ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 12 | December - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

"A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF ALCAFTADINE 0.25% VERSUS OLOPATADINE HYDROCHLORIDE 0.2% IN ALLERGIC CONJUNCTIVITIS AT A TERTIARY CARE HOSPITAL"

Pharmacology

Dr. Akila K Post graduate student, Department of Pharmacology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India.

Dr. Sriya Sridhar* Assistant Professor, Dept. of Ophthalmology, RRMCH, Bangalore; Former Fellow in Cornea and Refractive surgeries, Minto Ophthalmic hospital, Regional Institute of Ophthalmology, BMCRI, Bangalore *Corresponding Author

Dr. Swetha Sridhar Fellow in Dermatosurgery, Department of Dermatology, BMCRI, Bangalore.

Dr. C.R. Jayanthi Dean cum Director & Professor, Department of Pharmacology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

ABSTRACT

Background: Ocular itching is the hallmark symptom of allergic conjunctivitis, accompanied by tearing, conjunctival redness, eyelid swelling and chemosis. Alcaftadine and Olopatadine hydrochloride are classified as dual-acting antiallergic agents, used in treatment of Allergic conjunctivitis. **Objective:** To compare efficacy and safety of Alcaftadine 0.25% and Olopatadine hydrochloride 0.2% eye drops among patients with allergic conjunctivitis. **Settings and Design:** Ophthalmology out-patient department at Minto Ophthalmic Hospital, Bangalore Medical College and Research Institute, Bengaluru; prospective, randomized, comparative study. **Methods and Material:** This study was conducted among 120 patients suffering from grade 3 Allergic Conjunctivitis and efficacy measured in terms of proportion of patients achieving symptomatic relief of allergic ocular signs and symptoms from grade 3 to grade 0 from baseline to 2 weeks, using TOSS score (Total Ocular Symptoms Score) and Conjunctival Hyperaemia scale. Safety assessed by monitoring treatment-emergent adverse effects. Continuous data assessed by unpaired, paired 't' test and repeated measures-ANOVA and categorical data by chi-square test. p-value < 0.05 was considered as statistically significant, whereas < 0.001 as highly significant. **Results:** Greater proportion of patients achieved symptomatic relief in Alcaftadine group (98.3%) compared to Olopatadine hydrochloride group (90%) at end of 2 weeks. A significant and faster reduction in TOSS score was observed from baseline to 2 weeks in Alcaftadine treated group compared to Olopatadine hydrochloride group ($p<0.05$). Adverse events reported were headache, burning sensation and mild redness in both groups. **Conclusion:** Alcaftadine 0.25% demonstrated greater efficacy in reducing ocular signs and symptoms of Allergic conjunctivitis from baseline to 2 weeks, compared to Olopatadine hydrochloride 0.2% with minimal side-effects.

KEYWORDS

Allergic Conjunctivitis, Alcaftadine 0.25% eye drops, Olopatadine hydrochloride 0.2 % eye drops, TOSS score, Conjunctival Hyperaemia scale

INTRODUCTION:

Allergic conjunctivitis affects 40% of the global population. Activation of H1, H2 histamine receptors leads to ocular itching and vasodilatation respectively.[1-4]Olopatadine hydrochloride is a selective H1 receptor antagonist; mast-cell stabilizer with additional anti-inflammatory effects,[5] whereas Alcaftadine, a dual acting agent (anti-histaminic, mast-cell stabiliser with anti-inflammatory property), provides relief from ocular itching by inverse agonistic effects on H1 , H2 and H4 receptors.[6,7] Considering paucity of comparative studies, with regard to efficacy and safety amongst Indian patients, this study was undertaken. The objective was to compare the reduction in ocular signs and symptoms using Total Ocular Symptoms Score (TOSS).

