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Efficacy of Olopatadine In the Management of Allergic Conjunctivitis.

Sanu Sain[1]*, and Sivagami Dinesh[2].

[1]Department of Pharmacology, PRIMS College, Chennai, Tamil Nadu, India.
[2]Department of Pharmacology, Government Stanley Medical College, Chennai, Tamil Nadu, India.

ABSTRACT

Allergic conjunctivitis is the second most common cause of ocular morbidity in India and it accounts about 20% of cases attending ophthalmology clinics. Ocular itching and nasal symptoms adversely affect the quality of life of patients. This study was done to compare the efficacy and tolerability of 0.2% Olopatadine hydrochloride once daily with 2% sodium Cromoglycate four times daily in allergic conjunctivitis. After obtaining written informed consent, 120 patients who satisfy the eligibility criteria were enrolled into the study. Participants were randomly allocated into two groups; one receiving Olopatadine hydrochloride 0.2% ophthalmic solution OD and the other sodium Cromoglycate 2% ophthalmic solution QID for 4 weeks. Patients ocular signs and symptoms assessment were done by a 4 – point scale at the end of 2nd, 3rd and 4th week. Adverse events, if any will be noted during the study and patients will be followed up to two weeks. Change from baseline itching score were 2.5 in Olopatadine group compared to 2.2 in sodium Cromoglycate group (P value-0.006) during 4th week. Change from baseline redness score were 2.36 in Olopatadine group compared to sodium Cromoglycate group is 1.96 (P value0.002) during 4th week. Both treatments show reduction of signs and symptoms scores (P value<0.001) No treatment related adverse effects noted during study. Both 0.2% Olopatadine and 2% sodium Cromoglycate are effective in treating allergic conjunctivitis. 0.2% Olopatadine once daily shows better reduction of itching and redness score during 4th week than 2% sodium Cromoglycate. Both drugs are safe and well tolerated.

Keywords: Allergic Conjunctivitis, Histamine, Ocular itching, Olopatadine, Sodium Cromoglycate,

Corresponding author

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INTRODUCTION

Allergic diseases are the fifth leading diseases among chronic diseases in the world. It affects about 40% percentage of entire population.[1] There is a worldwide increase in allergic diseases over the last ten years.[2]The prevalence of allergic diseases among school children is generally increasing and varies from 0.3% to 20.5%. A single cause for allergic disease cannot be pointed out and we should consider a contribution of many factors like genetics, air pollution in urban areas, pets and early childhood exposure for the increase.[2]

Ocular allergy is one of the most common types of allergy. Ocular allergy accounts for 15% - 20% of population all over the world. It is common among school going children and adolescent age group. It is usually associated with other allergic diseases. It has a significant impact on the day to day activities and quality of life.[3]

The term allergic conjunctivitis includes Seasonal Allergic Conjunctivitis (SAC), Perennial Allergic Conjunctivitis (PAC), Vernal Kerato Conjunctivitis (VKC), and Atopic Kerato Conjunctivitis (AKC). However the clinical and pathophysiological features of AKC and VKC are quite different from SAC and PAC, in spite of common allergic markers. The uses of contact lenses or ocular prosthesis are associated with giant papillary conjunctivitis (GPC) which is often included in the group of ocular allergy, however they may not be considered as real allergic diseases.[4]

The most common form of ocular allergy is SAC, which represents about 90% of cases.[3] The most prevalent allergens for SAC are grass, tree, weed pollen and outdoor molds. Although the signs and symptoms of SAC are usually mild, it can hinder school performance, everyday activities, like reading, sleeping etc which results in overall reduction in the quality of life.[2] Allergic conjunctivitis is a type I hypersensitivity reaction mediated by IgE. The pathophysiology of allergic conjunctivitis starts with an initial histamine, tryptase, synthesis of prostaglandins and leukotrienes. In the later phase, there is activation of eosinophils, basophiles, T cells, macrophages and neutrophils leading to a chronic stage of the disease.[1]

