Original Article

Observer-masked trial comparing efficacy of topical olopatadine (0.1%), bepotastine (1.5%), and alcaftadine (0.25%) in mild to moderate allergic conjunctivitis

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Purpose: With increasing environmental pollution, the incidence of allergic conjunctivitis is increasing. Newer anti-allergic medications with combined anti-histaminic and mast cell stabilization action can help reducing the use of topical steroids for milder form of disease. There is no study directly comparing olopatadine (0.1%), bepotastine (1.5%), and alcaftadine (0.25%) for mild to moderate allergic conjunctivitis cases. Hence, we decided to methodically study the efficacy of three topical medications. **Methods:** Prospective, observer-masked clinical trial enrolled 45 patients with 15 patients in each of the three groups. Patients with mild to moderate allergic conjunctivitis were sequentially assigned to respective groups, and relief of symptoms and signs were noted upto 1-month follow-up. **Results:** All three topical medications faired almost equally in resolving symptoms of the patients with mild to moderate allergic conjunctivitis, and most of them reported complete relief after 1 week of use of medication. Few cases with limbal or palpebral papillae reported symptomatic relief after use of medication, but the resolution of these signs was not noted in all three groups. **Conclusion:** We concluded similar efficacy of three medications in relieving symptoms and inefficacy in regressing palpebral and limbal papillae in cases of allergic conjunctivitis.

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Ocular allergy is a commonly encountered pathology in clinical practice, with an increase in number of patients noticed in the last decade.[1-4] 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 allergan 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 major role.[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. There are a few masked trials available, but this study is a double-blinded, observer-masked trial directly comparing the efficacy of three topical anti-allergic medications in mild to moderate allergic conjunctivitis.

Methods

This was a prospective, observer-masked, single center clinical trial conducted at a tertiary care center in South India. The protocol was registered with the Ethics Committee of our Institute and adhered to the tenets of the Declaration of Helsinki. Consecutive 45 patients with mild to moderate allergic conjunctivitis [Table 1] presenting to outpatient department and willing to participate in the study were included after written informed consent. The criteria for exclusion were need for topical steroids or topical immunosuppressives, contact lens wearers, concurrent ocular diseases such as dry eye, planning to undergo ocular surgery during study period,

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known hypersensitivity to either agent, a history of alcohol or drug abuse, a positive history of an ocular herpetic infection, an active ocular infection, or any significant illness, actively taking systemic steroids or antihistamines within 7 days prior to enrolment, pregnant, planning to become pregnant, or nursing/lactating and use of any other topical ocular medications.

Patients were sequentially enrolled in one of the three groups according to computer-generated random numbers and given topical anti-allergic medication for twice daily use.
Group 1: Topical 0.1% Olopatadine eyedrops BID
Group 2: Topical 1.5% Bepotastine eyedrops BID
Group 3: Topical 0.25% Alcafatadine eyedrops BID

All patients received lubricants and were asked to use and note down whenever they needed these eyedrops. Patients were instructed to use gentle eyelid closure for at least 2 min after dosing, and to repeat instillation of a single drop, if there was uncertainty as to whether successful instillation of the treatment had occurred.

For uniform grading of symptoms and signs at each visit, we used scoring scales with 0 indicating no itch and 3 indicating constant desire to itch. Ocular redness and discharge were scored using 5-point scale (0–4), where 0 indicated no redness or no discharge and 4 indicated severe redness or copious discharge. Foreign body sensation and watering were graded using the 4-point scale (0–3), where 0 indicated absent symptoms and 3 indicated severe foreign body sensation or constant epiphora. In signs, upper tarsal papillae were graded using 4-point scale (0–3) with 0 indicating no papillae and 3 indicating predominance of giant papillae. Similarly, limbal activity was graded using 4-point scale with 0 indicating no limbal activity and 3 indicating Horner Tranta dots.[17]

Before starting treatment, patients filled a questionnaire grading their symptoms, and the signs were evaluated by a masked investigator [Table 2]. The instillation of the first eyedrop of anti-allergic medication was done in the outpatient department, and the patient was asked to fill the same questionnaire after 15 min and telephonically on the next day. Patients were reviewed at 1 week and 1 month. Masked investigator assessed signs, and patient completed the questionnaire form at review visits.