Subjects and Methods:

It is a prospective, randomized, comparative study conducted from May 2019 to December 2019, after obtaining Institutional Ethics Committee approval and written informed consent, patients of either sex aged 18-40 years, diagnosed with Allergic conjunctivitis with grade 1-3 ocular allergic symptoms were included in the study.[8] Patients not willing for written informed consent, patients with grade 4 severity of ocular allergic symptoms, patients with known hypersensitivity to the study medications or their components (including benzalkonium chloride), intraocular pressure of more than 21 mm Hg in either eye or any type of glaucoma, those on other medications which may interfere with the study like decongestants, prostaglandin derivatives, ocular or systemic NSAIDs and corticosteroids, those having active ocular infection or serious ocular pathological condition, a history of dry eye syndrome, patients who have undergone ocular surgical interventions within past 3 months, female patients who are pregnant or lactating or considering pregnancy, psychiatric or emotional disturbance in patients which would limit ability of the patients to comply were excluded.

120 patients suffering from Allergic Conjunctivitis were recruited after fulfilling the inclusion and exclusion criteria, allotted into two groups of 60 each and randomized in 1: 1 ratio, to receive either Alcaftadine 0.25% eye drops, 1 drop once daily or Olopatadine Hydrochloride 0.2 % eye drops, 1 drop once daily for 14 days. Demographic data, ocular and medical histories, concomitant medications, physical examination, clinical examination including recording of vital signs, ophthalmological examination and details of drug prescription by the treating Ophthalmologist were recorded in the study proforma 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. A deviation of ±1 day for first follow-up and ±2 days for subsequent follow-up were accepted. At each follow-up visit data on concomitant medications, ocular symptoms (graded by the patients) and ocular signs (graded by slit lamp examination by the investigator) and adverse events (AEs) were collected. In case of relapse, patient was asked to visit OPD on Day 21.

Ocular symptoms and signs recorded from baseline (Day 1) and adverse effects if any were recorded on follow-up visits (Day 3,7,14). The primary efficacy outcome measure was the proportion of patients achieving symptomatic relief of allergic ocular symptoms from grade 3 to grade 0 from baseline to 2 weeks using TOSS score (Total Ocular Symptoms Score) and conjunctival hyperaemia scale as shown in Table 1 (represents grading of ocular signs and symptoms)[8] and Table 2 (represents scale of assessment of conjunctival hyperaemia)[9] respectively and the secondary outcome was the number and severity of adverse events on the follow-up visits.

Table 1: Grading Of Ocular Signs And Symptoms [8]

SYMPTOMS	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Itching	Mild	Occasional	Frequently	Continuous
Watering	Absent	Occasional	Frequently	Continuous
Photophobia	Absent	Mild grade	Moderate grade (unable to open eye in intense light)	Severe grade (unable to open eye in normal light)
Lid oedema and chemosis	Absent	Absent	Only mild oedema	Oedema with chemosis

Conjunctival hyperaemia	Mild congestion	Pinkish discoloration of conjunctiva	Reddish discoloration of conjunctiva	Bright red conjunctiva

Table 2: Scale Of Assessment Of Conjunctival Hyperaemia [9]

Description	Hyperaemia degree	Right eye	Left eye
Normal	No	0	0
Inconsistent rose red hyperaemia	Trace	0.5	0.5
Reddish colour	Mild	1	1
Bright red colour	Moderate	2	2
Bright and intense diffuse hyperaemia	Severe	3	3

Sample size calculation:

Sample size is calculated using the formula :

$$N = \frac{(r+1)(Z_{\alpha/2}+Z_{1-\beta})^2 P(1-P)}{(p_1-p_2)^2}$$

n1 and n2 = sample size for Group 1 and Group 2

such that, N = n1 = n2

ratio r = n1/n2 = 1/1 = 1

Zα = normal deviate at a level of significance = 1.96 for 5% level of significance

$Z_{1-\beta}$ = normal deviate at 1-β +% power = 0.84 at 80% power

p_1=prevalence in group 1= 0.76 } [6]

p_2=prevalence in group 2= 0.5}

p_1-p_2= Difference in proportion of events in two groups= 0.26 [6]

P = Pooled prevalence = $(p_1+p_2)/2$ = 0.63

$$N = \frac{(1+1)(1.96+0.84)^2(0.63)(0.37)}{(0.26)^2} = \mathbf{54}$$

Considering 10% drop out rate, $N1 = \frac{N}{(1-q)}$

N1 =Total sample size including drop outs

N = Total sample size

q= anticipated drop outs = 0.1 (10%)

$$N1 = \frac{54}{1 - 0.1} = 60$$

A sample size of 120 was taken for better validation of results.

