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Research Article

Comparative Efficacy of Olopatadine 0.2%, Bepotastine 1.5% and Alcaftadine 0.25% in Treatment of Allergic Conjunctivitis

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Abstract

Objective: To compare the efficacy of 0.2% olopatadine, 1.5% bepotastine and 0.25% alcaftadine in treatment of allergic conjunctivitis.

Design: This was a prospective study conducted on 90 consecutive patients who presented to out-patient department with signs and symptoms of allergic conjunctivitis from December 2018 to July 2020 i.e. 20 months. Randomization was done by envelope method in which randomly generated treatment regimens were sealed within opaque envelopes and allocated to the patients after obtaining their informed consent.

Results: Out of 90 patients, 55 (61.11%) patients were males. Overall mean age was 16.67 ± 10.59 years. 74.44% patients resided in rural areas. 38(42.22%) patients had symptoms of allergic rhinitis such as running nose and sneezing. The mean time for beginning of itch relief after instilling eye drops at first visit was 6.35 ± 1.99 minutes with no significant difference between Group A, B and C ($p = 0.58$). Paired analysis of median itch scores showed significant improvement in median itch score ($p< 0.05$) at each follow-up visit when compared to the previous visit in all groups. On comparing the median symptom scores and sign scores, there was no statistically significant difference ($p > 0.05$) between the scores of group A, B and C at the time of presentation as well as at follow-up visit on day 1, day 3, 1 week, 1 month and 3 months. All the symptoms were completely resolved in group A, B and C by the end of 1 month. Papillary reaction persisted in 35(38.89%) of patients at the end of 3 months. The average cost of treatment for 1 month was 280.00 INR, 495.00 INR and 450 INR in Group A, Group B and Group C respectively which shows that olopatadine 0.2% was most cost-effective.

Conclusion: Olopatadine 0.2%, bepotastine 1.5% and alcaftadine 0.25% are comparable in treating symptoms and signs of mild to moderate allergic conjunctivitis. None of these drugs are effective as monotherapy in treating severe allergic conjunctivitis. Olopatadine 0.2% is most cost-effective and equally effective as bepotastine 1.5% and alcaftadine 0.25% in treating allergic conjunctivitis. Olopatadine 0.2% may be prescribed to patients as initial therapy considering the low socio-economic status of majority of patients in our country.

Keywords: Allergic; Conjunctivitis; Olopatadine; Bepotastine; Alcaftadine

Abbreviations

AC: Allergic Conjunctivitis; SAC: Seasonal Allergic Conjunctivitis; PAC: Perennial Allergic Conjunctivitis; VKC: Vernal Keratoconjunctivitis; AKC: Atopic Keratoconjunctivitis.

Introduction

Allergic conjunctivitis represents one of the most common ocular conditions encountered in clinical practice. It is an ocular manifestation of IgE immune responses to allergen exposure in sensitized individuals [1]. It can be classified as seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis and giant papillary conjunctivitis.

Allergic response in SAC and PAC results from interaction of allergens with IgE bound to sensitized mast cells [2]. VKC is a chronic allergic inflammation of the ocular surface mediated mainly by Th2- lymphocytes with overexpression of mast cells, eosinophils, neutrophils, Th2 derived cytokines, chemokines, adhesion molecules, growth factors, fibroblasts and lymphocytes [3]. AKC is the ocular manifestation of systemic altered immune response, often associated with atopic dermatitis and with other allergic disorders such as rhinitis and asthma.

Symptoms of allergic conjunctivitis include itching, redness, watering, foreign body sensation, photophobia and discharge. Patients often present with a papillary reaction of the upper tarsal conjunctiva and limbus ranging in size from 1 mm to giant cobblestone papillae. Other signs include bulbar conjunctival hyperemia, a thick mucus discharge and corneal involvement, including superficial punctate keratitis, epithelial erosions, shield ulcers or plaques. Trantas dots represent lymphocytic infiltration of the limbal conjunctiva and are a classic sign of VKC.

The most common treatment approach for management of AC is the use of a topical pharmacologic medication to reduce the inflammation combined with non-pharmacologic remedies (e.g. cold compresses or artificial tears) to provide temporary symptomatic relief [4]. Antihistamine–mast cell stabilizing agents are considered first-line therapeutics for AC at present because they offer acute symptomatic relief and control inflammation. The antihistaminic action reduces the early phase of ocular allergy response such as itching whereas mast cell stabilization inhibits the release of inflammatory mediators which is associated with late phase response of ocular allergy. Dual-acting H1 receptor antagonist and mast cell stabilizer agents include olopatadine, ketotifen, azelastine, epinastine, bepotastine and alcaftadine. In our study, we compared the efficacy of olopatadine 0.2%, bepotastine 1.5% and alcaftadine 0.25% in treatment of allergic conjunctivitis.

