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Original Research Article

Randomized Clinical Parallel Trial Comparing Safety and Efficacy of Alcaftadine 0.25%, Olopatadine Hydrochloride 0.2% and Bepotastine Besilate 1.5% in Allergic Conjunctivitis

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Abstract

Aim: The aim of the present study was to compare the efficacy and safety of Alcaftadine 0.25%, Olopatadine hydrochloride 0.2%, and Bepotastine besilate 1.5% ophthalmic solutions in the treatment of allergic conjunctivitis.

Methods: The study was an observer‐masked, randomized, prospective, parallel‐group study conducted at the Department of Ophthalmology for 18 months. A total of 270 patients were screened for the study, of whom 240 patients with mild or moderate allergic conjunctivitis, who met the required inclusion were enrolled in the study.

Results: In the present study, male was predominant in all the three groups as compared to females. Baseline mean TOSS scores for Alcaftadine group, Olopatadine group and Bepotastine besilate group were (7.63±2.38), (7.68±2.40) and (7.49±2.36) respectively. 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 ($p = 0.0007$). 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 (4.9 ± 1.58) compared to Alcaftadine (mean (5.2±1.57) and olopatadine (5.4±1.59) but this was not statistically significant. 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 ($p = 0.0032$, ANOVA—post hoc Tukey's analysis).

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

Ocular allergic diseases are common worldwide and mainly consist of conjunctivitis with or without involvement of cornea. Allergic Conjunctivitis (AC) is the most common type of ocular allergy and affects 6-30 % of the general population and up to 30% of children and adolescents. [1] It is continually exposed to a variety of airborne antigens that can lead to inflammation, termed allergic conjunctivitis, [2] which is an ocular surface inflammatory disease. It is predominantly Ig E‐mediated Type I hypersensitivity reaction where allergen binds to specific Ig E molecules, triggers mast cell degranulation and subsequent increase in histamine leading to activation of both H1 and H2 types of histamine receptors. [3] Eye allergies can be seasonal, perennial, or chronic; and, are a part of generalised allergic syndromes like seasonal or perennial keratoconjunctivitis which are directly related to allergic diseases like rhinitis, asthma, or other atopic conditions. [4]

Ocular allergic response is not confined to conjunctiva but is a disease affecting the entire ocular surface including conjunctiva, lids (with their high content of mast cells), cornea, tear film (with its immunoglobulins) and lacrimal gland. [5] Ocular surface diseases are classified into Seasonal Allergic Conjunctivitis (SAC), Perennial Allergic Conjunctivitis (PAC), Vernal Keratoconjunctivitis (VKC), Atopic Keratoconjunctivitis (AKC), contact blepharoconjunctivitis; and non-allergic hypersensitivity ailments like Giant Papillary Conjunctivitis (GPC). [6] It is characterized by signs and symptoms ranging from itching, watering, redness, foreign body sensation, burning, photophobia, lid edema, conjunctival hyperemia, chemosis, watery or mucoid discharge, papillary reaction to severe sight threatening corneal complications. [7,8]

Pharmacological treatment of allergic conjunctivitis includes H1 receptor blockade, mast cell stabilization, and blocking of cytokine production and prostaglandin formation. [9] Topical agents having dual antihistaminic and mast cell stabilising activity are first line measures in in mild to moderate cases; in refractory, complicated and severe cases, additional treatment options are corticosteroids and immunomodulators. [10] Commonly used topical anti-histamines are Olopatadine 0.2 %, Alcaftadine 0.25 % are approved once-daily and Bepotastine besilate 1.5%, twice daily dual-acting antiallergic agents. It helps in relieving acute symptoms in milder disease and reduce the use of topical steroids for the same. Olopatadine is a specific H1 inhibitor and has a rapid onset of action. It also has anti-inflammatory effects which include suppression of interleukins (IL) 6 and 8 production by inhibiting histamine related signalling pathways. [2,12] Alcaftadine is an antagonist at H1, H2, and H4 receptor and has onset of action within fifteen minutes that provides relief from ocular itching in early phase and also stabilizes mast cells by inhibiting release of mediators such as cytokines and lipid mediators in the late phase of an ocular allergic response and decreases chemotaxis, eosinophil activation thereby exerts anti-inflammatory property. [3,11,13,14] Bepotastine besilate 1.5% ophthalmic solution is the dual-action agent, which combines strong antihistaminic activity with mast cell-stabilizing properties to provide both rapid and long-lasting relief in allergic conjunctivitis. [15]

Hence, this study was undertaken to compare 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.