Statistical Analysis:

The data collected was analysed statistically using descriptive statistics namely mean, standard deviation and proportion/percentage wherever applicable. Continuous data was assessed by Unpaired 't' test used between the two groups and RM-ANOVA within the group and categorical data was assessed by chi-square test using VassarStats statistical computation. p-value less than 0.05 was considered as statistically significant, whereas less than 0.001 as highly significant.

RESULTS:

120 patients diagnosed with Allergic conjunctivitis with grade 3 ocular allergic symptoms who met inclusion criteria were enrolled in the study. Table 3 represents the baseline demographic profile of the patients included in the study. There was no statistical difference in age and gender in both the groups (p-value=1.00; p-value=0.74 respectively). Both the treatment groups were matched with respect to baseline demographic characteristics.

Table 3: Baseline Demographic Characteristics: (60 Patients In Each Group)

		Alcaftadine 0.25 % (n= 60 patients)	Olopatadine hydrochloride 0.2% (n= 60 patients)	p-value
Age in years(Mean ± SD)		27.9 ± 7.7	26.7 ± 5.38	1.00
Gender	Males	39	35	0.74
	Females	21	25	

p-value < 0.05 is considered statistically significant

Patients with mean age of 27.9 ± 7.7 years in Alcaftadine group and 26.7 ± 5.38 years in Olopatadine group. There were 39 (65%) males and 21 (35%) females in Alcaftadine group and 35 (58.3%) male and 25 (41.7%) female patients in the Olopatadine group.

Efficacy parameters:

The ocular symptoms and signs assessed using TOSS score (Total Ocular Symptoms Score) were itching (100%), tearing (83.3%), redness (71.6%), and swelling (19%) of conjunctiva.

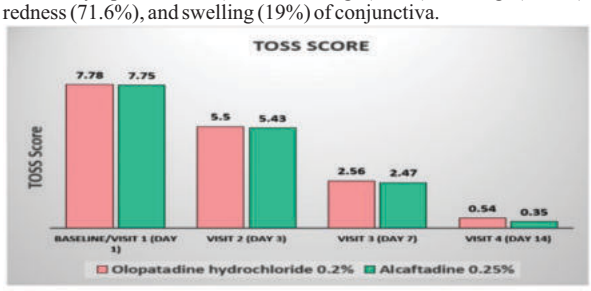

Figure 1: TOSS Score from visit 1 (baseline) to visit 4 in both the groups

Figure 1 shows the TOSS score from visit 1 (baseline) to visit 4 in both the groups. Table 4 and Figure 2 represents the number of patients with their Total Ocular Symptom Score at different visits from baseline visit 1 (Day 1) to visit 4 (Day 14).

Table 4: Number Of Patients With Their TOSS Score From Baseline Visit 1 To Visit 4

Visits	TOSS Score	No	Trace	Mild	Moderate	Severe
Visit 1 (Day 1)	Olopatadine	0	11	26	23	0
	Alcaftadine	0	11	25	24	0
Visit 2 (Day 3)	Olopatadine	0	16	44	0	0
	Alcaftadine	0	18	42	0	0
Visit 3 (Day 7)	Olopatadine	0	2	58	0	0
	Alcaftadine	0	4	56	0	0
Visit 4 (Day 14)	Olopatadine	35	25	0	0	0
	Alcaftadine	45	15	0	0	0

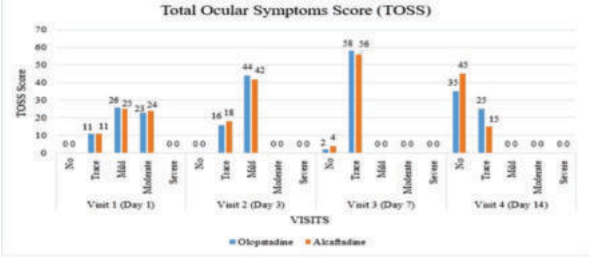

Figure 2: Total Ocular Symptom Score at different visits

Both the groups showed a significant improvement in TOSS score from baseline to 14 days. The total ocular symptom score showed consistent decrease in subsequent visit in both the study groups and it was statistically significant from baseline to 14th day (p = 0.03). Table 5 shows the TOSS score at different visits.

