is statistically significant (p = 0.0008).

A comparative study done by McCabe et al. showed Bepotastine provided better relief of ocular allergy symptoms and nonocular symptoms associated with Allergic conjunctivitis, that is, runny nose compared to olopatadine. The study also found that a higher percentage of patients preferred bepotastine over olopatadine for treatment.[22] The current study indicates a greater significant relief of Allergic conjunctivitis symptoms with Bepotastine besilate than olopatadine group at 14th day, which is statistically significant (p = 0.0008).

Trials have been conducted at a cellular level, animals treated with Olopatadine and Alcaftadine showed similar efficacy and safety profiles. One such study done by Ono SJ, et al. found a decrease in expression of the junctional protein, ZO-1, which is caused by allergen challenge with Alcaftadine compared to olopatadine. In addition, Alcaftadine showed significantly lower conjunctival eosinophil infiltration caused by allergen challenge in animal studies.[23]

Clinical trials, thus, have proved the efficacy of all three medications for relief of symptoms of allergic conjunctivitis and found differences between medications in one or the other parameter. In our study, all three medications are effective in control of allergy symptoms with bepotastine group and Alcaftadine groups showing statistical significance as compared to olopatadine group in alleviating the allergic conjunctivitis symptoms.

Conclusion

According to the findings of the current investigation, all three topical ophthalmic medicines employed in the study are safe and effective in the treatment of allergic conjunctivitis. Bepotastine and Alcaftadine, on the other hand, appear to outperform Olopatadine in curing the symptoms of allergic conjunctivitis.

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