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Original Research Article

Comparative Assessment of Alcaftadine 0.25%, Olopatadine Hydrochloride 0.2% and Bepotastine Besilate 1.5% as Anti-Allergic Conjunctivitis Agents

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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 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=0.0006). 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 (5.57 ± 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 ($p = 0.0021$).

Conclusion: we concluded that 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, Olopatadine, allergic conjunctivitis.

Introduction

Allergic conjunctivitis is one of the most common conditions requiring treatment by ophthalmologists, optometrists, and allergists.[1] While prevalence studies of conjunctivitis alone are limited, epidemiologic data have been derived from studies of the commonly coexisting nasal symptoms or rhino conjunctivitis and are wide ranging with large global variations[2,3] In the United States, the Allergies in America survey conducted in 2006 estimated that 14.2% of the adult population had been affected by allergic rhino conjunctivitis, while a more recent analysis based on National Health and Nutrition Examination Survey III data in a sample size of 20,010 adults found that 40% of participants were affected by allergic rhino conjunctivitis in a 12-month period.[2,4,5] The International Study of Asthma and Allergy in Childhood spanning 52 countries reported that allergic conjunctivitis affects 1.4–39.7% of children and adolescents.[6] Ocular itching, the hallmark symptom of allergic conjunctivitis, is often accompanied by tearing, conjunctival redness, eyelid swelling, and chemosis[7] Allergic conjunctivitis is mediated by immunoglobulin E-activated degranulation of mast cells and the release of a cascade of inflammatory mediators, including histamine, in response to allergens.[8,9] Histamine release and activation of histamine H1 receptors in the conjunctiva leads to ocular itching, while stimulation of H2 receptors on the ocular surface results in vasodilation and is associated with ocular redness, eyelid swelling, and chemosis.[10,11] Recent evidence suggests that histamine binding to and activation of H4 receptors also play a role in allergic conjunctivitis[12,13] Topical ophthalmic antihistamines are the primary treatment options for allergic conjunctivitis. Currently, alcaftadine 0.25% and olopatadine 0.2% are the only approved once-daily ophthalmic solutions for allergic conjunctivitis in the United States.[14,19] Both olopatadine and alcaftadine are classified as dual-action antiallergic agents, directly inhibiting histamine receptor activation and indirectly reducing allergic responses by stabilizing mast cells.20 [20]. Clinical studies evaluating alcaftadine and olopatadine as treatment options for allergic conjunctivitis have used the conjunctival allergen challenge (CAC) model to assess clinical efficacy.[21,22] The CAC model was designed to mimic the signs and symptoms of an ocular allergic response in a controlled setting, providing an alternative to environmental allergy trials that are subject to variable allergen exposures. The model has been established as the standard for demonstrating efficacy and safety of topical ophthalmic antiallergic solutions seeking approval from the United States Food and Drug Administration.[21] CAC testing consists of instillation of the study drug or comparator(s) into the eye followed by an allergen challenge at a predetermined time post-instillation. The effect is then graded using a standardized severity scale, allowing assessment of both the onset of action and duration of effect.[15,17,22]Two recently completed similarly designed studies are the first to have compared the efficacy and duration of action of once-daily alcaftadine 0.25% and olopatadine 0.2% and placebo using the CAC model. The first study demonstrated that alcaftadine 0.25% was safe and effective in preventing signs and symptoms

of allergic conjunctivitis at both 16 and 24 h after treatment instillation.[23] Differences in treatment effect between alcaftadine 0.25% and olopatadine 0.2% were most pronounced at the earliest time point post-CAC, when alcaftadine 0.25% ophthalmic solution was statistically superior to olopatadine 0.2% ophthalmic solution. The second study further assessed treatment outcome and confirmed statistical superiority of treatment with alcaftadine 0.25% relative to olopatadine 0.2% in mean itch reduction at the same time point post-CAC, at 16 h after treatment instillation.[24]

Material and methods

This randomized, prospective, parallel-group study was done the Department of Ophthalmology, Patna Medical College and Hospital, Patna, Bihar, India. 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.

Methodology

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)[25] 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 21.0). 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

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 = 0.0006) (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 (5.57 ± 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 = 0.0021) (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)	0.0006

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)	0.0021

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.[26]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.[25] 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.[27]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.[28] 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[29] This study results also showed Alcaftadine is better in reducing the Allergic conjunctivitis symptoms compared to Olopatadine at 14^{th} 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 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.[30] The current study indicates a greater significant relief of Allergic conjunctivitis symptoms with Bepotastine besilate than olopatadine group at 14^{th} 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.[31]

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

The present study concluded that 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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