

## Original research article

# In Allergic Conjunctivitis, Comparative Assessment of the Safety and Effectiveness of Alcaftadine 0.25 Percent, Olopatadine Hydrochloride 0.2 Percent, and Bepotastine Besilate 1.5 Percent

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## Abstract

**Aim:** The aim of the present study 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 150 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:** A total of 180 patients were screened for the study of which 150 patients with mild or moderate allergic conjunctivitis, who met the required inclusion and exclusion criteria were included in the study. The 4 major complaints recorded by patients were itching (50 patients, 100%), redness (37 patients, 74%), tearing (42 patients, 84%), and swelling (20 patients, 40%). 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 ( $p = 0.0006$ ). 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 ( $5.77 \pm 1.46$ ) compared to Alcaftadine (mean ( $6.36 \pm 1.58$ )) and olopatadine ( $6.36 \pm 1.58$ ) 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 ( $p = 0.0025$ )

**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

Allergies are the fifth leading cause of the world's chronic illnesses, affecting 40% of the population.<sup>1</sup> Globally, in the last 10 years, there has been a drastic increase in allergic diseases. The occurrence of allergic diseases among children is rising moderately in between 0.3% and

20.5%. There are so many causative factors such as genetics, pets, air pollution, and early childhood exposure being the reasons for this increase.<sup>2</sup> Among the causes of ocular morbidity in India, allergic conjunctivitis is at the second position and involves about 15%–20% of people attending ophthalmology clinic. School absenteeism in children is common because of its distressing symptoms.<sup>3</sup> Allergic conjunctivitis includes persistent allergic conjunctivitis, seasonal allergic conjunctivitis (SAC), vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis. SAC is about 25%–50% of cases.<sup>4</sup> Number of causes have been considered for this increase such as genetics, air pollution, pets, etc.<sup>5</sup> 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.<sup>6</sup> Seasonal and perennial conjunctivitis are in response to exposure to specific allergen and are predominantly mediated by IgE antibodies activating the mast cells.<sup>7,8</sup> VKC is in response to non-specific allergens and is mediated mainly by Th2 cells, but mast cells and eosinophils also play a major role.<sup>9,10</sup> Atopic conjunctivitis occurs in patients predisposed to atopy. It is mediated by both Th2 response and mast cells.<sup>11</sup> Avoidance of allergens and lubricants plays a key role in the management of allergic conjunctivitis. Addition of anti-histaminics such as levocabastine reduce inflammation, whereas mast cell stabilizers prevent mast cell degranulation on exposure to allergens.<sup>12,13</sup> Topical corticosteroids are the most potent agents to control inflammatory symptoms, but their use is not devoid of side-effects.<sup>14,15</sup> Recently, introduced topical agents have both anti-histaminic and mast cell stabilization action.<sup>16</sup> 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 in the Department of Ophthalmology, Nalanda medical college and hospital Patna, Bihar, India, for 1 year, after taking the approval of the protocol review committee and institutional ethics committee.

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 150 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)<sup>17</sup> 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 50 subjects in each treatment group. All data were analyzed by Microsoft Excel and Statistical Package for Social Sciences (SPSS version 22.0). Continuous variables are presented as mean  $\pm$  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

### 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 180 patients were screened for the study of which 150 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 (50 patients, 100%), redness (37 patients, 74%), tearing (42 patients, 84%), and swelling (20 patients, 40%). 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 14<sup>th</sup> day in all the groups ( $p = 0.0006$ ) (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 ( $5.77 \pm 1.46$ ) compared to Alcaftadine (mean ( $6.36 \pm 1.58$ )) and olopatadine ( $6.36 \pm 1.58$ ) but this was not statistically significant.

Total ocular symptom score at 14<sup>th</sup> 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 14<sup>th</sup> 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 14<sup>th</sup> 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 14<sup>th</sup> day compared to olopatadine group ( $p = 0.0025$ ) (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=50)	Group B Olopatadine (n=50)	Group C Bepotastine (n=50)	P-value
Age (years) (Mean±SD)	30.15±11.02	30.48±9.02	31.02±9.82	0.16
<b>Gender n (%)</b>				
Male	34 (68%)	29(58%)	40 (80%)	0.18
Female	16 (32%)	21 (42%)	10 (20%)	
Total Ocular Symptom Score (TOSS)	8.94±2.22	8.74±2.63	8.23±2.19	0.69

**Table 3: Total ocular symptom score at different visits**

Parameter	Group A Alcaftadine (n=50) Mean (SD)	Group B Olopatadine (n=50) Mean (SD)	Group C Bepotastine (n=50) Mean (SD)	P-value
Day 1 (Baseline)	8.26 (2.33)	8.26 (2.33)	8.09 (2.26)	0.67
Day 3	6.36 (1.58)	6.36 (1.58)	5.77 (1.46)	0.17
Day 7	2.8(1.22)	2.7 (0.78)	2.6 (1.02)	0.21
Day 14	0.4 (0.45)	0.6 (0.59)	0.3 (0.38)	0.0006

**Table 4: Conjunctival hyperaemia score at different visits**

Variable	Group A Alcaftadine (n=50) Mean (SD)	Group B Olopatadine (n=50) Mean (SD)	Group C Bepotastine (n=50) Mean (SD)	P-value
Day 1 (Baseline)	1.6 (0.71)	1.7 (0.72)	1.7 (0.64)	0.7
Day 3	0.8 (0.56)	0.8 (0.56)	0.8 (0.49)	0.8
Day 7	0.3 (0.19)	0.3 (0.19)	0.3 (0.19)	0.9
Day 14	0.007 (0.08)	0.05 (0.15)	0.005 (0.08)	0.0025

## Discussion

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.<sup>18</sup> This study is a double-blinded, observer masked, randomized study directly comparing the efficacy of three topical anti-allergic medications, that is, Alcaftadine, olopatadine, and bepotastine in mild to moderate allergic conjunctivitis. These topical agents are FDA approved for use in allergic conjunctivitis, but trials compared these three medications are limited.

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.<sup>17</sup> 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.<sup>19</sup> 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.<sup>20</sup> 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.<sup>21</sup> This study results also showed Alcaftadine is better in reducing the Allergic conjunctivitis symptoms compared to Olopatadine at 14<sup>th</sup> day, which is statistically significant ( $p = 0.0006$ ).

A comparative study done by McCabe et al. showed Bepotastine provided better relief of ocular allergy symptoms and non ocular 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.<sup>22</sup> The current study indicates a greater significant relief of Allergic conjunctivitis symptoms with Bepotastine besilate than olopatadine group at 14<sup>th</sup> day, which is statistically significant ( $p = 0.0006$ ).

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.<sup>23</sup>

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

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.

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