

RESEARCH ARTICLE

Efficacy and tolerability comparison of olopatadine, ketotifen, and epinastine in seasonal allergic conjunctivitis: A prospective open-label comparative study

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ABSTRACT

Background: Seasonal allergic conjunctivitis (SAC) is the most common allergic disease affecting the eye, with an estimated prevalence of 15–20%. Although sequelae affecting patients' vision are rare, the symptoms are distressing and may have a significant socioeconomic impact, affecting the quality of life, daily activities, productivity, school performance, etc. The latest generation multiple action topical antiallergic agents such as olopatadine, ketotifen, and epinastine possess antihistaminic, mast cell stabilizing, and anti-inflammatory actions and are now been recommended as the first-line agents in the treatment of SAC.


Aims and Objectives: This study aims to compare the efficacy and tolerability of olopatadine, ketotifen, and epinastine in SAC. **Materials and Methods:** A prospective, comparative study enrolled 90 subjects with SAC. They were randomized into three groups of 30 each, to receive olopatadine, ketotifen, or epinastine. The study medications were instilled into the affected eyes (one/both) twice daily for 4 weeks. The primary outcome measure was change in clinical parameters of SAC, which was assessed by grading on a 4-point scale (none to severe). The treatment response was monitored during the follow-up visits at 1, 2, 3, and 4 weeks. The tolerability was assessed by monitoring the adverse events (AEs). **Results:** All the study drugs showed comparable efficacy in reducing conjunctival hyperemia, papillary reaction, and itching. Among them, olopatadine was distinctly more effective than other two drugs at all the visits. Ketotifen and epinastine were equally effective in relieving conjunctival hyperemia, and epinastine was more effective in relieving papillary reaction and ocular itching compared to ketotifen. The study medications showed good tolerability with less severe AEs. **Conclusion:** In the present study, olopatadine was more effective in relieving symptoms and signs of SAC compared to epinastine and ketotifen.

KEY WORDS: Seasonal Allergic Conjunctivitis; Olopatadine; Ketotifen; Epinastine

INTRODUCTION

Allergic conjunctivitis is one of the most common non-traumatic extraocular inflammatory conditions includes

seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis, atopic keratoconjunctivitis, and drug-induced allergic conjunctivitis.^[1] SAC is also known as vernal conjunctivitis or spring catarrh, is the most common form of allergic conjunctivitis constituting 90% of cases. It is most frequently caused by grass, tree and weed pollens, and outdoor molds which peak at different times of the year. It occurs on a seasonal (usually in summer rather than spring) basis often as part of seasonal rhinoconjunctivitis (hay fever) affecting adults and children with the family history of atopy.^[1-3] It is characterized by recurrent bilateral conjunctivitis which usually presents with itching, redness, lacrimation, burning,

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stinging, photophobia, and watery/mucoid discharge. These episodes are often accompanied by clinical signs of lid edema, conjunctival chemosis, hyperemia, and papillary reactions that can be appreciated on examination.^[3,4]

Management of SAC is aimed at preventing and alleviating symptoms and it mainly focuses on allergen elimination, cold compression, artificial tears, modulation of immune system, and pharmacological inhibition of the chemical mediators involved in the immune response such as topical antihistaminics, nonsteroidal anti-inflammatory drugs (NSAIDs), mast cell stabilizers, and steroids. Among pharmacotherapy although considered very effective, the use of topical corticosteroids is limited by well-known side effects such as cataract, glaucoma, and increased susceptibility to infection, and hence, not the preferred option except for severe refractory forms of allergic conjunctivitis. Topical is known to produce adverse effects such as corneal stinging, burning, conjunctival hyperemia, punctate keratopathy, and persistent epithelial erosion. H₁ blockers generally have limited efficacy in SAC. However, certain new generation multiple action topical antiallergic agents such as olopatadine, ketotifen, and epinastine possess antihistaminic, mast cell stabilizing, and anti-inflammatory actions without the classical topical or systemic steroidal side effects and are now been recommended as the first-line agents in the treatment of SAC.^[5-7] As there are few studies and reports regarding the comparative efficacy and tolerability of the topical antihistaminics in SAC in Indian population, the present study was taken up.