Table 5: Total Ocular Symptom Score At Different Visits

Visits	Alcaftadine 0.25 %	Olopatadine hydrochloride 0.2%	p-value
Baseline/Visit 1 (Day 1)	7.75 ± 0.6	7.78 ± 0.59	0.93
Visit 2 (Day 3)	5.43 ± 0.41	5.5 ± 0.4	0.91
Visit 3 (Day 7)	2.47 ± 0.26	2.56 ± 0.23	0.57
Visit 4 (Day 14)	0.35 ± 0.11	0.54 ± 0.14	0.03*

*p-value < 0.05 is considered statistically significant

Conjunctival Hyperaemia grading from baseline to day 14 is represented in Table 6 and Figure 3. Conjunctival hyperaemia was significantly reduced in both the treatment groups. There is no statistical significance between the groups while assessing conjunctival hyperaemia scale in all the visits.

Table 6: Conjunctival Hyperaemia Scale From Visit 1 (baseline) To Visit 4 In Both The Groups

Visits	Alcaftadine 0.25 %	Olopatadine hydrochloride 0.2%	p-value
Baseline/Visit 1 (Day 1)	1.38 ± 0.22	1.4 ± 0.23	0.92
Visit 2 (Day 3)	0.85 ± 0.156	0.87 ± 0.157	0.88
Visit 3 (Day 7)	0.35 ± 0.072	0.37 ± 0.073	0.63
Visit 4 (Day 14)	0.008 ± 0.0167	0.05 ± 0.039	0.05

p-value < 0.05 is considered statistically significant

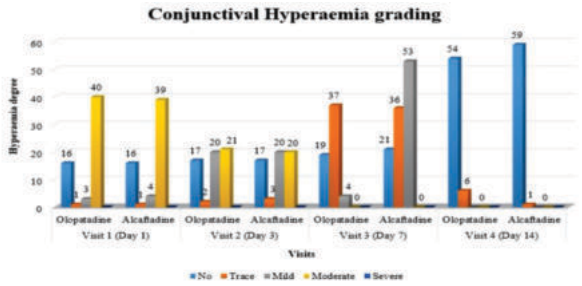

Figure 3: Conjunctival Hyperaemia grading from baseline (Day 1) to visit-4 (Day 14)

Within the individual group of Alcaftadine 0.25% (Table 7) and Olopatadine hydrochloride 0.2 % (Table 8), the TOSS score and Conjunctival Hyperaemia scale were statistically highly significant ($p<0.001$) from baseline to follow-up visit 4. The number of patients in Alcaftadine group who achieved faster symptomatic relief were higher, compared to Olopatadine hydrochloride 0.2 % group.

Table 7: TOSS Score and Conjunctival Hyperaemia scale (within Alcaftadine 0.25% group)

Assessment	Visit 1 (Day 1)	Visit 2 (Day 3)	Visit 3 (Day 7)	Visit 4 (Day 14)	p-value
TOSS Score	7.75 ± 0.6	5.43 ± 0.41	2.47 ± 0.26	0.35 ± 0.11	<0.001*
Conjunctival Hyperaemia scale	1.38 ± 0.22	0.85 ± 0.15	0.35 ± 0.072	0.008 ± 0.0167	<0.001*

*p-value < 0.001 is considered as highly significant

Table 8: TOSS Score and Conjunctival Hyperaemia scale (within Olopatadine hydrochloride 0.2% group)

Assessment	Visit 1 (Day 1)	Visit 2 (Day 3)	Visit 3 (Day 7)	Visit 4 (Day 14)	p-value
TOSS Score	7.78 ± 0.59	5.5 ± 0.4	2.56 ± 0.23	0.54 ± 0.14	<0.001*
Conjunctival Hyperaemia scale	1.4 ± 0.23	0.87 ± 0.157	0.37 ± 0.073	0.05 ± 0.039	<0.001*

*p-value < 0.001 is considered as highly significant

Safety Parameter

Adverse drug reactions encountered in our study were headache, burning sensation, dizziness and mild redness in the conjunctiva. All four ADRs were mild, self-limiting and did not require the discontinuation of therapy. Table 9 represents the adverse drug reactions in both the groups.

