Original Research Article

Comparative evaluation of efficacy and safety of bepotastine besilate 1.5% ophthalmic solution versus olopatadine hydrochloride 0.1% ophthalmic solution in patients with vernal keratoconjunctivitis

Priya Gupta[1]*, Seema Baishnab[1], Parveen Rewri[2]

[1]Department of Pharmacology, [2]Department of Ophthalmology, Maharaja Agrasen Medical College, Agroha, Haryana, India

*Correspondence:
Dr. Priya Gupta,
Email: pgpreety@gmail.com

ABSTRACT

Background: Vernal keratoconjunctivitis (VKC) is a chronic, seasonally exacerbated, allergic ocular inflammation. It affect children and young adults and has male predominance. The first line of treatment often used is dual acting drugs like olopatadine and bepotastine. It combine the immediate histamine receptor antagonism, coupled with mast cell stabilization with other anti-inflammatory properties. The present study was conducted to compare the efficacy and safety of olopatadine 0.1% and bepotastine 1.5% eye drops in VKC patients.

Methods: This was a prospective, open label, randomized and comparative clinical study conducted for 21 days. 65 patients of VKC of 5-15 years of either sex were randomized in two study arm. Arm A, given bepotastine 1.5% and arm B, given olopatadine 0.1% twice daily for 21 days. Symptoms and signs scoring of VKC along with safety assessment were recorded on baseline and at time of follow up on 7th day and 21st day.

Results: After 3 weeks of drug therapy, patients in both arms showed improvement in the symptoms and signs scoring of VKC. There was no statistically significant difference between the two treatment arms. However, improvement in clinical parameters particularly ocular itching, which is the main complaint of patients with VKC was more in bepotastine arm as compared to olopatadine treated arm. Both the drugs were well tolerated without any serious adverse effect.

Conclusions: Both olopatadine and bepotastine were found to be effective in alleviating the clinical symptoms and signs of VKC. However, bepotastine performed better in reducing ocular itch than olopatadine.

Keywords: Bepotastine, Efficacy, Olopatadine, Vernal keratoconjunctivitis

INTRODUCTION

Allergic diseases have dramatically increased in the last decades.[1,2] World allergy organization estimates that 20% to 30% of the world's population suffers from some form of allergic disease.[3] They are common among all ages but more common in children. Ocular allergy represents one of the most common ocular conditions encountered in clinical practice.[4] The increase in incidence of ocular allergic conditions are mainly accountable to climatic change, increased pollution, pollen loads and patient's increased sensitivity for immunological response to these environmental changes.[5]

The most common form of ocular allergy is allergic conjunctivitis which is a condition which affects the conjunctiva, eyelids and cornea and it is often associated with non-ocular symptoms and signs of rhinitis or sinusitis.[6] It is one of the most common reasons for school absenteeism in children because of its distressful

symptoms.[7,8] The various types of allergic conjunctivitis are seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary conjunctivitis (GPC).[9-11] However, clinical and pathophysiological features of AKC and VKC are quite different from SAC and PAC in spite of some common markers of allergy.[12]

VKC is a chronic, recurrent, bilateral inflammatory disease affecting cornea and conjunctiva of young children mostly in their first decade of life.[13] It is typically a disease of young males which usually resolves after puberty.[14,15] Adult can also get affected in which no sex predisposition is seen.[16,17] Hypersensitivity of the body's immune system to allergens is the main etiological factor. Disease is common in people having other signs of allergic disorders, such as asthma, eczema, hay fever and rhinitis.[18] VKC has a wide geographical distribution, and usually occurs in warm, dry areas.[19]

Almost all patients with VKC note ocular pruritus.[18,20] The term morning misery captures the discomfort, blepharospasm and mucous discharge often manifesting in these patients upon awakening.[21] Other symptoms consist of tearing, irritation, redness and photophobia.[22] Sign and symptoms of VKC show exacerbations during spring and summer seasons, but a small percentage of patient have the perennial form.[23]

It is an immunoglobulin-E (IgE) and T-cell mediated allergic reaction with additional, ill-defined, nonspecific, hypersensitivity responses.[12,18] VKC is not difficult to diagnose by clinical examination of the eye. Horner-Trantas dots and large cobblestone papillae are indicative of this condition.