MATERIALS AND METHODS

Study Design

This randomized, comparative, open-label, parallel-group study was done in a tertiary care hospital (Kempegowda Institute of Medical Sciences) from January 2014 to June 2015.

Ethical Consideration

The study was approved by the Institutional Ethics Committee (IEC certificate has attached).

Study Population

Subjects with SAC are attending the ophthalmology outpatient department (OPD), Kempegowda Institute of Medical Sciences, Hospital and Research Centre, KR Road, VV Puram, Bangalore-4.

Study Procedure

After obtaining approval and clearance from the IEC, 90 subjects with SAC visiting the OPD of ophthalmology at

Kempegowda Institute of Medical Sciences, Hospital and Research Centre, Bangalore, were included in the study. The study subjects were recruited by random sampling method from January 2014 to June 2015. Written informed consent was obtained from all the study subjects after fully explaining the study procedure to their satisfaction, in both English and vernacular language (for subjects under 18 years, informed consent was taken from parents/legal representatives). Anonymity, confidentiality, and professional secrecy were maintained for all the study subjects. Subjects fulfilling the following inclusion criteria were included in the study: (1) Patients of all age groups above 3 years from either gender diagnosed as SAC with itching of variable severity and seasonal exacerbations, (2) more than 2–3 episodes SAC in the past 2 years, (3) SAC with both palpebral and bulbar manifestations, and (4) willingness to give informed consent and availability for regular follow-up. Subjects with the following criteria were excluded from the study: (1) Acute systemic allergic manifestations such as severe bronchial asthma and coexisting allergic rhinitis on systemic therapy, (2) presence of any other forms of allergic conjunctivitis – giant papillary conjunctivitis and atopic conjunctivitis, (3) active bacterial/viral conjunctivitis, (4) h/o ocular herpes, severe dry eye, lesions involving cornea, (5) SAC associated with ocular surface disease, (6) subjects who had used topical steroids/NSAIDs in the past 2 weeks, and (7) subjects who had participated in any clinical trial for SAC in the past 2 weeks. All the subjects were examined for visual acuity and any other intraocular pathology by slit-lamp examination. The study medications were instilled into the affected eyes (one/both) twice daily for 4 weeks. Patient's attendants were properly instructed regarding the installation and proper preservation of the medications. Clinical signs and symptoms were assessed at baseline and at weekly intervals for 4 weeks. The clinical parameters of SAC such as ocular itching, hyperemia/congestion, and regression of papillary lesions were assessed by grading on a 4-point scale (none to severe). The tolerability was assessed by observing and monitoring for any adverse reactions/events during the study period. Furthermore, the study subjects were instructed to report/consult in the event of any adverse effects/reactions during the study period.

Statistical Analysis

To ensure proper randomization and comparability at baseline, one-way ANOVA was applied to study the distribution of age; Chi-square test and Fisher's exact test (cells containing observations <5) were used to study the distribution among gender, religion, and occupation. The results are considered significant whenever $P \leq 0$. Friedman test was used to study the change in individual symptom scores during various visits in olopatadine group, and repeated measures ANOVA was used to study the change in individual symptom scores during various visits in ketotifen and epinastine groups.

Primary Outcome

The primary outcome measure was changed in clinical parameters of SAC, which was assessed by grading on a 4-point scale.

RESULTS

In the present study, 90 subjects with SAC were assessed for efficacy and tolerability of the study medications. Table 1 summarizes the age distribution in the study subjects. The mean age was 24.71 ± 10.98 years, with majority of subjects (57.78%) in the age group between 16 and 30 years. There was no statistically significant difference in the mean age between the three study groups ($P = 0.717$). Figure 1 shows the gender difference. There was no statistically significant gender difference between the study groups ($P = 0.491$). Tables 2-4 summarize treatment outcome of olopatadine, ketotifen, and

epinastine group from baseline to each follow-up visits and percentage change from baseline. The adverse effects of the study drugs are shown in Figure 2.