The treatment and management goals of allergic conjunctivitis are to minimize the inflammatory cascade associated with allergic response in the early stages of the pathological mechanism. It is noted that the activation of histamine receptors on immune and non immune cells are associated with allergen-induced inflammation of the conjunctiva and its associated ocular allergic manifestations, including itching, edema, and hyperaemia and tearing.[5] The treatment of Allergic conjunctivitis depends on severity and avoidance of allergens is helpful to alleviate symptoms. The medications which are available for the treatment of allergic conjunctivitis belongs to different classes ranging from H1 Receptor antagonist (Levocabastine, Emedastine, Bepostatine and Alcaftadine), Mast cell stabilizers (Sodium Lodoxamide, Pemirolast, Nedocromil Sodium), Antihistamines with mast cell stabilizing property (Ketotifen Fumarate, Azelastine, and Olopatadine), Topical Non Steroidal Anti-Inflammatory Drugs (NSAIDs) like ketorolac, Vasoconstrictors like Naphazoline, Pheniramine, Topical Steroids, and oral Antihistamines.

Olopatadine is a H_1 selective antagonist with a mast cell stabilizing property, along with suppressing action on TNF ∞, IL -6 and IL -8, release. It is a well tolerated drug which gives rapid and long duration of relief from signs and symptoms of Allergic conjunctivitis.[6] Sodium Cromoglycate is a mast cell stabilizer. Studies show that sodium Cromoglycate selectively and rapidly phosphorylates proteins in mast cell membrane, which is responsible for stopping the secretion and mast cell re-stabilization after degranulation[7]

Recently Olopatadine hydrochloride 0.2% ophthalmic solution has been approved to be given as single daily dosage for Allergic conjunctivitis. Few studies were done in Allergic conjunctivitis comparing efficacy and tolerability of 0.1% Olopatadine and sodium Cromoglycate 2% in India, but few in Tamil Nadu.

Objective

To compare the efficacy and tolerability of Olopatadine 0.2% ophthalmic solution administered OD with sodium Cromoglycate 2% ophthalmic solution administered QID in allergic conjunctivitis

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METHODOLOGY

Study setting

This study was done as a double blind, randomized, prospective, open labelled comparative study in the Department of Ophthalmology and Department of Pharmacology of our medical college between March 2015 and February 2016.

Study Population

Patients clinically diagnosed with allergic conjunctivitis at our outpatient clinic of ophthalmology department of our medical college were included in the study. Based on the previously published literature, the mean (standard deviation) scores for ocular itching with Olopatadine and Sodium Cromoglycate were 2.45 (0.82) and 1.75 (0.81) respectively. At 95% level of significance and 90% power, the sample size was estimated to be 28.46 in each group. Accounting 10% for non response, the sample size was calculated as 31.3 and was rounded off to 40 in each group. A total of 120 patients were enrolled, of which three patients dropped out. For the final analysis, 117 were included, 59 in Group A and 58 in Group B.

Inclusion criteria:

- All patients age >4 years with clinically diagnosed allergic conjunctivitis.
- Consenting for the study
- Willing to do follow up visits.

Exclusion criteria:

- Patients age <4 yrs.
- Patients having active ocular infections, serious ocular pathological conditions.
- Patients having ocular surface disorders like pterygium, dry eyes blepharitis, history of ocular surgery within 3 months.
- Patients who have known hypersensitivity to the study drugs including benzalkonium chloride which is used as preservative in ophthalmic solution
- If the patients have used the study medications 1 week before the start of the study.
- Patients who are unwilling to discontinue contact lens during study period.
- Pregnant and lactating women.
- Patient taking oral immune-suppressive agents like steroids, topical medications, artificial tear drops, steroid eye drops.

