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Original Research Article.

Comparative Evaluation of Efficacy and Safety of Bepotastine Besilate versus Olopatadine and Ketorolac Combination in Patients with Vernal Keratoconjunctivitis

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ABSTRACT

Objective: Comparative evaluation of efficacy and safety of Bepotastine besilate versus Olopatadine and Ketorolac combination in patients with vernal keratoconjunctivitis.

Materials and Methods: This was a prospective, open label, randomized, comparative clinical study. Hundred patients of vernal keratoconjunctivitis between 6 to 20 years of age of either sex willing to give informed consent were enrolled in the study. In Group 1, 50 patients received Bepotastine besilate (0.15%) eye drops twice daily for 8 weeks whereas in Group 2, 50 patients received Olopatadine (0.2%) and Ketorolac (0.4%) combination eye drops twice daily for 8 weeks. Symptoms and signs scoring of VKC were recorded on baseline and at the time of follow up at 4 and 8 weeks. Safety assessments were also done in both the drug groups during the study period for any serious adverse effects.

Results: After the 2 months of drug therapy, patients in both the groups showed improvement in the symptoms and signs scoring of VKC. However, there was no statistically significant difference between the two treatment groups at 4th and 8th week. Both the drugs were well tolerated without any serious adverse effect.

Conclusion: Both bepotastine besilate versus olopatadine and Ketorolac combination ophthalmic solutions were found to be effective in alleviating the clinical symptoms and signs of VKC.

Keywords: Mast Cell Stabilizer, Topical NSAIDs, Newer H1-antihistaminics, SAEs, Vernal Keratoconjunctivitis.

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is an atopic condition of the external ocular surface. It is most common and most severe in hot, dry environments such as the Mediterranean basin, West Africa and the Indian subcontinent.[1] In these areas, upto 3% of eye clinic patients present with VKC and 10% of outpatient appointments are made for signs and symptoms related to VKC.[2] Commonly, VKC can be divided into three distinct phenotypes namely tarsal, limbal and mixed types of VKC. VKC commonly occurs in school-age children. A male preponderance has been observed, especially in patients under 20 years of age, among whom the male is to female ratio is 3:1 whereas the ratio in older than 20 years[3] of age is 1:1.

VKC mainly appears seasonally but can be perennial, chronic or with acute exacerbations. It is an Immunoglobulin-E (IgE) and T-cell mediated allergic reaction with additional, ill-defined, nonspecific, hypersensitivity responses.[4]

The predominant eye symptoms are itching, discharge, tearing, eye irritation and to some extent, photophobia. In 1988, Buckley coined the term "morning misery" for VKC which described the active disease state of patients with severe discomfort, blepharospasm and mucous discharge from eyes leaving them incapacitated upon awakening and "frequently resulting in lateness for school".[5] Because conjunctivitis typically shows recurrence in spring time, it is named as vernal. In some patients, rhinitis and asthma coexist with VKC.[6]

On external examination, the lids can be erythematous and thickened. The classic finding of giant papillae of more than 1 mm diameter is located most commonly on the upper tarsal conjunctiva. The tarsal conjunctiva develops a cobblestone appearance and in active disease, can have mucus accumulation between the papillae. In the limbal form, the conjunctiva may show gelatinous limbal papillae associated with epithelial infiltrates

called Horner-Trantas dots. These are focal collections of degenerated eosinophils and epithelial cells. The cornea may become involved in VKC, and the corneal changes ranges from mild (punctate epithelial erosions) to severe (macroerosions and ulcers).[7]

VKC is not difficult to diagnose by clinical examination of the eye. Horner-Trantas dots and large cobblestone papillae are indicative of this condition. VKC is differentiated from other ocular allergic conditions through a comprehensive clinical history and ophthalmic examination. Conjunctival scrapings or tear cytology can be useful, revealing increased leukocytes in the conjunctiva, particularly eosinophils.[8]

In VKC, first line treatment includes allergen identification and avoidance, avoidance of eye rubbing and contact lens wear during symptomatic periods, treatment of tear film dysfunction, cold compresses, topical dual-acting antihistaminics or mast cell stabilizers, oral non-sedating anti-H_1 antihistaminics and treatment of coexisting allergic rhinitis (AR). Second line treatment consider preservative-free topical therapy, short course of topical steroids and oral steroids and allergen immunotherapy (AIT) given by subcutaneous or sublingual route. Third line treatment includes topical immuno-modulators i.e, calcineurin inhibitors, omalizumab which is an anti-IgE monoclonal antibody is prescribed in severe cases of VKC or AKC, especially in the presence of concurrent asthma or chronic urticaria.[9]