DISCUSSION

In the present study, of 90 patients, 46 were male and 44 were female patients. The mean age in olopatadine, ketotifen, and epinastine group was 24.16 ± 10.22 , 23.93 ± 9.54 , and 26.06 ± 13.19 years, respectively. There were no significant differences found among the groups with respect to demographic data and clinical characteristics in their baseline scores. The parameters assessed were hyperemia, regression of papillary lesions, and ocular itching, by grading on a 4-point scale (none to severe). There was a progressive decrease in the individual symptom scores at different visits with all the three study medications. Overall, the outcome measures of all three medications shown that olopatadine was significantly more

Table 1: Age distribution ($n=90$)

Age group (years)	Olopatadine n (%)	Ketotifen n (%)	Epinastine n (%)	Total n (%)
3-15	7 (23.33)	6 (20)	7 (23.33)	20 (22.22)
16-30	18 (60)	18 (60)	16 (53.33)	52 (57.78)
31-45	3 (10)	5 (16.67)	5 (16.67)	13 (14.44)
46-65	2 (6.67)	1 (3.33)	2 (6.67)	5 (5.56)
Total	30 (100)	30 (100)	30 (100)	90 (100)
Mean age \pm standard deviation	24.16 \pm 10.22	23.93 \pm 9.54	26.06 \pm 13.19	24.71 \pm 10.98

There was no statistically significant difference between the groups. $F=0.333$, $P=0.717$ (One-way ANOVA)

Table 2: Treatment outcome ($n=30$) – olopatadine group

Treatment outcome	Baselin score Mean \pm SD	Visit 1 (1 week) Mean \pm SD	Visit 2 (2 weeks) Mean \pm SD	Visit 3 (3 weeks) Mean \pm SD	Visit 4 (4 weeks) Mean \pm SD	Change in score from baseline Mean \pm SD	% change from baseline	* P value
Conjunctival hyperemia	2.26 \pm 0.52	1.13 \pm 0.43	0.5 \pm 0.50	0.13 \pm 0.34	0.06 \pm 0.25	-2.20 \pm 0.61	97.34	0.0005
Papillary reaction	1.6 \pm 0.56	1.1 \pm 0.30	0.4 \pm 0.56	0.33 \pm 0.47	0.33 \pm 0.47	-1.24 \pm 0.87	79.37	0.0005
Ocular itching	2.06 \pm 0.52	0.9 \pm 0.60	0.3 \pm 0.46	0.03 \pm 0.182	0 \pm 0	-2.03 \pm 0.498	100	0.0005

*Friedman test with $P<0.0005$. All the above parameters improved considerably with the significant P value and the highest improvement was observed with ocular itching. SD: Standard deviation

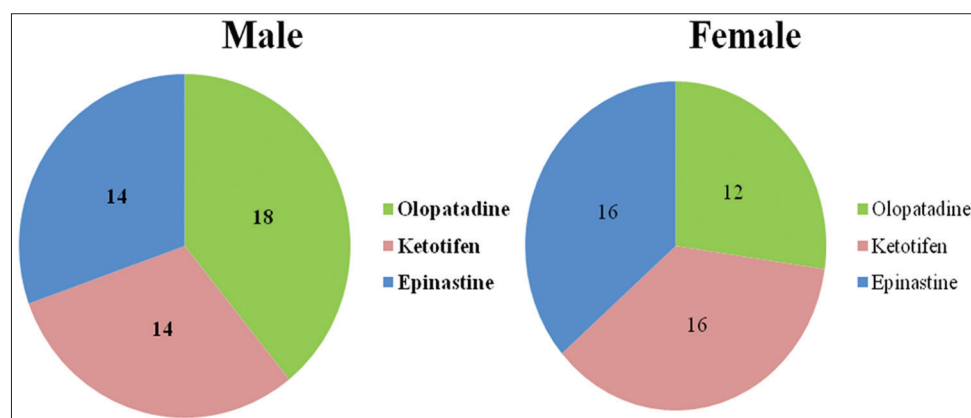


Figure 1: Gender distribution ($n = 90$). Gender distribution is statistically similar between the groups with $P = 0.491$ (Chi-square test)