Ethical approval and informed consent

Approval was obtained from the institutional ethics committee prior to the commencement of the study. Each participant was explained in detail about the study and written informed consent was obtained prior to the randomization. For the patients less than the age of 18 years, their parents were explained about the study purpose procedures and a written informed consent was obtained from them. If the participant was illiterate, left thumb impression was sought. This was done in the presence of an impartial witness.

Duration of study:

The total duration of the study was 6 weeks. The first four weeks consisted for intervention period and the last two weeks consisted of follow up period.

Sample size:

The total participants enrolled in the study consisted of 120 patients, divided into two groups-

Group A- Olopatadine – 60 patients
Group B- Sodium Cromoglycate -60 patients

Study Procedure:

Screening

After getting informed consent, the demographic details of 145 patients were obtained and recoded. After taking complete medical history, clinical examination, slit lamp examination of eyes were done by an ophthalmologist. After screening 145 patients, 120 patients who satisfy the inclusion and exclusion criteria were enrolled n the study during 1st visit.

Randomization and blinding

Each participant was randomized into Group A (Olopatadine) or Group B (Sodium cromoglycate) by simple randomization using odd/even number method. Randomization process was carried out by an external person, not part of the study team. Both the participants and the principal investigator and his team were blind to the randomization process.

Treatment Plan

Group A- Olopatadine hydrochloride 0.2% ophthalmic solution 1 drop on affected eye OD for 4 weeks
Group B – sodium Cromoglycate 2% ophthalmic solution 1 drop on affected eye QID for 4 weeks.

Follow Up Visits:

After baseline (visit 1) history taking, clinical examination, slit lamp examination of eyes of the patients in each group, group A and group B were given medications for 2 week. To assure compliance, the patients were asked to mark the time when they are instilling medication and record on his/her own impression on relief of symptoms during each day in a dairy (provided during visit 1). The patients were also asked to return back the empty bottles of medications and diary during follow up visits. Follow up visits were made at 2nd week, 3rd week and 4th week adverse effects were noted during each visit and in case of any serious adverse effect patient were asked to report immediately to the hospital or investigator. After 4thweek medications were stopped and they were asked to come on 6thweek for post treatment follow up.

Assessment of Patients

The assessment of patient is done by history taking, clinical examination and slit examination by ophthalmologist. The ocular signs such as conjunctival congestion, chemosis, lid edema were assessed the signs are graded depending upon the severity (grade 0-absent, grade 1-mild, grade 2-moderate, grade 3 severe). The ocular symptoms like itching, discomfort, stinging, photophobia and watering foreign body sensation were assessed by the interviewing the patients and graded according to severity grade 0 – absent, grade 1-mild, grade 2-moderate, grade 3 severe were assessed by interviewing the patients.[3]

Assessment of Efficacy, Safety and Tolerability

The change in mean scores from baseline for signs and symptoms during 2nd week and 4thweek were compared between two groups. Treatment related adverse events, compliance of patients were compared between the two groups.

Data analysis

The obtained data was analyzed statistically using SPSS 20 software Descriptive data were analyzed by Chi square test. The reduction of signs and symptoms scores during (visit 1) within the groups were analyzed using wilcoxon signed rank test. Comparison between the groups A and groups B in reduction of symptoms and signs scores were analyzed using Mann Whitney U test. P value ≤ 0.05 considered to be statistically significant.