The aim of the present study was to compare the efficacy and safety of Alcaftadine 0.25%, Olopatadine hydrochloride 0.2%, and Bepotastine besilate 1.5% ophthalmic solutions in the treatment of allergic conjunctivitis.

Materials and Methods

The study was an observer-masked, randomized, prospective, parallel-group study conducted at the Department of Ophthalmology, Nalanda Medical College and Hospital, Patna, Bihar, India for 18 months . A total of 270 patients were screened for the study of whom 240 patients with mild or moderate allergic conjunctivitis, who met the required inclusion and exclusion criteria were enrolled in the study.

Diagnosis of allergic conjunctivitis was made clinically according to the presence of classical signs and symptoms. Total Ocular Symptom Scoring System (TOSS) scoring was used to grade the signs and symptoms. All patients aged between 18 and 60 years belonging to either gender, with mild-to-moderate allergic conjunctivitis[16] presenting to outpatient department were included after obtaining written informed consent.

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 240 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. A deviation of ±1 a day for the first follow‑up and ±2 days for subsequent follow‑up was accepted. At each follow‑up visit data on concomitant medications, ocular symptoms and ocular signs using hyperaemia score [16] 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 80 subjects in each treatment group. All data were analyzed by Microsoft Excel and Statistical Package for Social Sciences (SPSS version 26.0). 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 $p < 0.05$ was considered to be statistically significant.

Results

Table 1: Baseline demographic characteristics

	Group A Alcaftadine (*n*=80)	**Group B Olopatadine (*n*=80)**	**Group C Bepotastine (*n*=80)**	***P***
Age (years) (Mean±SD)	27.63±9.18	28.62±9.16	29.07±8.82	0.22
Gender ‑ *n* (%)				0.32
Male	52 (65%)	42 (52.50%)	60 (75%)	
Female	28 (35%)	38 (47.5%)	20 (25%)	
Total Ocular Symptom Score (TOSS)	7.63±2.38	7.68±2.40	7.49±2.36	0.7

In the present study, male was predominant in all the three groups as compared to females. Baseline mean TOSS scores for Alcaftadine group, Olopatadine group and Bepotastine besilate group were (7.63±2.38), (7.68±2.40) and (7.49±2.36) respectively.

Table 2: Total ocular symptom score at different visits

Variable	**Group A Alcaftadine (*n*=80) Mean (SD)**	**Group B Olopatadine (*n*=80) Mean (SD)**	**Group C Bepotastine (*n*=80) Mean (SD)**	***P*- valu**
Day 1 (Baseline)	7.63 (2.38)	7.68 (2.40)	7.49 (2.36)	0.7
Day 3	5.2 (1.57)	5.4 (1.59)	4.9 (1.58)	0.12
Day 7	2.5 (1.05)	2.5 (0.95)	2.3 (1.06)	0.36
Day 14	0.2 (0.45)	0.5 (0.58)	0.1 (0.38)	0.0007

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 ($p = 0.0007$). 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 (4.9 ± 1.58) compared to Alcaftadine (mean (5.2 ± 1.57) and olopatadine (5.4 ± 1.59) but this was not statistically significant.

Table 3: Conjunctival hyperaemia score at different visits

Variable	**Group A Alcaftadine (*n*=80) Mean (SD)**	**Group B Olopatadine (*n*=80) Mean (SD)**	**Group C Bepotastine (*n*=80) Mean (SD)**	***P*- value**
Day 1 (Baseline)	1.5 (0.85)	1.5 (0.87)	1.3 (0.87)	0.7
Day 3	0.9 (0.61)	0.8 (0.62)	0.9 (0.59)	0.6
Day 7	0.4 (0.26)	0.5 (0.25)	0.4 (0.29)	0.7
Day 14	0.009 (0.07)	0.05 (0.17)	0.008 (0.04)	0.0032

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 nonsignificant 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 was 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 ($p = 0.0032$, ANOVA—post hoc Tukey's analysis).