Table 3: Treatment outcome (n=30) – ketotifen group

Study parameters	Baseline score Mean±SD	Visit 1 (1 week) Mean±SD	Visit 2 (2 weeks) Mean±SD	Visit 3 (3 weeks) Mean±SD	Visit 4 (4 weeks) Mean±SD	Change in score from baseline Mean±SD	% change from baseline	*P value
Conjunctival hyperemia	2.43±0.50	2.3±0.7	1.56±0.50	1.2±0.40	1.06±0.25	-1.36±0.49	56.37	0.0005
Papillary reaction	1.7±0.46	1.7±0.46	1.4±0.49	1.33±0.47	1.13±0.34	-0.56±0.47	33.52	0.0005
Ocular itching	2.06±0.58	2.03±0.55	1.3±0.46	1.06±0.25	1±0	-1.06±0.58	51.45	0.0005

*Repeated measure ANOVA (Significant) $F=87.834$, $P<0.0005$. All the above parameters improved considerably with the significant P value and the highest improvement was observed with conjunctival hyperemia. SD: Standard deviation

Table 4: Treatment outcome (n=30) – epinastine group

Study parameters	Baseline score Mean±SD	Visit 1 (1 week) Mean±SD	Visit 2 (2 weeks) Mean±SD	Visit 3 (3 weeks) Mean±SD	Visit 4 (4 weeks) Mean±SD	Change in score from baseline Mean±SD	% change from baseline	*P value
Conjunctival hyperemia	2.26±0.52	1.56±0.56	1.1±0.30	1.03±0.18	0.96±0.17	-1.29±0.52	57.52	0.0005
Papillary reaction	1.8±0.40	1.56±0.50	1.3±0.46	1.13±0.34	1.03±0.18	-0.80±0.47	42.77	0.0005
Ocular itching	2±0.45	1.33±0.60	1.06±0.25	0.86±0.34	0.8±0.40	-1.25±0.63	60	0.0005

*Repeated measure ANOVA (Significant); $F=44.708$, $P<0.0005$. All the above parameters improved considerably with the significant P value and the highest improvement was observed with ocular itching. SD: Standard deviation