Mast cell stabilizers are the first-line drugs in management of VKC. Olopatadine (0.1%) is the first dual acting anti allergic drug to receive FDA approval as both an antihistaminic and a mast cell stabilizer, potentially reducing the need for multi-drug therapy. Its dual mechanism of action is an advantage and the drug may be used both as a therapeutic and prophylactic agent.[10] It also confers the drug superior in terms of clinical effectiveness, rapid onset and longer duration of action. Its dosing regimen is one drop topical instillation twice daily. It has been shown to be effective against ocular pruritis up to 8 hours. It is well tolerated and can be used in children 2 years and older. The most frequently reported side effects were dry eye, pruritis, stickiness and taste perversion.[11]

Non-steroidal anti-inflammatory drug (NSAIDs) such as Ketorolac works through the inhibition of cyclo-oxygenase enzyme, which produces prostaglandins. It is used as additive drugs to reduce the conjunctival hyperemia and itching related to prostaglandin D_2 and prostaglandin E_2 production. Ketorolac (0.5%) is approved by US-FDA for both SAC and VKC.[12] Application of topical NSAIDS is limited due to stinging and burning sensation. Despite these facts Ketorolac tromethamine formulation has shown significant effectiveness in the treatment of acute allergic conjunctivitis.[13]

Bepotastine besilate is a newer anti-allergic agent with multiple mechanism of action. It is a dual acting agent as it is highly selective histamine (H1) receptor antagonist with potent mast cell-stabilizing effects. The anti-inflammatory actions of bepotastine besilate include inhibition of leukotriene B_4 production and attenuating eosinophil chemotaxis and activation.[14] The conjunctival allergen challenge (CAC) based clinical trials established that bepotastine besilate ophthalmic solution (BBOS) (1.0% or 1.5%) provided a statistically and clinically significant reduction in ocular itching for up to 8 hours post-instillation in clinical trials as well as statistically significant reductions in conjunctival hyperemia associated with allergic conjunctivitis.[15]

Topical Corticosteroids can also be used in more severe variants of ocular allergy. Corticosteroids possess immunosuppressive and anti-proliferative properties but they have some limitations like elevation of intraocular pressure and cataract formation.[16]

MATERIALS AND METHODS

This was a prospective, open label, randomized, comparative clinical study. The present study was conducted by the Department of Pharmacology and Regional Institute of Ophthalmology, Pt. B.D. Sharma PGIMS, Rohtak. In present study patients of either sex between 6 to 20 years of age who attended the OPD in Ophthalmology department with vernal keratoconjunctivitis were selected.

The study was conducted over a period of 1 year and 100 patients were included. Study was done in accordance with the principles of Good Clinical Practice (ICH-GCP) and Declaration of Helsinki. An informed consent was obtained from all patients enrolled for the study. The study was approved by Institutional Review Board (IRB).

Each study group minimally had 50 patients and had received either topical eye drops of Bepotastine besilate (0.15%) or Olopatadine (0.2%) with Ketorolac (0.4%) combination treatment for a period of 8 weeks i.e two months. A detailed Ophthalomological history with reference to subjective complaints was obtained from the patients at week 0 and followed up at week 4 and week 8. Clinical signs were assessed in all the patients at week 0, week 4 and week 8. Safety assessment was done at baseline and at the end of the study.

Clinical Assessment

1. Clinical Symptoms Score Grading[17]

The measurement standard of the symptoms was evaluated by the same investigator through the direct questioning and observation. The clinical improvement was assessed based on subjective complaints grading score which is used to assess the severity of symptoms namely itching, tearing, redness, foreign body discomfort, visual disturbance and photobhobia. All the efficacy variables were assessed for both eyes at each visit. These parameters were assessed on a pre-determined 4-point scale where grade 0 means no symptoms, grade 1 means mild symptoms, grade 2 means moderate symptoms and grade 3 means severe symptoms of VKC.

The total score was calculated from 0 (asymptomatic) to 15 (very symptomatic). A decrease in the score with treatment was considered meaningful. The score was calculated at the baseline (before drug administration) and then at the end of 4 and 8 weeks.