Table 9: Adverse Drug Reactions In Both The Groups

Adverse drug reaction	Olopatadine 2%	Alcaftadine 2.5%	p value
Headache	2	1	0.35
Burning sensation	3	1	
Dizziness	0	2	
Mild redness	1	1	

p-value < 0.05 is considered statistically significant

DISCUSSION:

The conjunctiva of the eye is continually exposed to a variety of airborne antigens that can lead to inflammation, often termed allergic conjunctivitis. Allergic conjunctivitis is an ocular surface inflammatory disease that is predominantly IgE-mediated Type I hypersensitivity reaction where allergen binds to specific IgE molecules, triggers mast cell degranulation and subsequent increase in histamine release leading to activation of both H1 and H2 types of histamine receptors leading to ocular itching and vasodilatation associated with ocular redness, eyelid swelling and chemosis respectively.

Pharmacological treatment of Allergic Conjunctivitis includes H1 receptor blockage, mast cell stabilization, and blocking of cytokine production and prostaglandin formation. Topical antihistamines are first line agents in treatment of Allergic conjunctivitis. Currently, Alcaftadine 0.25% and Olopatadine hydrochloride 0.2% are the only approved once-daily, dual acting anti-allergic agents for allergic conjunctivitis which includes inhibition of histamine receptor activation directly and reduction of allergic responses by stabilising mast cells indirectly.[6,10]

Olopatadine hydrochloride is a selective histamine H1 receptor antagonist and mast-cell stabilizer with additional anti-inflammatory effects such as suppression of interleukins (IL) 6 and 8 production by inhibiting histamine related signalling pathways.[6] Alcaftadine is an anti-allergic agent that provides relief from ocular itching by inverse agonistic effects on H1 , H2 and H4 histamine receptors in early phase and also stabilises mast cells by inhibiting release of mediators such as cytokines and lipid mediators in late phase of ocular allergic response in allergic conjunctivitis. Also, it decreases chemotaxis and inhibits eosinophil activation thereby exerts anti-inflammatory property.[6,11] In the present study, the mean age was comparable and matched in both the groups. The majority of patients enrolled in our study were 26.7 ± 5.38 years in Olopatadine group and 27.9 ± 7.7 years in Alcaftadine group. There were 35 (58.3%) male and 25 (41.7%) female patients in the Olopatadine group and 39 (65%) males and 21 (35%) females in Alcaftadine group, suggesting a slight male preponderance, that was also observed in a study by Nakatani H et al,[9] which could be due to the socioeconomic status of the patients visiting our Government hospital and the social set up where majority of the females do not report to the hospital.

The present study was conducted to compare the efficacy and safety of dual-acting, once daily, topical antihistamine solutions, Alcaftadine 0.25% versus Olopatadine hydrochloride 0.2% eye drops in treatment of allergic conjunctivitis. Our findings of the study showed greater reduction in TOSS (Total Ocular Symptom Score) from baseline to 2 weeks in Alcaftadine group compared to Olopatadine hydrochloride group (statistically significant, $p<0.05$*). Similarly, the Conjunctival Hyperaemia scale also showed larger reduction within the group of Alcaftadine and Olopatadine treated patients ($p<0.001$*) from baseline (Day 1) to follow-up visit (Day 14).

The study confirmed the treatment outcome differences between Alcaftadine 0.25% and Olopatadine hydrochloride 0.2 % eye drops. Alcaftadine 0.25% treated group achieved faster symptomatic relief of allergic ocular symptoms from grade 3 to grade 0, using TOSS score (Total Ocular Symptoms Score) at visit 2 (Day 3) and visit 3 (Day 7) than Olopatadine hydrochloride 0.2 % group. There was a significant reduction in ocular symptoms and signs at the end of study (Day 14/visit 4) in Alcaftadine group than Olopatadine hydrochloride group. The common adverse effects in both groups were headache, burning sensation and mild redness.