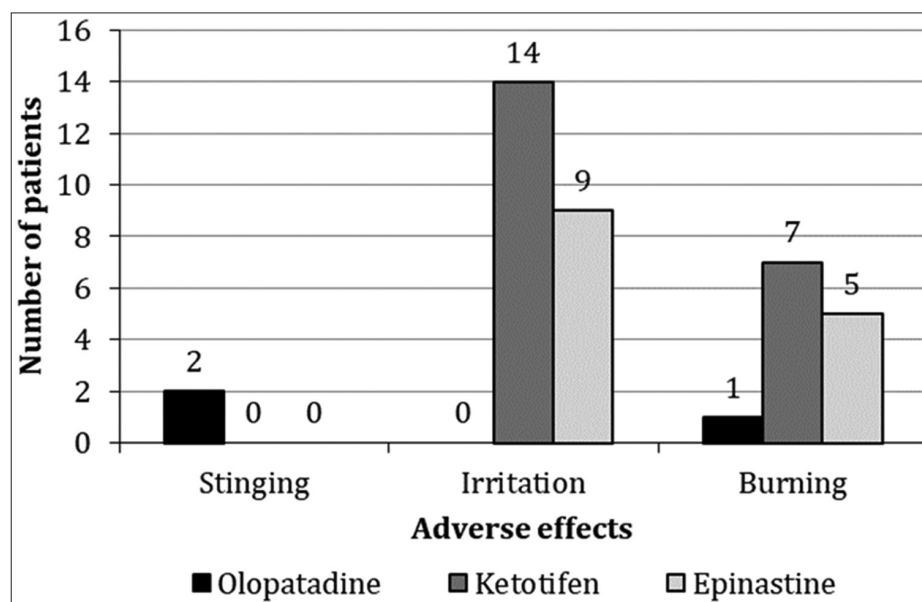


Figure 2: Treatment outcome ($n = 90$). Only 10% of the study subjects in olopatadine group had adverse effects followed by epinastine (30%) and ketotifen (53.33%). Common adverse effect was irritation, 46.67% in ketotifen and 30% in epinastine group

effective in suppressing the various parameters at all stages of observation compared to ketotifen and epinastine. However, epinastine and ketotifen showed comparable efficacy in relieving conjunctival hyperemia, epinastine was more effective in relieving papillary reaction and ocular itching when compared to ketotifen. Both the drugs were significantly less effective compared to olopatadine. All the study medications were well tolerated with mild adverse effects.

The mean age (24.71 ± 10.98 years) is in line with the finding by Borazan *et al.*, in which the mean age was 26.20 ± 10.07 years.^[8] Individual symptom scores at

different visits with the olopatadine group were as follows: 97.34% improvement of conjunctival hyperemia, 79.37% improvement with papillary reaction, and ocular itching was 100%. Although all the parameters improved considerably with a significant P value, the highest improvement was observed with ocular itching. The previous randomized studies have also demonstrated the effectiveness of olopatadine on signs and symptoms of allergic conjunctivitis either with placebo, NSAIDs, or with other dual-acting agents.^[9,10] The study by Yaylali *et al.* also supports that olopatadine was found to be significantly more effective than NSAIDs (ketorolac)

in the alleviation of the clinical parameters, the highest improvement with ocular itching.^[11] In ketotifen group, the effect on the outcome measures was 56.37% improvement with conjunctival hyperemia, 33.52% with papillary reaction, and 51.45% in ocular itching. In ketotifen group, the highest improvement was observed with conjunctival hyperemia, as observed in other studies. The study correlates with the study by Kidd *et al.* which also showed that ketotifen is effective in relieving the signs and symptoms of SAC.^[3] Effect of epinastine on the outcome measures was as follows: Improvement in conjunctival hyperemia was 57.52%, 42.77% with papillary reaction, and 60% in ocular itching. In the epinastine study group, the highest improvement was observed with ocular itching.^[12,13] Similar observations were made in several other studies; however, one study by Whitcup *et al.* has shown that epinastine is non-inferior to levocabastine in controlling itching and hyperemia.^[13] The modified Hartwig and Siegel scale classifies severity of adverse drug reaction (ADR) as mild, moderate, or severe, depending on factors such as requirement for change in treatment, duration of hospital stay, and disability produced by the ADR. All the study subjects have reported only mild ADRs, which were self-limiting and able to resolve overtime without any intervention and did not contribute to the prolongation of length of stay. Similar observations were made in several other studies.^[14,15] The reported adverse effects were 10% of the study subjects in olopatadine group followed by epinastine (30%) and ketotifen (53.33%). Common adverse effect was irritation, 46.67% in ketotifen and 30% in epinastine group. Olopatadine appeared to have better tolerability as it produced stinging in only two subjects. Other studies like Aguilar and Mah *et al.* have also shown almost similar observations.^[9,16]

This study has generated a very useful data as there is a paucity of data comparing the efficacy and tolerability of olopatadine, ketotifen, and epinastine in SAC patients in Indian population. The main limitations of the present study were small sample size and we could not blind the study medications.

CONCLUSION

SAC can be effectively treated by multiple action topical antihistaminics. Olopatadine can be considered as the mainstay or primary option due to the proven efficacy and good tolerability. Other two drugs such as epinastine and ketotifen can be considered as alternatives.

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