Methods

A prospective study was conducted on 90 patients of allergic conjunctivitis visiting a tertiary care centre in North India after random selection. Randomization was done by envelope method. Randomly generated treatment regimens were sealed within opaque envelopes and were allocated to the patients after obtaining their informed consent. This study was conducted after obtaining approval from Institutional Review Board in accordance with the Declaration of Helsinki. Patients with a history of recent ocular surgery or retinal disease, signs of active ocular infection, hypersensitivity to any of the study drugs or its components and pregnant or lactating women were excluded from our study.

Patients presenting with symptoms of allergic conjunctivitis with history suggestive of the same were examined with the help of a slit-lamp to look for conjunctival hyperemia, papillary reaction, chemosis, lid edema and corneal epithelial signs. Symptoms such as itching, lacrimation, redness, foreign body sensation and discharge were graded on a 4-point scale wherein 0 denoted no symptoms and 3 denoted severe symptoms. Signs such as eyelid edema, bulbar conjunctival edema, palpebral hyperemia, papillary reaction and corneal epithelial signs were graded in a similar manner from 0 – 3 wherein 0 denoted absence of signs and 3 denoted severe signs.

Patients of group A were given olopatadine 0.2% ophthalmic solution (Winolap DS®, Sun Pharmaceutical Industries Ltd, Mumbai, India) once daily in the morning. Patients of group B were given bepotastine 1.5% ophthalmic solution (Bepofree®, Mankind Pharma, New Delhi, India) twice daily in the morning and evening. Patients of group C were given alcaftadine 0.25% ophthalmic solution (Al-

carex®, Ajanta Pharma, Mumbai, India) once daily in the morning. First dose was instilled under direct supervision at the time of presentation to note the average time for beginning of itch relief in each patient. Follow-up was done on day 1, day 3, at 1 week, 1 month and 3 months. Patients who showed minimal or no improvement at the end of one week were prescribed fluorometholone 0.1% thrice daily, tapered gradually over a period of 15 days.

All data was analyzed by IBM® SPSS® Statistics ver. 26 (Armonk, NY, USA). Chi square test was applied to compare gender and rural/urban distribution data between the three groups. Age distribution between the groups was analysed using one-way ANOVA test. Wilcoxon signed rank test was used to do paired analysis of median itch scores at each follow-up visit in each group. Inter-group comparison of median symptom scores and sign scores was done using Kruskal Wallis test. p value less than 0.05 was considered as statistically significant.

Results

Out of 90 patients, 55 (61.11%) patients were males and 35 (38.89%) were females. The mean age of subjects was 17.27 ± 11 years in group A, 19 ± 11.67 years in group B and 13.5 ± 8.33 years in group C. Overall mean age was noted to be 16.67 ± 10.59 years (Age wise distribution: Table 1).

Age group (years)	Group A	Group B	Group C	Total	Percentage
0-15	15	14	20	49	54.44%
16-30	12	9	8	29	32.22%
31-45	3	7	2	12	13.33%
Total	30	30	30	90	100%

Table 1: Age-wise distribution.

A total of 67(74.44%) patients with allergic conjunctivitis resided in rural areas. 38(42.22%) patients had symptoms of allergic rhinitis such as running nose and sneezing along with symptoms of allergic conjunctivitis.

At the time of presentation, itching was found to be the most common symptom present in 90 (100%) patients followed by lacrimation and redness present in 58 (64.44%) and 56 (62.22%) patients respectively. Discharge and foreign body sensation were less common and were present in 17 (18.89%) and 12 (13.33%) patients respectively (Figure 1). Mean time for beginning of itch relief after instilling eye drops at first visit was 6.83 ± 2.01 minutes, 6.17 ± 1.70 minutes and 6.07 ± 2.21 minutes in group A, B and C respectively ($p > 0.05$). Overall, the mean time for beginning of itch relief was 6.35 ± 1.99 minutes. Paired analysis of median itch scores at each follow up visit was done in Group A, B and C and a significant improvement in median itch score ($p < 0.05$) was noted at each follow-up visit when compared to the previous visit in all three groups (Table 2).