2. Clinical Signs Grading[18]

Clinicians were advised to consistently use the same grading system. Grades range from 0, where no clinical action is required to 4, where clinical action is urgently required. The clinical improvement was assessed based on clinical signs grading score. The patients were evaluated at the baseline (before drug administration) and then at the end of 4 and 8 weeks after the initiation of therapy. The different signs were evaluated by using grading system. Sign scores were calculated by grading conjunctival hyperaemia, mucus discharge, tarsal papillae, tranta's dots and corneal involvement. These parameters were assessed on a pre-determined 4-point scale where grade 0 means no signs, grade 1 means mild signs, grade 2 means moderate signs and grade 3 means severe signs of VKC.

The total score was calculated from 0 (asymptomatic) to 15 (very symptomatic). A decrease in the score with treatment was considered meaningful.

Safety Assessment

Patients were assessed on receiving bepotastine (0.15%) eye drops (Group A) versus olopatadine (0.2%) with Ketorolac (0.4%) eye drop combination (Group-B) treatment to observe for the occurrence of any adverse effects probably related to drugs. Any other unusual adverse events reported by the patients were also recorded. Patients having major toxicity to any of the above mentioned topical drug necessitating discontinuation of treatment were withdrawn from the study and appropriate treatment was given.

RESULTS

This study was planned to compare the efficacy of two different regimens, one being topical bepotastine besilate (Group A) and another being topical olopatadine with ketorolac combination (Group B) received twice daily for 8 weeks.

The efficacy assessment was done at baseline and subsequently the patients of VKC were followed at 4 & 8 weeks for the following parameters i.e. clinical symptoms score grading and Clinical signs scoring.

1. Clinical Grading System

The clinical improvement was assessed based on clinical parameters for evaluation of symptoms of VKC, which were itching, tearing, hyperemia, visual disturbance, photophobia and mucus discharge while signs of VKC conjunctival hyperemia, tarsal papillae, limbal tranta spots, corneal involvement were assessed . These parameters were assessed on a pre-determined clinical 4-point grading system as: 0= absent, 1= mild, 2= moderate and 3=severe

a) Clinical Symptoms Score

The subjective score was calculated in all the patients of either group before drug administration at baseline and further re-assessed at the end of 4 and 8 weeks.

CLINICAL SYMPTOMS SCORING IN GROUP A

Intragroup Analysis (Table 1)

In Group A, the baseline clinical symptom score was 7.68 ± 0.38 which reduced to 5.12 ± 0.32 at 4 weeks and 2.120 ± 0.18 at 8 weeks. There was statistically significant reduction in clinical symptoms score when compared to baseline at 4weeks (2.56 ± 0.22) and 8 weeks (5.56 ± 0.32). The maximum improvement of 71% was seen at 8 weeks.

CLINICAL SYMPTOMS SCORING IN GROUP B

Intragroup Analysis (Table 2)

In Group B, the baseline clinical symptom score was 7.06 ± 0.39 which reduced to 4.58 ± 0.35 at 4 weeks and 2.1 ± 0.19 at 8 weeks. There was statistically significant reduction in clinical symptoms score when compared to baseline at 4 weeks (2.48 ± 0.19) and 8 weeks (4.96 ± 0.31). The maximum improvement of 69% was seen at 8 weeks.

Table 1: Intragroup Comparison of Clinical Symptoms Score in Group A (N=50)

Time interval	Bepotastine besilate (Group A) (n=50)		p-value
	Mean±SEM	Change from baseline Mean±SEM (%)	
Baseline	7.68 ± 0.38	-	-
Week 4	5.12 ± 0.32	2.56 ± 0.22 (33%)	<0.001*
Week 8	2.12 ± 0.18	5.56 ± 0.32 (71%)	<0.001*

All values are expressed as Mean±SEM; *Comparison of values at end of week 4 and week 8 with baseline values is statistically significant (p<0.001)

Table 2: Intragroup Comparison of Clinical Symptoms Score in Group B (N=50)

Time interval	Olopatadine and Ketorolac combination (Group B) (n=50)		p-value
	Mean±SEM	Change from baseline Mean±SEM (%)	
Baseline	7.06 ± 0.39	-	-
Week 4	4.58 ± 0.35	2.48 ± 0.19 (37%)	<0.001*
Week 8	2.1 ± 0.19	4.96 ± 0.31 (69%)	<0.001*

All values are expressed as Mean±SEM; *Comparison of p-values at end of week 4 and week 8 with baseline values is statistically significant (p<0.001).