The sample size was calculated to detect a difference in means of 0.70 units assuming that the common standard

Table 1: Classification of allergic conjunctivitis

	Mild	Moderate	Severe	Blinding
Bulbar Conjunctiva	Congestion	Congestion	Thickening and Trantas spots	Granulomas
Tarsal Conjunctiva	Micro papillae	Macro (1mm) papillae	Giant (>1mm) papillae	Mega Cobblestones
Cornea	-	Micro erosions	Macroerosions	Shield ulcer
Limbus	-	Focal (<180) degrees inflammation	Diffuse (>180) degrees inflammation	Limbal deficiency

Table 2: Proforma used for recording symptoms and signs of patients at each visit

SYMPTOMS					
	At presentation (date)	15 min	1 Day	1 week	1 month
Redness (0-4)					
Discharge (0-4)					
Foreign body sensation (0-3+)					
Itching (0-3+)					
Photophobia (0-3+)					
Tearing (0-3+)					
Need for lubricants	NA				
Overall comfort (0-5)					
Discomfort with use of eyedrop	NA				
Time after which symptoms started improving					
SIGNS					
	At presentation (date)		1 week		1 month
Papillae (0-3+)					
Limbal involvement (0-3+)					
Corneal involvement (0-3+)					
Discharge (0-3+)					
Conjunctival hyperemia (0-3+)					
Overall	NA				
Need for steroids	NA				
Would you like to continue the eyedrop?					

deviation is 1.00.[18] At power of 85% and at a confidence level of 95%, the sample size determined was 15 subjects in each treatment group. Data analysis was done using Microsoft excel and Statistical Package for the Social Sciences (SPSS) version 11.5. Descriptive data were presented as mean and SD (for quantitative data) and frequency and proportions (for qualitative data). Tests of significance included ANOVA for quantitative data and Chi-squared or Fisher's exact test for qualitative data. All *P* values were two-tailed at a significance level of 0.05. Intention to treat analysis was done in this trial.

Results

We did not have any study drop out as all the patients came for follow-up visits. Age and gender distribution of patients in three groups is shown in Table 3. Number of patients with moderate allergic conjunctivitis in three groups were group 1: 6/15 (40%); group 2: 5/15 (33.3%); and group 3: 4/15 (26.6%). Mean time for the beginning of relief of itching was comparable in three groups with no statistically significant difference ($P > 0.05$, range 5-15 min, mean: group 1- 8.67, group 2-8.33, group 3-8.33 min). All three medications showed statistically significant relief in itching, with effect starting in minutes and complete relief of itching at 1-week follow-up. [Shown in Table 4 and Figure 1] After 15 min of instillation of eyedrop, patients in all three groups had either no or minimal itching (itch score of 0 or 1), illustrating quick onset of action of all three medications. All three medications helped in relief of other symptoms such as redness, watering, discharge, and foreign body sensation with complete symptomatic relief in 1 week time [Figure 2]. None of the patients needed topical steroid for worsening symptoms. All three medications were well-tolerated except for mild burning sensation noticed by a few patients, which was transient in nature. Such symptoms were noted by 2 patients (13%) in group 1, 4 patients (26%) in group 2, and 6 patients (40%) in group 3.

Table 3: Age and gender distribution of patients in each group

Groups	Age distribution	Gender distribution
Group 1	10-20 years: 2 20-30 years: 8 30-40 years: 5	Male: 5 Female: 10
Group 2	10-20 years: 4 20-30 years: 9 30-40 years: 2	Male: 8 Female: 7
Group 3	10-20 years: 4 20-30 years: 8 30-40 years: 3	Male: 9 Female: 6