A study by Meena MK et al,[8] showed that Alcaftadine 0.25 % ophthalmic solution provided greater symptomatic relief of ocular itching post-administration with similar safety profile, compared to Olopatadine hydrochloride 0.2 %. It also mentioned that there were significantly lower mean ocular itch scores in Alcaftadine 0.25 % treated patients than Olopatadine hydrochloride 0.2 % group at 2nd and 3rd follow-up. The study also confirmed the difference in treatment outcomes between Alcaftadine 0.25% and Olopatadine 0.2 % in preventing signs and symptoms of Allergic conjunctivitis on day 3 and day 7 of post-treatment instillation. In the present study, Alcaftadine 0.25 % showed statistically significant reduction in TOSS score on Day 14 (visit 4), compared to Olopatadine group.

A study by Greiner JV et al [11] showed that Alcaftadine 0.25 % and Olopatadine 0.2% had significant lower mean scores of ocular itching and conjunctival redness compared to placebo at visit 3 and 4. Also, Alcaftadine 0.25 % was found to be effective and superior over placebo, by reducing ocular symptoms and signs at 15 minutes and 16 hours post instillation suggesting rapid onset of action and substantial duration of action. Headache was one of the adverse events observed in this present study was similar to study by Greiner JV et al.[11]

A study by Singh S et al mentioned that Alcaftadine showed marginal superiority in efficacy of reducing ocular itching and conjunctival redness score and found equally safe, when compared to Olopatadine group.[12]

In a study by Nakatani H et al,[9] revealed that Alcaftadine 0.25 %

dosed 8 hours prior to allergen challenge was found to be effective or superior in preventing ocular signs and symptoms of Japanese cedar pollen-induced allergic conjunctivitis, compared to Olopatadine 0.2 % ophthalmic solution (challenged 4 hours post dose). The results of the study showed statistical significance in reduction of ocular itching score and conjunctival hyperaemia scale in Alcaftadine 0.25 % group compared to Olopatadine 0.2 % group. Also, the age and gender of patients enrolled in our study were similar to the study by Nakatani H et al.

A study by Ackerman et al,[13] showed differences in relief of itch between Alcaftadine 0.25% and Olopatadine 0.2% ophthalmic solutions, at the earliest time point measured post-Conjunctival allergen challenge (3 minutes) and effective in preventing ocular itching at 16- and 24-hours post-instillation in a Conjunctival Allergen Challenge (CAC). Also, it stated that Alcaftadine group was only active treatment that provided statistical significance in relief of chemosis post 24 hour instillation.[3] The current study showed patients achieved faster relief of itching, redness, tearing and chemosis of conjunctiva at day 14 (follow-up visit 4) more in Alcaftadine group compared to Olopatadine hydrochloride group.

In pooled analysis of two multicenter, randomized clinical trials, done by McLaurin EB et al,[6] revealed that Alcaftadine and Olopatadine hydrochloride was superior to placebo at relieving ocular itching Alcaftadine 0.25 % ophthalmic solution provided greater relief at 16 hour post-administration and significant lower mean itch score at 3 minutes post Conjunctival Allergen Challenge (CAC) with similar safety profile, compared to Olopatadine hydrochloride 0.2 %

A study on conjunctival epithelium and eosinophil recruitment in a murine model with allergic conjunctivitis by Ono SJ et al,[10] mentioned that Alcaftadine significantly inhibited eosinophil recruitment by a broad spectrum of H1, H2 and H4 histamine receptors antagonism and have a protective effect on epithelial tight junction protein expression in conjunctiva, compared to Olopatadine hydrochloride treated group. It also demonstrated the ability to protect epithelial tight junction protein markers from allergic inflammation-based degradation whereas Olopatadine failed to protect from degradation ZO-1 junctional protein.[9]

The present study shows that Alcaftadine 0.25 % is superior in efficacy and safety, when compared to Olopatadine hydrochloride 0.2 % in the treatment of Allergic conjunctivitis. This is a prospective, randomized study design and use of standard validated tools such as TOSS score and Conjunctival Hyperaemia scale for assessing efficacy of treatments has added strength to the study. The study was limited by its relatively smaller sample size. Therefore, further studies with larger sample size is required to evaluate the efficacy and safety of Alcaftadine 0.25 % versus Olopatadine 0.2 % in treatment of Allergic Conjunctivitis.

CONCLUSION:

In Allergic conjunctivitis, both Alcaftadine 0.25% and Olopatadine hydrochloride 0.2 % were found effective in relieving ocular signs and symptoms, but Alcaftadine 0.25 % was found to be superior in terms of efficacy, compared to Olopatadine hydrochloride 0.2 % with minimal side-effects.

