Research Article

A Study on the use of Topical Bepotastine besilate Ophthalmic solution (BBOS) 0.15% in the Treatment of Vernal Keratoconjunctivitis at Tertiary Care Hospital, Haryana

Jyoti Dahiya[1], Vivek Sharma[2], Sumit Sachdeva[3], Srishti[4], M C Gupta[5]
Demonstrator[1], Professor[2,3], Post graduate[4], Senior professor & Head[5]
[1,2,4,5]Department of Pharmacology, [3]Regional institute of Ophthalmology, Pt. B.D. Sharma PGIMS Rohtak, Haryana, India.
***Corresponding author's E-mail:** drjyoti6668@gmail.com

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ABSTRACT

The aim of this study is to Evaluation of Efficacy and Safety of Bepotastine Besilate 0.15% Ophthalmic Solution in Patients of Vernal Keratoconjunctivitis (VKC). This was a prospective, open label and randomized clinical study. Fifty patients of vernal keratoconjunctivitis between 6 to 20 years of age of either sex willing to give informed consent were enrolled in the study. Patients received Bepotastine besilate (0.15%) eye drops twice daily for 8 weeks. Symptoms scoring 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 the drug group during the study period for any serious adverse effects. After the 2 months of drug therapy, patients showed improvement in the symptoms and signs scoring of Vernal keratoconjunctivitis. There was statistically significant difference between the treatment group at 4th and 8th week. The drugs were well tolerated without any serious adverse effect. Bepotastine besilate ophthalmic solution were found to be effective in alleviating the clinical symptoms and signs of VKC.

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

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INTRODUCTION

The eye is a frequent target of inflammation in both local and systemic allergic reactions.[1] Allergic conjunctivitis (AC) is one of the most common allergic disease of the eye. The term allergic conjunctivitis refers to a collection of hypersensitivity disorders that affect the lid and conjunctiva. Increasing prevalence of allergic conjunctivitis has been reported over the past 20 years. The incidence of allergic diseases has increased dramatically in the last decade.[2] A study done by Farouk et al,[3] in Kuwait University Hospital in Sana, Yemen showed that allergic eye diseases are the second most common diagnosis in the eye clinics after refractive errors.

Various clinical forms are included in the classification of ocular allergy namely seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and drug induced dermato-conjunctivitis. Corneal involvement is typically restricted to the two most severe forms of ocular allergy namely vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), which requires particular care in their management.[4]

VKC is a severe inflammatory disease of the external ocular surface that appears in children, most often boys between 4 to 7 years of age and tends to resolve at puberty. In 1846 Scientist Arlt first described VKC who described three cases of perilimbal swelling in young patients. It is rare, chronic form of ocular allergy that can cause severe ocular damage.[4] An Indian study by Saboo et al,[5] has reported that 12% of patients of VKC lies above 20 years of age. VKC is more frequent in warmer, windy climates, in the Mediterranean area, central Africa, Japan, India, and South America. VKC is a disease showing maximal racial and geographical variation.

It is an Immunoglobulin-E (IgE) and T-cell mediated allergic reaction with additional, ill-defined, nonspecific, hypersensitivity responses. 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".[6] Because conjunctivitis typically shows recurrence in spring time, it is named as vernal.

On external examination of the eye, 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. Histamine is responsible for the early phase of the allergic response, characterized by ocular itching, discharge, tearing, conjunctival redness, eye irritation and photophobia. After 6 to 24 hours later, eosinophils and

other inflammatory cells infiltrate the conjunctival and nasal mucosa, causing eyelid swelling, further ocular hyperemia, congestion and sneezing.[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.[4] 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]

Management of AC is increasingly becoming a global health problem, due to its impact on patient quality of life, performance, and productivity. In VKC, first line treatment includes allergen identification and avoidance, avoidance of eye rubbing and cold compresses, topical dual-acting antihistaminics or mast cell stabilizers, oral non-sedating anti-H_1 antihistaminics. Second line treatment consider preservative-free topical therapy, short course of topical steroids and oral steroids. 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.[9]

Bepotastine besilate (BB) is a second-generation, topically active, dual-mechanism drug possessing highly selective direct histamine H1-receptor-antagonistic action and inhibitory effects on histamine release from mast cells. It also acts to suppress eosinophilic migration into inflammatory sites, and also inhibit the activation of eosinophils and maturation of eosinophil precursors in allergic inflammation.[10]

Ophthalmic bepotastine (1%) was shown to inhibit platelet activating factor (PAF) induced conjunctival eosinophil infiltration in a guinea pig model. The inhibitory effect of bepotastine in this model was similar to that of olopatadine and significantly more effective than ketotifen (0.05%).[11] Interleukin-5 (IL-5) derived from activated T-cells enhances proliferation, differentiation and survival of eosinophils. In patients with allergic symptoms, high serum concentrations of IL-5 have been detected. An in-vitro experiment showed that bepotastine inhibits IL-5 secretion from peripheral blood mononuclear cells in response to antigenic stimulation.[12]