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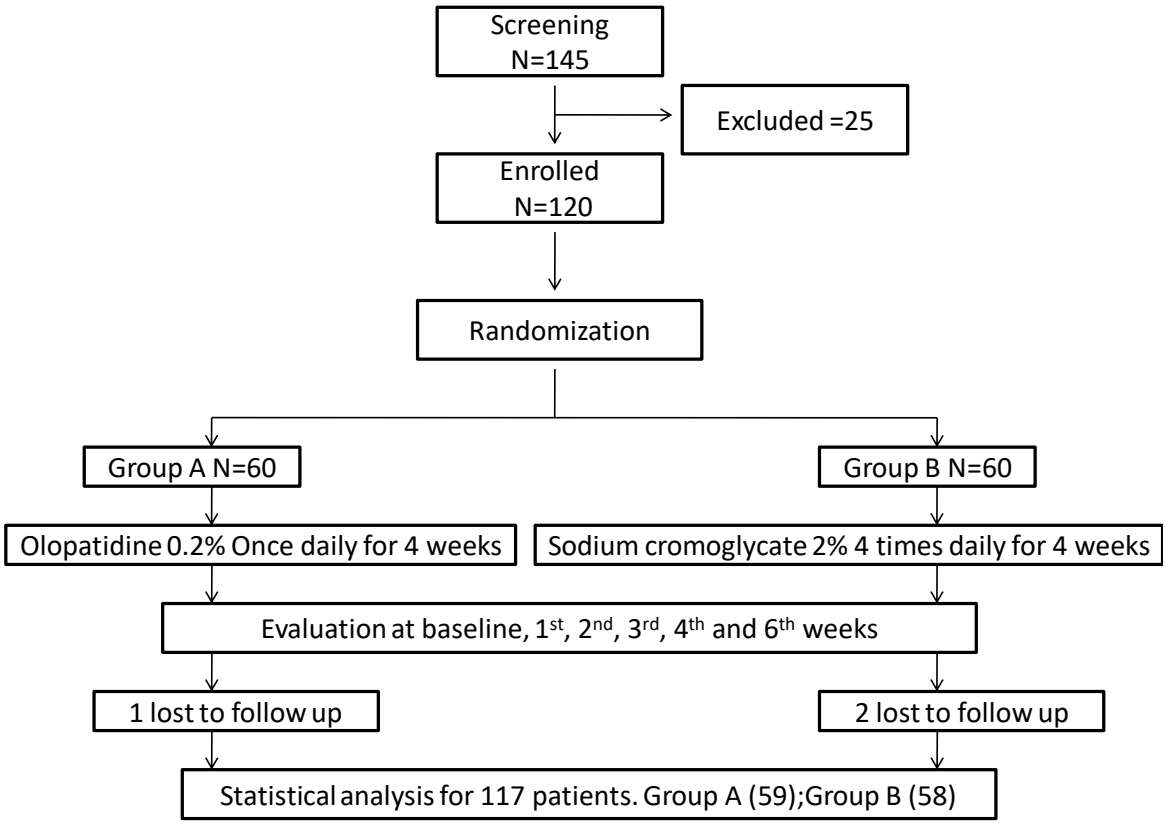
Study protocol



RESULTS

This study was conducted to compare the efficacy and tolerability of Olopatadine to sodium Cromoglycate in allergic conjunctivitis patients among 117 participants. The mean age of the study participants in Group A was 16.04 years and in Group B was 16.43 years. The background details of the study participants are given in table 1.

Table-1: Background characteristics of the study participants

S. No	Characteristics	Group A N=59		Group B N=58	
		n	%	n	%
1	**Age (in years)**				
	<15	36	61.1	35	60.3
	>15	23	38.9	23	39.6
2	**Sex**				
	Male	37	63	37	64
	Female	22	37	21	36

The comparison of mean scores of eye symptoms (itching) between baseline and each visit for both the groups is given in table 2. It was observed that the mean scores drastically reduced in Group A, compared to group B. Moreover the mean scores showed a decline from the second visit onwards. The difference in the mean scores were found to be statistically significant ($p<0.05$)

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Table 2: Mean scores of itching among the study participants

S. No	Itching	Group A	Group B	Mann Whitney U test
		Mean Score +SD	Mean Score +SD	P value
1	Baseline	2.6±0.494	2.45± 0.534	0.127
2	Visit 2	1.02±0.676	1.15 ±0.708	0.232
3	Visit 3	0.2±0.403	0.57± 0.5325	0.01*
4	Visit 4	0.1±0.237	0.25 ±0.473	0.04*
	Wilcoxon Signed Rank P value.	0.01 *	0.01*	