Table 3: Intergroup Comparison Of Clinical Symptoms Score In Group A And Group B (N=50 in Each group)

Time interval	Bepotastine besilate (Group A) (n=50)	Olopatadine and Ketorolac combination (Group B) (n=50)	p-value (intergroup)
Baseline	7.68 ± 0.38	7.06 ± 0.39	-
Week 4	5.12 ± 0.32	4.58 ± 0.35	0.266
Week 8	2.12 ± 0.18	2.1 ± 0.19	0.988

All values are expressed as Mean ± SEM; Intergroup comparison of values at end of week 4 and week 8 with baseline values is not statistically significant (p<0.001).

INTERGROUP ANALYSIS (Table 3)

On intergroup analysis, at the end of 4 and 8 weeks there was no statistically significant difference in reduction in clinical symptoms score. The results were equivocal in both the groups as there was improvement in clinical symptom score in 69% in group A versus 71% in group B in VKC patients at the end of 8 weeks when compared to baseline values.

b) Clinical signs score

The clinical signs score was calculated in all the patients of either group before drug administration at baseline and further re-assessed at the end of 4 and 8 weeks.

CLINICAL SIGNS SCORING IN GROUP A

Intragroup analysis (Table-4)

In Group A, baseline score was 3.92 ± 0.21 which reduced to 2.20 ± 0.15 at 4 weeks and 1.06 ± 0.11 at 8 weeks. There was statistically significant decrease in clinical symptoms score when compared to baseline at 4 and 8 weeks. The maximum reduction in clinical symptoms score was seen at 8 weeks (71%).

CLINICAL SIGNS SCORING IN GROUP B

Intragroup analysis (Table-5)

In Group B, reduction in clinical signs score was statistically significant at 4 and 8 weeks as compared to baseline score (3.40 ± 0.22). The clinical signs score was reduced to 1.86 ± 0.15 at 4 weeks and 0.92 ± 0.09 at 8 weeks. The maximum reduction was seen at 8 weeks (72%).

INTERGROUP ANALYSIS (Table 6)

On intergroup analysis, at the end of 4 and 8 weeks there was no statistically significant difference in reduction in clinical signs score. The results were equivocal in both the groups which is indicative of the fact that both the drugs were equally effective in improving the VKC signs.

Table 4: Intragroup Comparison of Clinical Signs Score in Group A (N=50)

Time interval	Bepotastine besilate (Group A) (n=50)		p-value (intragroup)
	Mean±SEM	Change from baseline Mean±SEM (%)	
Baseline	3.92 ± 0.21	-	-
Week 4	2.20 ± 0.15	1.72 ± 0.14(42%)	<0.001*
Week 8	1.06 ± 0.11	2.86 ± 0.17(71%)	<0.001*

All values are expressed as Mean±SEM; *Comparison of values at end of week 4 and week 8 with baseline values is statistically significant (p<0.001).

Table 5: Intragroup Comparison of Clinical Signs Score in Group B (N=50)

Time interval	Olopatadine and ketorolac combination (Group B) (n=50)		p-value (intragroup)
	Mean±SEM	Change from baseline Mean±SEM (%)	
Baseline	3.40 ± 0.22	-	-
Week 4	1.86 ± 0.15	1.54 ± 0.15(42%)	<0.001*
Week 8	0.92 ± 0.09	2.48 ± 0.19(72%)	<0.001*

All values are expressed as Mean±SEM; *Comparison of values at end of week 4 and week 8 with baseline values is statistically significant (p<0.001).

Table 6: Intergroup Comparison of Clinical Signs Score in Group A And Group B (N=50 in Each Group)

Time interval	Bepotastine besilate (Group A) (n=50)	Olopatadine and ketorolac combination (Group B) (n=50)	p-value (intergroup)
Baseline	3.92 ± 0.21	3.40 ± 0.22	-
Week 4	2.20 ± 0.15	1.86 ± 0.15	0.115
Week 8	1.06 ± 0.11	0.92 ± 0.09	0.489

All values are expressed as Mean ± SEM; Intergroup comparison of values at end of week 4 and week 8 with baseline values is not statistically significant.

Safety Assessment

The patients were observed for the side effects like headache, eye burning, blurred vision, pharyngitis, dry eye, pruritus, rhinitis, taste perversions, drowsiness. Patients were also enquired for any other side effects. A total of 43 patients out of 100 showed adverse drug reactions. The most common ADRs in Group A were nasopharyngitis (n=5, 22%), headache (n=4,18%) and eye irritation (n=4,18%). Other ADRs reported were taste perversions (n=3), pruritis (n=3), dry eyes (n=2) and blurred vision (n=1).