Table 4: Adverse drug reactions of treatment groups

Adverse drug reaction	Group A	Group B	Group C
Headache	2	1	2
Burning sensation	4	1	1
Dizziness	0	2	1
Mild redness	1	1	2
Taste impairment	0	1	2

Most common adverse events were burning sensation in Alcaftadine group and taste impairment in bepotastine group, followed by headache in Alcaftadine group, dizziness in olopatadine and mild redness in bepotastine group were noted. No significant difference in the number of adverse events was noted among the three groups.

Discussion

Allergic Conjunctivitis (AC) is the inflammation of conjunctiva in response to an allergen. It is one of the most common forms of conjunctivitis. Ocular allergies affect 6%-30% of the general population. [17] Recent clinical observations suggests that ocular allergic response is not confined to conjunctiva but is a disease affecting the entire ocular surface including conjunctiva, lids(with their high content of mast cells), cornea, tear film(with its immunoglobulins) and lacrimal gland. [18] It is characterized by signs and symptoms ranging from itching, watering, redness, foreign body sensation, burning, photophobia, lid edema, conjunctival hyperemia, chemosis, watery or mucoid discharge, papillary reaction to severe sight threatening corneal complications. [19,20] The exposure of conjunctiva to an allergen initiates an immunological hypersensitivity reaction that heralds the onset of allergic eye disease. Early phase response occurs when allergen specific IgE binds to Fc receptors on surface of mast cells leading to its degranulation and release of pre formed mediators mainly histamine and newly synthesized mediators mainly PGD2. The released histamine binds to H1 receptor on cell surfaces of conjunctival tissue resulting in vasodilatation and increased vascular permeability which is responsible for itching, burning and tearing. Binding to H2 receptor results in increased mucus production at ocular surface. [21] PGD2, considered being ten times more potent than histamine [22], increases conjunctival micro vascular permeability leading to redness, itching, chemosis and mucus production.

In the present study, male was predominant in all the three groups as compared to females. Baseline mean TOSS scores for Alcaftadine group, Olopatadine group and Bepotastine besilate group were (7.63±2.38), (7.68±2.40) and (7.49±2.36) respectively. 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 ($p = 0.0007$). 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 (4.9 ± 1.58) compared to Alcaftadine (mean (5.2 ± 1.57) and olopatadine (5.4 ± 1.59) but this was not statistically significant. 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. 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. 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. 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

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 nonsignificant 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 was 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 ($p = 0.0032$, ANOVA—post hoc Tukey's analysis). In a study of 50 patients of VKC, Shruti V et al., demonstrated that Bepotastine 1.5% eye drops provided better and quicker relief of watering, ocular discomfort, and conjunctival hyperaemia after 8 weeks of follow-up; olopatadine 0.1% eye drops provided faster improvement in papillary hypertrophy. However, both drugs were equally effective in reducing itching. [23] In another comparative study from north India, Gupta P et al., randomised 65 patients of VKC aged 5-15 years in two study arms. Patients in arm A were given Bepotastine 1.5% and those in arm B were given Olopatadine 0.1% twice daily. After three weeks of therapy, patients in both arms showed similar improvement in the composite symptoms and signs severity scores. In contrast to Shruti V et al., they have shown that reduction in ocular itching score was more in the bepotastine arm as compared to the olopatadine arm.[24] Both the studies, however, didn't mention whether they have excluded severe cases of VKC who would have required other pharmacological interventions in addition to topical dual-action agents. [24]

Most common adverse events were burning sensation in Alcaftadine group and taste impairment in bepotastine group, followed by headache in Alcaftadine group, dizziness in olopatadine and mild redness in bepotastine group were noted. No significant difference in the number of adverse events was noted among the three groups.

Conclusion

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.

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