*significant at P≤0.05, highly significant at P≤0.01, very high significant at P≤0.001

The comparison of mean scores of eye symptoms (redness) between baseline and each visit for both the groups is given in table 3. It was observed that the mean scores drastically reduced in Group A, compared to group B. Moreover the mean scores showed a decline from the third visit onwards. The difference in the mean scores were found to be statistically significant (p<0.05)

Table 3: Mean scores of redness among the study participants

S. No	Redness	Group A	Group B	Mann Whitney U test
		Mean Score +SD	Mean Score +SD	P value
1	Baseline	2.51±0.504	2.4± 0.560	0.367
2	Visit 2	1.23±0.722	1.25 ±0.531	0.857
3	Visit 3	0.42±0.532	0.65± 0.503	0.037*
4	Visit 4	0.15±0.363	0.43 ±0.479	0.001*
	Wilcoxon Signed Rank P value.	P<0.001*	0.001*	

*significant at P≤0.05, highly significant at P≤0.01, very high significant at P≤0.001

The comparison of mean scores of eye symptoms (chemosis) between baseline and each visit for both the groups is given in table 4. It was observed that the mean scores drastically reduced in Group A, compared to group B. Moreover the mean scores showed a decline from the second visit onwards. However there was no statistically significant difference between the two groups for each visit. The overall difference in the mean scores between the two groups were found to be statistically significant (p<0.05)

Table 4: Mean scores of chemosis among the study participants

S. No	Chemosis	Group A	Group B	Mann Whitney U test
		Mean Score +SD	Mean Score +SD	P value
1	Baseline	0.85±0.685	0.70± 0.618	0.238
2	Visit 2	0.24±0.426	0.30 ±0.462	0.411
3	Visit 3	0.1±0.302	0.12± 0.342	0.571
4	Visit 4	0.00±0.000	0.03 ±0.181	0.156
	Wilcoxon Signed Rank P value.	P<0.001*	P<0.001*	

*significant at P≤0.05, highly significant at P≤0.01, very high significant at P≤0.001

The comparison of mean scores of eye symptoms (lid oedema) between baseline and each visit for both the groups is given in table 5. It was observed that the mean scores drastically reduced in Group A, compared to group B. Moreover the mean scores showed a decline from the third visit onwards. However there was no statistically significant difference between the two groups for each visit. The overall difference in the mean scores between the two groups were found to be statistically significant (p<0.05)

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Table 5: Mean scores of lid oedema among the study participants.

S. No	Lid oedema	Group A	Group B	Mann Whitney U test
		Mean Score +SD	Mean Score +SD	P value
1	Baseline	0.69±0.65	0.61± 0.62	0.603
2	Visit 2	0.25±0.439	0.28 ±0.459	0.681
3	Visit 3	0.1±0.305	0.12± 0.329	0.77
4	Visit 4	0.02±0.13	0.08 ±0.283	0.095
	Wilcoxon Signed Rank P value.	P<0.001*	P<0.001*	

*significant at P≤0.05, highly significant at P≤0.01, very high significant at P≤0.001

The comparison of mean scores of eye symptoms (tearing) between baseline and each visit for both the groups is given in table 6. It was observed that the mean scores drastically reduced in Group A, compared to group B. Moreover the mean scores showed a decline from the third visit onwards. However there was no statistically significant difference between the two groups for each visit. The overall difference in the mean scores between the two groups were found to be statistically significant (p<0.05)

Table 6: Mean scores of tearing among the study participants.