Headache was the most common ADR in patients of Group B (n=5, 24%) followed by eye irritation (n=4, 19%), nasopharyngitis (n=3,14%), dry eye (n=3,14%) and pruritis (n=3,14%). Other ADRs reported were blurred vision (n=2) and rhinitis (n=1).

Among the two groups, Group A showed the most number of ADRs in a total of 22 patients (44%). Twenty one (40%) patients showed ADRs in Group B. No patient discontinued the study medication due to adverse drug reactions in any of the group.

Figure 1: Intergroup Comparison of Clinical Symptom Score in Both the Groups

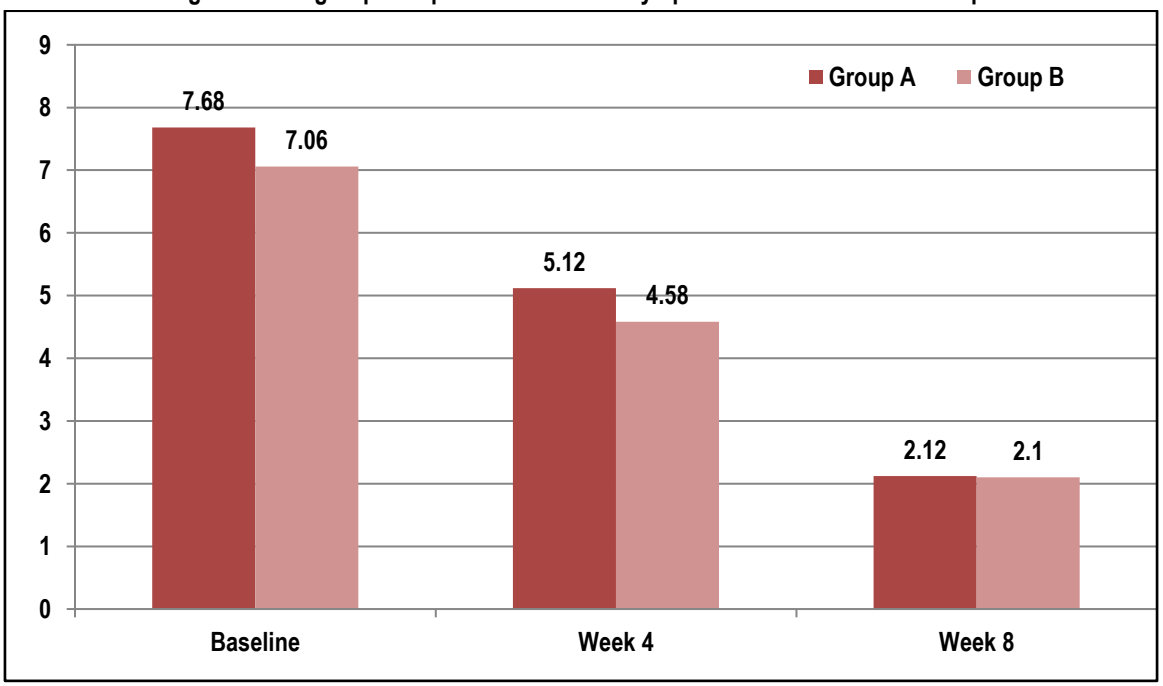
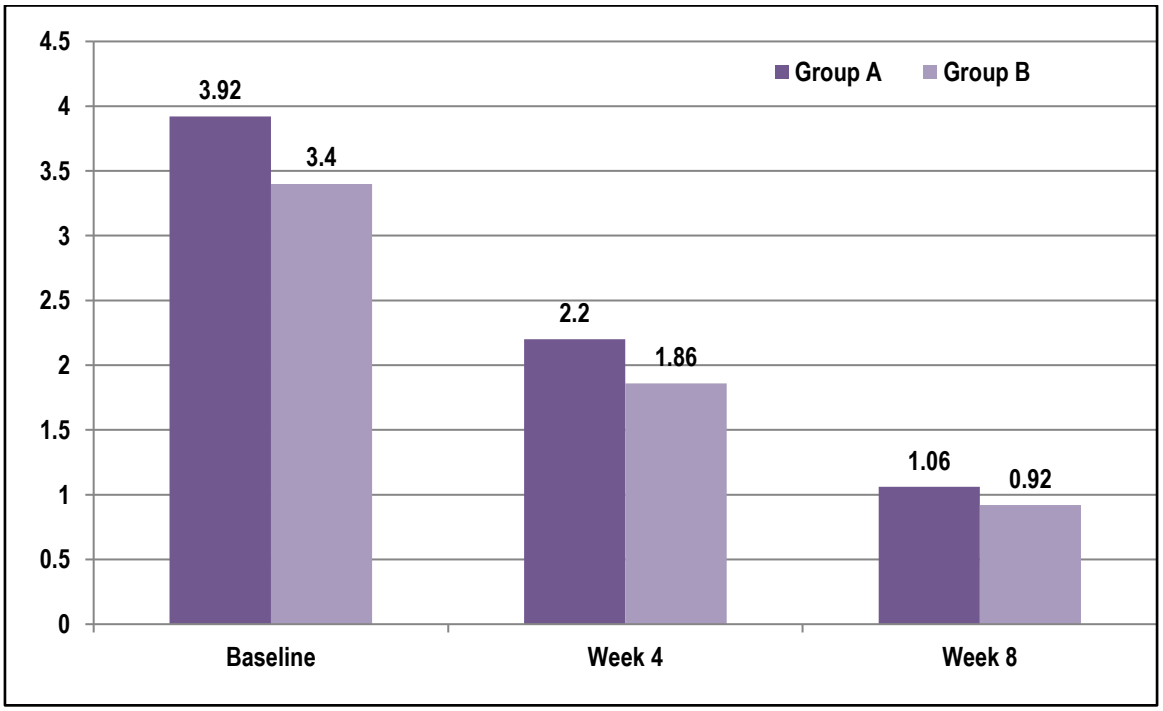