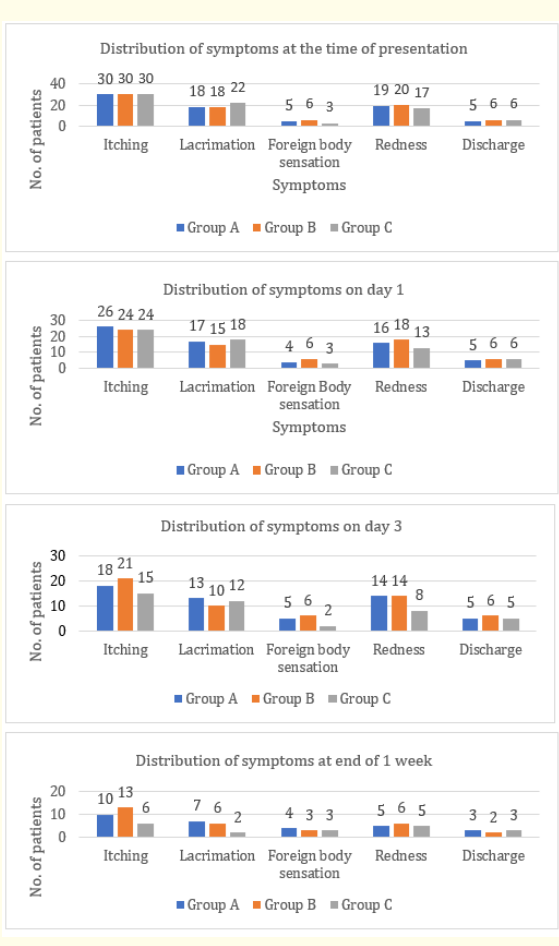

Figure 1: Frequency of symptoms.

On comparing the median scores for itching, lacrimation, redness, foreign body sensation, redness and discharge, there was no statistically significant difference between the symptom scores of group A, B and C at the time of presentation as well as at follow-up visit on day 1, day 3 and 1 week. All the symptoms were completely

Pairs in each group	Time intervals	Median itch scores	p value
Group A	At presentation	1	0.003
	1 day	1	
	Day 1	1	0.0002
	Day 3	1	
	Day 3	1	0.0005
	At end of 1 week	0	
Group B	At presentation	2	0.0001
	Day 1	1	
	Day 1	1	0.03
	Day 3	1	
	Day 3	1	0.0002
	At end of 1 week	0	
Group C	At presentation	1	0.0001
	Day 1	1	
	Day 1	1	0.001
	Day 3	0.5	
	Day 3	0.5	0.001
	At end of 1 week	0	

Table 2: Paired analysis of median itch scores

resolved in group A, B and C by the end of 1 month. Papillary reaction was the most common sign present at the time of presentation present in 77 (85.56%) patients followed by palpebral hyperemia present in 74 (82.22%) patients. Eyelid edema, bulbar conjunctival edema, Horner Trantas dots and corneal epithelial signs were less common signs present in 29 (32.22%), 23(25.56%), 15(16.67%) and 12 (13.33%) patients respectively. No statistically significant difference between median sign scores was noted in Group A, B and C ($p > 0.05$) at the time of presentation and follow-up visit on day 1, day 3, at the end of 1 week, 1 month and 3 months. Complete resolution of bulbar conjunctival edema and corneal epithelial signs occurred in all the study subjects in group A, B and C at the end of 1 month. Eyelid edema and palpebral hyperemia were completely resolved in all the study subjects in group A, B and C at the end of 3 months. Papillary reaction persisted in 35(38.89%) of patients at the end of 3 months (Figure 2).

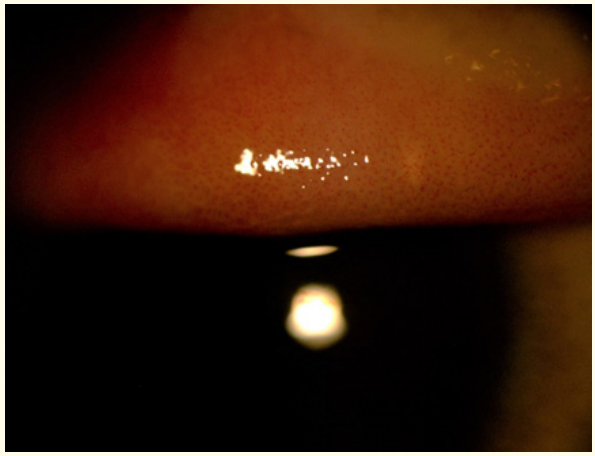

Figure 2: Papillary reaction.

The average cost of treatment for 1 month was 280.00 INR (3.92 USD), 495.00 INR (6.93 USD) and 450 INR (6.3 USD) in group A, group B and group C respectively which shows that olopatadine 0.2% was most cost-effective followed by alcaftadine 0.25% while bepotastine was least cost-effective.

Olopatadine 0.2%, bepotastine 1.5% and alcaftadine 0.25% had limited efficacy in treating symptoms and signs of severe allergic conjunctivitis so topical corticosteroids had to be prescribed as adjunct therapy for such cases.

Discussion

Allergic conjunctivitis is a common allergic disorder estimated to affect up to 15-20% of the population worldwide [5]. It is often under-reported, underdiagnosed and thus, undertreated.