S. No	Tearing	Group A	Group B	Mann Whitney U test
		Mean Score +SD	Mean Score +SD	P value
1	Baseline	1.33±0.617	1.34± 0.515	0.769
2	Visit 2	0.29±0.457	0.31 ±0.467	0.991
3	Visit 3	0.12±0.305	0.05± 0.223	0.188
4	Visit 4	0.02±0.13	0.03±0.184	0.56
	Wilcoxon Signed Rank P value.	P<0.001*	P<0.001*	

*significant at P≤0.05, highly significant at P≤0.01, very high significant at P≤0.001

The comparison of mean scores of eye symptoms (discomfort) between baseline and each visit for both the groups is given in table 7. It was observed that the mean scores drastically reduced in Group A, compared to group B. Moreover the mean scores showed a decline from the third visit onwards. However there was no statistically significant difference between the two groups for each visit. The overall difference in the mean scores between the two groups were found to be statistically significant (p<0.05)

Table 7: Mean scores of discomfort among the study participants.

S. No	Discomfort	Group A	Group B	Mann Whitney U test
		Mean Score +SD	Mean Score +SD	P value
1	Baseline	1.67±0.876	1.60± 0.527	0.886
2	Visit 2	0.62±0.738	0.65 ±0.633	0.574
3	Visit 3	0.283±0.454	0.30± 0.497	0.954
4	Visit 4	0.07±0.252	0.08 ±0.278	0.780
	Wilcoxon Signed Rank P value.	P<0.001*	P<0.001*	

*significant at P≤0.05, highly significant at P≤0.01, very high significant at P≤0.001

The comparison of mean scores of eye symptoms (photophobia) between baseline and each visit for both the groups is given in table 8. It was observed that the mean scores drastically reduced in Group A, compared to group B. Moreover the mean scores showed a decline from the third visit onwards. However there was no statistically significant difference between the two groups for each visit. The overall difference in the mean scores between the two groups were found to be statistically significant (p<0.05)

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Table 8: Mean scores of photophobia among the study participants.

S. No	Photophobia	Group A	Group B	Mann Whitney U test
		Mean Score +SD	Mean Score +SD	P value
1	Baseline	0.46±0.502	0.32± 0.467	0.135
2	Visit 2	0.08±0.183	0.06 ±0.256	0.834
3	Visit 3	0.00±0.000	0.02± 0.131	0.317
4	Visit 4	0.00±0.000	0.00±0.000	1.000
	Wilcoxon Signed Rank P value.	P<0.001*	P<0.001*	

*significant at P≤0.05, highly significant at P≤0.01, very high significant at P≤0.001

The comparison of mean scores of eye symptoms (foreign body sensation) between baseline and each visit for both the groups is given in table 9. It was observed that the mean scores drastically reduced in Group A, compared to group B. Moreover the mean scores showed a decline from the third visit onwards. However there was no statistically significant difference between the two groups for each visit. The overall difference in the mean scores between the two groups were found to be statistically significant (p<0.05)

Table 9: Mean scores of foreign body sensation among the study participants.

S. No	Foreign body sensation	Group A	Group B	Mann Whitney U test
		Mean Score +SD	Mean Score +SD	P value
1	Baseline	2.28±0.457	2.12± 0.564	0.079
2	Visit 2	0.52±0.598	0.40 ±0.459	0.262
3	Visit 3	0.07±0.254	0.02± 0.131	0.730
4	Visit 4	0.00±0.000	0.03±0.033	0.156
	Wilcoxon Signed Rank P value.	P<0.001*	P<0.001*	

*significant at P≤0.05, highly significant at P≤0.01, very high significant at P≤0.001

The comparison of mean scores of eye symptoms (stinging) between baseline and each visit for both the groups is given in table 10. It was observed that the mean scores drastically reduced in Group A, compared to group B. Moreover the mean scores showed a decline from the third visit onwards. However there was no statistically significant difference between the two groups for each visit. The overall difference in the mean scores between the two groups were found to be statistically significant (p<0.05)

Table 10: Mean scores of foreign body sensation among the study participants.