In 2000, BB was approved in Japan as an oral treatment for allergic rhinitis and in 2001, an indication of pruritus associated with urticaria and other skin diseases was added. A topical ophthalmic formulation (bepotastine besilate ophthalmic solution [BBOS] 1.5%) was approved by the US FDA in 2009 for the treatment of pruritus associated with AC, with twice-daily dosing in patients aged ≥2 years.[13] The conjunctival allergen challenge (CAC) based clinical trials established that BBOS 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.[14] A significantly greater proportion of these subjects preferred BBOS 1.5% over olopatadine hydrochloride 0.2% for relief of ocular itching, and also for relief of nasal pruritus.[15]

Adverse effect profile

Most common reported adverse reaction occurred in approximately 25% of subjects was altered taste following instillation of drug. Other adverse reactions occurring in 2 to 5% of subjects were eye irritation, headache and nasopharyngitis. In post-Marketing surveillance studies, hypersensitivity reactions have been rarely reported. The hypersensitivity reactions may include itching, body rash and swelling of lips, tongue and throat.[16]

MATERIALS AND METHODS

This was a prospective, open label and randomized 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 50 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 the patients enrolled for the study. The study was approved by Institutional Review Board (IRB).

Selection Criteria

Inclusion criteria

1. Patients between 6 to 20 years of age.
2. Patients presenting with watering, redness and itching in eyes or presence of papillae and follicles in the upper tarsal conjunctiva.
3. Patients who were ready to give written informed consent.

Exclusion criteria

1. Contact lens wearers during the period of study.
2. Patients with ocular disorders such as glaucoma, cataract, blepharitis or uveitis.
3. Patients who are not willing for follow up.
4. Any history of ocular trauma or recent surgery in either eyes.
5. Patients on systemic corticosteroids.
6. Patients with a history of intolerance or hypersensitivity to the study drugs.
7. Patient who did not agreed for the informed consent.

Study group minimally had 50 patients and had received topical eye drops of Bepotastine besilate (0.15%) 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.

Statistical Analysis

Data was tabulated in Microsoft Excel Sheet. Data was expressed as Mean ± SEM, number (%) depending on nature of data. Data was subjected to descriptive statistical analysis. The results of all the demographic data, subjective complaints grading score and clinical signs grading score were compiled and analyzed using paired "t" test or unpaired "t" test as appropriate.

Clinical Assessment

Clinical Symptoms Score Grading

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.

Clinical Signs Grading

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 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 topical bepotastine besilate 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.

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 group before drug administration at baseline and further reassessed at the end of 4 and 8 weeks.

Clinical Symptoms Scoring (Table 1)

The baseline clinical symptom score was 8.57 ± 0.47 which reduced to 6.22 ± 0.23 at 4 weeks and 3.23 ± 0.27 at 8 weeks.

Table 1: Intragroup Comparison of Clinical Symptoms Score In Bepotastine Besilate Group (N=50)

Time interval	Bepotastine besilate (n=50)		p-value
	Mean ± SEM	Change from baseline Mean ± SEM (%)	
Baseline	8.75 ± 0.47	-	-
Week 4	6.22 ± 0.23	2.53 ± 0.24 **(28.9%)**	<0.001*
Week 8	3.23 ± 0.27	5.52 ± 0.20 **(63%)**	<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).

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 63% was seen at 8 weeks.

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 Bepotastine Besilate Group

Intragroup analysis (Table-2)

In Bepotastine besilate Group, baseline score was 4.83 ± 0.32 which reduced to 3.31 ± 0.26 at 4 weeks and 2.15 ± 0.22 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 (55%).

Table 2: Intragroup Comparison of Clinical Signs Score in Bepotastine Besilate Group (N=50)

Time interval	Bepotastine besilate (n=50)		p-value (intragroup)
	Mean±SEM	Change from baseline Mean±SEM (%)	
Baseline	4.83 ± 0.32	-	-
Week 4	3.31 ± 0.26	1.52 ± 0.06 (31.4%)	<0.001*
Week 8	2.15 ± 0.22	2.68 ± 0.04 (55.4%)	<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).

CONCLUSION

In the present study, the bepotastine besilate groups showed statistically significant improvement in both the symptom scoring and sign scoring at 8 weeks and the improvement was seen as early as 4 week of treatment. The improvement was consistent over 8 weeks. There would be a probability of further benefit with drug continuation beyond 8 weeks as the clinical improvement was maximal at 8 weeks. Bepotastine besilate plays an important role in decreasing clinical symptoms and signs scoring. 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 specially VKC. Bepotastine besilate provide quick symptomatic relief due to immediate histamine receptor antagonism, which alleviates itching and redness, coupled with the long-term disease-modifying benefit of mast cell stabilization.[52] The findings of the study matches with the pharmacological profile of the monotherapy.

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