Funding: Nil

Conflict of Interest: Nil

Acknowledgement:
The corresponding author would like to thank Dr. Bhavyadharshini. M, Senior Resident, Department of Pharmacology, for writing and editorial assistance.

REFERENCES:

1. Collum L, Kilmartin DJ. Acute Allergic Conjunctivitis. In: Abelson MB, editor. Allergic diseases of the eye. Philadelphia: W.B.Saunders Co; 2000.pp.108-132.
2. Ackerman S, Smith LM, Gomes PJ. Ocular itch associated with Allergic conjunctivitis: latest Evidence and Clinical Management. Therapeutic Advances in Chronic Disease.2016;7(1):52-67.
3. Gong L, Sun X, Qu J, Wang L, Zhang M, Zhang H, et al. Loteprednol etabonate suspension 0.2% administered QID compared With Olopatadine solution 0.1% administered BID in the treatment of Seasonal Allergic Conjunctivitis: A multicenter, randomized, investigator-masked, parallel group study in Chinese patients. Clinical Therapeutics. 2012;34(6):1259-1272.
4. Chigbu DI, Coyne AM. Update and Clinical utility of Alcaftadine ophthalmic solution 0.25% in the treatment of allergic conjunctivitis. Clinical Ophthalmology. 2015; 9(7):1215-25.
5. Borazan M, Karalezli A, Akova YA, Akman A, Kiyici H, Erbek SS. Efficacy of olopatadine HCl 0.1%, ketotifen fumarate 0.025%, epinastine HCl 0.05%, emedastine 0.05% and fluorometholone acetate 0.1% ophthalmic solutions for seasonal allergic conjunctivitis: a placebo-controlled environmental trial. Acta Ophthalmol. 2009;87(5):549–554.
6. McLaurin EB, Marisco NP, Ackerman SL, Ciolono JB, Williams JM, Villanueva L, et al. Ocular itch relief with Alcaftadine 0.25% versus Olopatadine 0.2% in Allergic conjunctivitis : Pooled analysis of two multicentre randomized clinical trials. Adv Ther . 2014;31(10):1059-71.
7. Gallois-Bernos AC, Thurmond RL. Alcaftadine, a new antihistamine with combined antagonistic activity at histamine H1, H2 and H4 receptors. Journal of Receptor, Ligand and Channel Research. 2012;5(12):9-20.
8. Meena MK, Gupta V. Alcaftadine 0.25% versus Olopatadine 0.2% in Allergic conjunctivitis. International Journal of Scientific Research. 2018;7(3):53-55.
9. Nakatani H, Gomes P, Bradford R, Guo Q, Safyan E, Hollander DA. Alcaftadine 0.25 % versus Olopatadine 0.1 % in preventing Cedar Pollen Allergic Conjunctivitis in Japan: A Randomized study. Ocular Immunology and Inflammation. 2018;00(00):1-10.
10. Ono SJ, Lane K. Comparison of effects of Alcaftadine and Olopatadine on conjunctival epithelium and eosinophil recruitment in a murine model of allergic conjunctivitis. Drug Design, Development and Therapy. 2011;5(2):77-84.
11. Greiner JV, Swanson KE, Ingerman A. Evaluation of Alcaftadine 0.25 % ophthalmic solution in acute allergic conjunctivitis at 15 minutes and 16 hours after instillation versus Placebo and Olopatadine 0.1%. Clin Ophthalmol. 2011;5(1): 87-93.
12. Singh S, Mote R, Shukla S, Khatri K. A comparative, Randomized, Double blind, Parallel group and non-cross over, Multicentric Clinical Study with Alcaftadine eye drops or Olopatadine Hydrochloride eye drops in subjects suffering from Allergic Conjunctivitis. European Journal of Biomedical and Pharmaceutical Sciences. 2017;4(6):253.
13. Ackerman S, D'Ambrosio F, Greiner JV, Villanueva L, Ciolino JB, Hollander DA. A multicenter evaluation of the efficacy and duration of action of Alcaftadine 0.25% and Olopatadine 0.2% in the conjunctival allergen challenge model. Journal of Asthma and Allergy.2013;6(4):43–52.