Figure 2: Intergroup Comparison of signs Score in Both the Groups



DISCUSSION

The analysis of clinical symptoms score and clinical signs score in the present study showed that both the study groups had statistically significant reduction of score at 8 weeks. In both the study groups, the statistically significant reduction occurred at visit 1, i.e. at week 4 indicating a similar onset of action and clinical improvement with the two drug groups. During subsequent visits, there was a gradual further decrease in the symptom and sign score indicating that the improvement was sustained throughout the study period without loss of efficacy. There would be a probability of further improvement with drug continuation beyond 8 weeks as the maximum response was seen at 8 weeks. In both the groups, drugs were comparable regarding the reduction in symptoms scoring but there was no statistically significant difference between the two groups. In our study bepotastine besilate showed better response (71%) than olopatadine and ketorolac combination (69%) regarding clinical symptomatic cure, although the difference was not statistically significant.

The improvement is on the expected lines as new antihistaminics that combine mast cell stabilizing properties and histamine receptor antagonism, such as bepotastine and olopatadine are presently available and show evident benefits in treating all forms of ocular allergy. The advantage offered by these agents is the rapidity of symptomatic relief in patients of VKC by immediate histamine receptor antagonism, which alleviates conjunctival itching and redness, coupled with the long-term disease-modifying benefit of mast cell stabilization.[19] Also NSAIDS employed in ocular allergy treatment inhibit both cyclo-oxygenase (COX)-1 and COX-2 enzymes.[20] Ketorolac has shown a proven effect on reducing conjunctival itching.[21] So, due to which clinical symptom score decreased significantly at 1st visit i.e. week 4. This reduction matches the pharmacological profile of the bepotastine besilate and the combination drug therapy of olopatadine with ketorolac.

Moreover, as per the safety assessment, discontinuation due to adverse effect is none in our study. Most events were reported as mild and transient, with no patients discontinuing therapy due to any serious adverse effects (SAEs) during the study period. Some ADRs like drowsiness was not reported by any of the patient.

CONCLUSION

There was statistically significant reduction in clinical symptoms and signs score of VKC, which were the primary efficacy parameters, in both the study groups. Both bepotastine besilate and olopatadine with ketorolac combination administered topically in eyes of patients suffering from VKC, were effective in reducing signs and symptoms. Also there were no serious adverse effects in either of the treatment groups. Common adverse effects observed in group A were nasopharyngitis, headache and eye irritation while in group B there were headache and eye irritation So, from present study it can be concluded that bepotastine possesses similar efficacy and comparable safety profile with olopatadine and ketorolac combination. However, further multicentric studies with larger number of patients are required to reach any definite conclusion regarding superiority of individual drug regimen in patients of VKC.

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