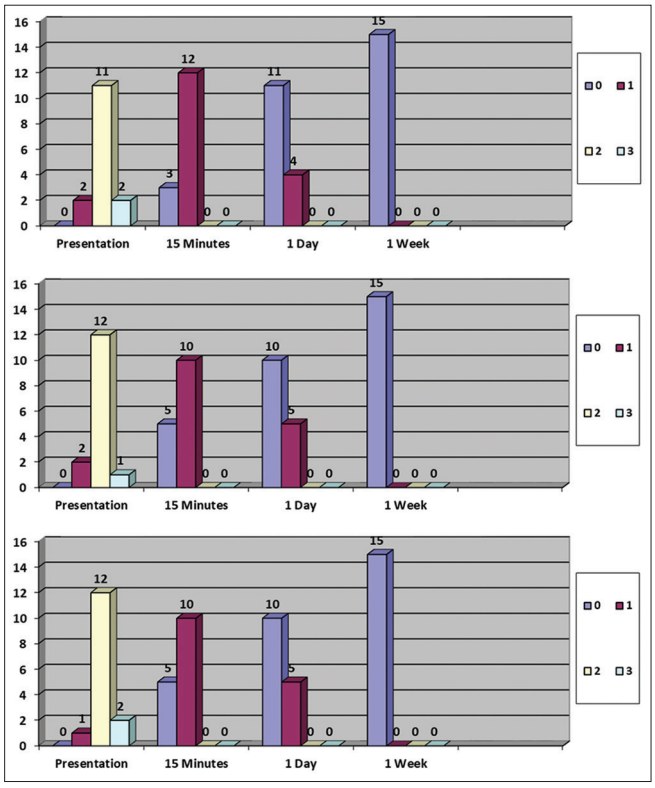

Figure 1: Bar graphs showing distribution of itch score of patients in three groups at various time intervals

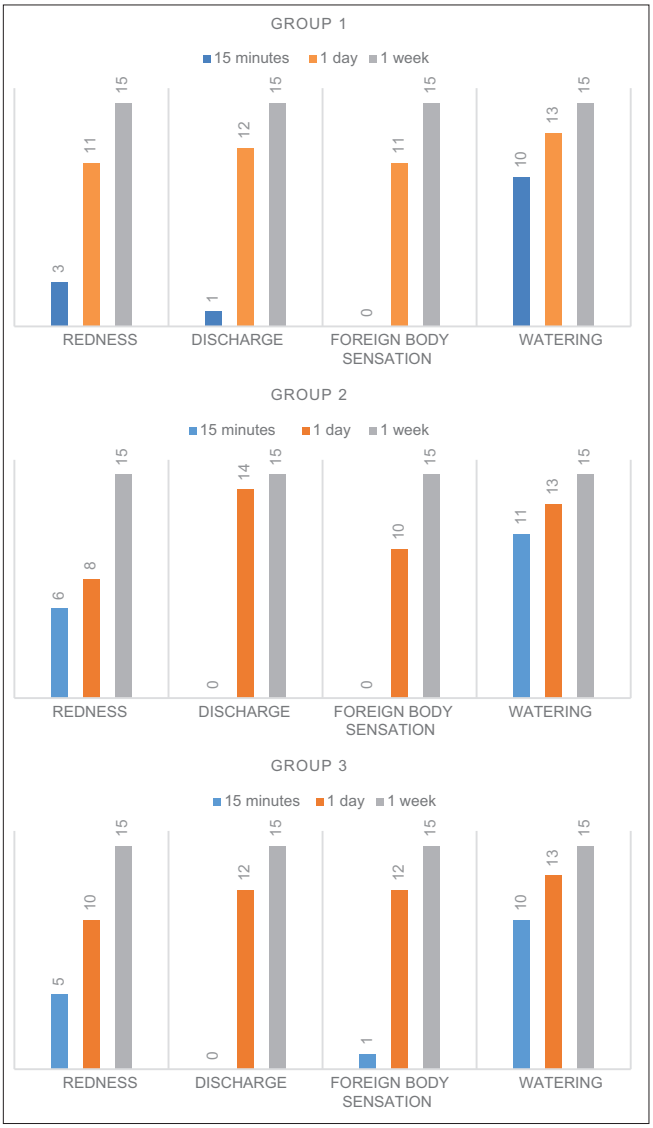

Figure 2: Bar diagrams showing number of patients with relief of symptoms at various time points. Relief is considered as absence of symptom or two-point reduction from the level at presentation