The present study was conducted on 90 consecutive patients who presented to our out-patient department with symptoms of allergic conjunctivitis from December 2018 to July 2020 i.e. 20

months. 120 patients were initially enrolled in the study out of which 14 patients were lost to follow-up and 16 patients needed adjunctive steroid therapy due to severity of symptoms. A higher incidence of allergic conjunctivitis in males (61.11%) than females (38.89%) was noted in our study. This is in accordance with the study conducted in 2019 by P Kahol., *et al*. in North India which revealed higher prevalence of the disease in males (13.44%) than females (10.71%) [6]. Overall mean age was noted to be 16.67 ± 10.59 years showing preponderance of allergic conjunctivitis in younger age group. Higher incidence in younger population has also been observed by Rosario N., *et al*. in 2011 and Thong BY in 2017 [7,8].

In our study, itching was found to be the most common symptom present in 90 (100%) patients. La Rosa M., *et al*. also found itching as most common symptom which may range from mild to severely debilitating [2]. Other symptoms include tearing, redness, foreign body sensation, mucous discharge and eyelid swelling. A vast co-prevalence of allergic rhinitis and allergic conjunctivitis has been demonstrated in a review article by Bielory L [9]. We also found allergic rhinitis as an associated condition in 38(42.22%) patients.

In recent years, dual-action agents combining both topical antihistamine and mast cell-stabilizing properties were found to be the treatment of choice for mild forms of allergic conjunctivitis [10]. In our study, we compared efficacy of olopatadine 0.2%, bepotastine 1.5% and alcaftadine 0.25% in treating signs and symptoms of allergic conjunctivitis. These drugs have been found effective in relieving signs and symptoms of allergic conjunctivitis [11-13]. A rapid onset as early as 3 minutes and long acting action of olopatadine 0.2%, bepotastine 1.5% and alcaftadine 0.25% has been demonstrated in various studies [14-18]. In our study, mean time for beginning of itch relief was calculated as 6.35 ± 1.99 minutes (range 3-12 minutes). Paired analysis of median itch scores at each follow-up visit showed significant improvement in itch scores ($p < 0.05$) at each subsequent visit in all three groups.

All three medications were found to be comparable in relieving symptoms and no significant difference ($p > 0.05$) was noted between the median symptom scores at each follow-up visit. All the symptoms were completely resolved by the end of 1 month. Similarly, difference between median sign scores of group A, B and C was found to be statistically insignificant ($p > 0.05$). These medications were not effective in resolution of papillary reaction as it persisted in 35 (38.89%) patients at the end of 3 months. There is only one study in existing literature comparing these drugs in a single trial but the concentration of olopatadine used was 0.1%. Our results are coherent with the study conducted by Dudeja., *et al.* which proved equal efficacy of olopatadine 0.1%, bepotastine 1.5% and alcaftadine 0.25% in resolving symptoms of the patients with mild to moderate allergic conjunctivitis but the resolution of these signs was not noted in all three groups [19].

None of the patients with severe disease were relieved of their symptoms at the end of 1 week. Fluorometholone 0.1% was prescribed as thrice daily dose initially with gradual tapering over 2 weeks followed by switch to monotherapy with the drugs evaluated in our study. We found that all patients were relieved of their symptoms with this protocol. Corticosteroids have a wider target spectrum, including inhibition of cyclooxygenase and phospholipase A2, which in turn regulate a variety of proinflammatory mediators which explains rapid reduction in overall scores with topical corticosteroids, as observed in study conducted by Li Z., *et al*. [20].

Majority of the patients visiting the hospitals of India have poor socio-economic status so, cost-effectiveness becomes a vital concern. We calculated the average cost of treatment for 1 month with these medications. Olopatadine 0.2% was found to be most cost-effective followed by alcaftadine 0.25% while bepotastine 1.5% was least cost-effective.

Our study had a few limitations. The sample size in our study was relatively small comparative to the prevalence of allergic conjunctivitis in our region. There was variability noted in technique of instilling eye drops because most patients enrolled in our study belonged to weak socio-economic status and were poorly educated. Allergen avoidance was difficult in majority of patients as most of them belonged to rural background where dust exposure was frequent. Olopatadine 0.2%, bepotastine 1.5% and alcaftadine 0.25% had limited efficacy in treating severe allergic conjunctivitis. These patients were prescribed topical fluorometholone 0.1% as adjunct therapy for control of their signs and symptoms.

Conclusion

Olopatadine 0.2%, bepotastine 1.5% and alcaftadine 0.25% are comparable in treating symptoms and signs of mild to moderate allergic conjunctivitis. None of these drugs are effective as monotherapy in treating severe allergic conjunctivitis. Among olopatadine 0.2%, bepotastine 1.5% and alcaftadine 0.25%, olopatadine 0.2% is most cost-effective and equally effective as bepotastine 1.5% and alcaftadine 0.25% in treating allergic conjunctivitis. Olopatadine 0.2% may be prescribed to patients as initial therapy considering low socio-economic status of majority of patients in developing nations.

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