S. No	Stinging	Group A	Group B	Mann Whitney U test
		Mean Score +SD	Mean Score +SD	P value
1	Baseline	2.27±0.485	2.1± 0.667	0.358
2	Visit 2	0.15±0.363	0.217 ±0.627	0.451
3	Visit 3	0.07±0.254	0.133± 0.438	0.225
4	Visit 4	0.02±0.13	0.05±0.329	0.172
	Wilcoxon Signed Rank P value.	P<0.001*	P<0.001*	

*significant at P≤0.05, highly significant at P≤0.01, very high significant at P≤0.001

The mean change in the signs and symptoms in comparison with 2nd and 4th week scores are given in table 11. There was minimal difference in the scores between the two groups at the second week. However, at 4th week, significant improvement in the scores were seen with redness and itching (p<0.05).

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Table 11: Mean Change in signs and Symptoms at 2nd week and 4th week

S. No	Symptom	Mean change from baseline in 2nd week			Mean change from baseline in 4th week		Mannwhitney U test
		Group A	Group B	P value	Group A	Group B	P value
1	Redness	1.26	1.15	0.350	2.36	1.96	0.002*
2	Itching	1.58	1.4	0.248	2.5	2.2	0.006*
3	Chemosis	0.62	0.4	0.06	0.85	0.67	0.152
4	Eye Lid Edema	0.43	0.33	0.318	0.67	0.53	0.262
5	Watering	1.01	1.033	0.668	1.28	1.3	0.889
6	Photophobia	0.37	0.23	0.113	0.45	0.32	0.135
7	Discomfort	1.05	0.95	0.291	1.6	1.51	0.790
8	Foreign body Sensation	1.75	1.72	0.683	2.28	2.08	0.087
9	Stinging	2.05	1.87	0.058	2.18	2.02	0.138

*Significant at P≤0.05, highly significant at P≤0.01, very high significant at P≤0.001

DISCUSSION

To choose the best drug in allergic conjunctivitis with understanding of underlying mechanisms implicated in triggering the allergy is very important. Olopatadine with a wide action spectrum has shown to be very effective in allergic conjunctivitis [8]. This study was done among 117 participants, with 59 in Group A (Olopatadine) and Group B (Sodium cromoglycate). Both the groups were similar and comparable.

In this study, both the groups have demonstrated significant progress in the reduction of the allergy symptoms during the follow up period. The Olopatadine group has demonstrated significant improvement in the scores of the allergy symptoms, especially itching and redness (P<0.01). However, on a timeline comparison, it was observed that effective reduction of the scores occurred only at 4th week while during the second week, though there were reductions in the scores, the difference observed was statistically not significant.

Olopatadine acts as Histamine H1 receptor antagonist, and also by suppressing the chemical mediators and eosinophil infiltration.[9] Olopatadine had demonstrated inhibition of mast cell activation, reduction in histamine and TNF-α release and upregulation of proinflammatory mediators in an in vitro model of conjuctival epithelial cells. It also demonstrated reduction of histamine tear cells and allergic inflammation in the in vivo models.[10] Though several studies document the best evidence with Sodium cromoglycate, Olopatadine shows significant difference in the relieving of symptoms and a better compliance compared to Sodium cromoglycate in our study.[11] Trials also demonstrated a significant reduction in the mean ocular itching at 7 minutes (0.23) with Olopatadine compared to other drugs (0.37). Mean conjunctival hyperaemia was also significantly lower on the first day with Olopatadine. [12]

CONCLUSION

Both Olopatadine 0.2% 1 drop once daily and sodium Cromoglycate 2% 1 drop four times are effective in reducing symptoms and signs of allergic conjunctivitis during 2nd and 4th week. Olopatadine 0.2% once daily is found to be more effective than sodium Cromoglycate 2% four times daily in reducing redness and itching scores during 4th week.. Treatment with Olopatadine 0.2% once daily has more patient's compliance than sodium Cromoglycate 2% four times daily. Both Olopatadine 0.2% once daily and sodium Cromoglycate 2% four times daily show good patient tolerability and safety profile.

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