Table 4: Paired analysis of mean itch scores at various time intervals (in three groups)

Pairs in each group	Time intervals	Mean itch score	Standard deviation
Group 1			
Pair 1	At presentation	2.0	0.535
	15 min	0.8	0.414
Pair 2	15 min	0.8	0.414
	1 day	0.27	0.458
Pair 3	1 day	0.27	0.458
	1 week	0.0	-
Group 2			
Pair 1	At presentation	1.93	0.458
	15 min	0.67	0.488
Pair 2	15 min	0.67	0.488
	1 day	0.33	0.488
Pair 3	1 day	0.33	0.488
	1 week	0.0	-
Group 3			
Pair 1	At presentation	2.07	0.458
	15 min	0.67	0.488
Pair 2	15 min	0.67	0.488
	1 day	0.33	0.488
Pair 3	1 day	0.33	0.488
	1 week	0.0	-

As we included cases with only mild to moderate allergic conjunctivitis, severe upper tarsal papillae or Horner Tranta dots were not noted in the study group. Patients included in the study had ocular signs such as few upper tarsal papillae and limbal hyperemia, which did not respond to these topical medications.

Discussion

Most of the earlier studies comparing the efficacy of anti-allergic medications were according to conjunctival allergan challenge.[18-23] 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.

Alcaftadine 0.25%, olopatadine 0.2%, and bepotastine 1.5% eyedrops have been proved to be safe and well-tolerated topical medication for allergic conjunctivitis.[18,19,21-23] These have been shown to have mild transient side-effects and are food and drug administration (FDA) approved. Our study resonated the same, and the medications were found to be safe, with minimal transient side effects of burning sensation noticed by a few patients (more in group 3). Most patients responded to treatment and were willing to continue the eyedrop, if indicated.

Efficacy of these anti-allergic medications over placebo has been proved in previous studies.[18,19,21-23] All three medications showed significant relief in symptoms of redness and itching, which was proved statistically. Our study corroborated with these study results and all three medications showed statistically significant relief in symptoms, with effect starting within minutes of instillation of eyedrops.

Comparative trials done earlier have not compared these three medications in a single randomized control trial. Among 0.25% alcaftadine and 0.2% olopatadine in a study using conjunctival allergan challenge, alcaftadine was found superior to olopatadine at the earliest time point (3 min post-challenge). Only alcaftadine provided significant relief in chemosis at 16 and 24 h post-instillation.[18] Similar superiority of alcafatadine over olopatadine was noted in another study enrolling 284 subjects. They found that subjects treated with alcaftadine had a lower overall mean itch score at 3, 5, and 7 min than the subjects treated with olopatadine.[19,22] At a cellular level, animals treated with olopatadine and alcaftadine showed similar efficacy profiles and mast cell numbers. Alcaftadine prevented a decrease in expression of the junctional protein, ZO-1, which is caused by allergan challenge. In addition, animals treated with alcaftadine showed significantly lower conjunctival eosinophil infiltration.[24] In a comparative study involving 1.5% bepotastine besilate and 0.2% olopatadine and bepotastine showed better relief of ocular allergy symptoms and relief of runny nose.They found that a higher percentage of patients preferred bepotastine over olopatadine for treatment.[20] Clinical trials, thus, proved efficacy of all three medications for relief of symptoms of allergic conjunctivitis but found differences between medications in one or the other parameters. In our study, all the three medications faired equally well in control of allergic symptoms, with no statistically significant difference between them.

An additional part of our study was an independent masked observer for evaluation of signs of allergic conjunctivitis. We found that these medications did not help in regression of signs such as limbal or palpebral papillae. This hints toward the benefit of these medications for symptomatic relief alone in cases of allergic conjunctivitis. More potent anti-allergic medications like topical steroids should be considered in cases with significant palpebral and limbal papillae.

Although our sample size is small, we conducted a thorough observer-masked evaluation of each case at regular intervals for 1 month.

Conclusion

We concluded a similar efficacy of three medications in relieving symptoms and inefficacy in regressing signs in cases of allergic conjunctivitis.

Patient consent

Written informed consent was taken from every patient included in the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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