Patients with VKC experience significant morbidity, which affects the quality of life.[24] The management generally involves preventive measures, non-pharmacologic as well as pharmacologic measures.[25] Preventive measures include identification of provocative allergens and avoidance or reduction, as much as possible, of contact with known allergens and appropriate management of environmental exposure.[26] The non-pharmacologic measures include avoiding eye rubbing, use of cool compresses and refrigerated artificial tears throughout the day has been found to be effective in reducing eyelid and periorbital edema and removing allergens.[27] The pharmacological treatment include variety of currently available drugs to treat VKC that include anti-histamines, mast-cell stabilizers, dual acting agents, corticosteroids and immunomodulators.[25,28]

A new generation of drugs such as bepotastine, olopatadine, epinastine, ketotifen and azelastine has shown dual activity of mast-cell stability and H1 receptor antagonism makes them suitable for twice-daily dosing.[25] Besides these action they also exert anti-inflammatory effects through several different mechanisms.[18] These class of drugs comprise the first line of pharmacological treatment.

On literature survey we find very few clinical studies directly comparing bepotastine besilate 1.5% and olopatadine hydrochloride 0.1%. This study compared patient-perceived relief of ocular itch which is the main symptom of our disease along with other symptoms and signs in treating VKC with bepotastine besilate 1.5% compared with olopatadine hydrochloride 0.1% for 21 days.

METHODS

Study design

This was a prospective, open label, randomized, comparative clinical study conducted from February 2019 to March 2020. Study was conducted by the department of pharmacology in collaboration with the outpatient department of ophthalmology of Maharaja Agrasen medical college, Agroha (Hisar).

Study population includes patients of either sex between 5 to 15 years of age who attended the OPD in ophthalmology department with VKC, satisfying the eligibility criteria.

About 65 patients attending the outpatient clinic in ophthalmology were recruited. The sample size was selected as per disease prevalence and was analysed using appropriate statistical test.

Sample size involves arm A-bepotastine eye drops (33 patients). Arm B-olopatadine (32 patients). There was a total of 65 patients.

Inclusion criteria

All enrolled patients of either sex from 5-15 years of age, having a diagnosis of VKC, willing to give written informed consent by their parents/legal representative guardians were included in this study.

Exclusion criteria

Patients having a known hypersensitivity to either agent, who are blind or having single eye, planning surgery during trial period, suffering with dry eyes and Schirmer <10, inability to come for regular follow ups, who are actively taking steroids or antihistamines within 7 days prior to enrolment were excluded from this study.

Study was done in accordance with the principles of good clinical practice (ICH-GCP) and declaration of Helsinki. The study was conducted after obtaining the approval from institutional ethics committee. The study approval reference number was MAMC/Pharma/IEC/18/261.

For the purpose of study, 72 patients were enrolled, of which 7 were excluded from the study.

Of 65 patients recruited in the study, 33 were randomly allotted by simple randomisation (odd and even OPD number) to arm A and 32 patients was in arm B. In arm A, subjects were given bepotastine eye drops 1.5% twice daily and arm B, subjects were given olopatadine eye drops 0.1% twice daily for 21 days. All the patients received the commercial preparation of study medicines which is available in the hospital/market. Same brand and formulations was used throughout the study. A detailed ophthalomological history with reference to subjective complaints was obtained from the patients along with assessment of clinical signs was done at baseline and followed up on 7th day and 21st day. Safety assessment was done at baseline and at the end of the study.

Efficacy 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. Grading of the clinical symptoms was slightly modified to allow for a more detailed assessment of the parameters of interest (Table 1). A 3-grade score system (0 corresponding to no symptom at all, 1 to mild and 2 to moderate and 3 to marked symptom) determined the degree of ocular itch, photophobia, foreign body sensation/discomfort, tearing, mucoid discharge. Grading of symptoms and severity of VKC was also done based on ARIA criteria. A decrease in the score with treatment was considered meaningful.

Clinical signs score grading

Clinicians were advised to consistently use the same grading system. The clinical improvement was assessed based on clinical signs grading score. Grading of the clinical signs was slightly modified to allow for a more detailed assessment of the parameters of interest (Table 2). A 3-grade score system (0 corresponding to no sign at all, 1 to mild and 2 to moderate and 3 to marked sign) determined the degree of lid edema, conjunctival chemosis, conjunctival injection, conjunctival mucous, papillary hypertrophy, limbal changes, keratitis, trantas. A decrease in the score with treatment was considered meaningful.

The score was calculated at baseline (before drug administration) and then on 7th day and 21st day. Inter and intra arm comparison between mean scores from baseline was done. Treatment related adverse events, compliance of patients were compared between the two arms.

Grading of symptoms and severity of VKC based on ARIA criteria[29]

This was done by asking questions given in ARIA criteria to the subject regarding persistence of symptoms and severity of symptoms.

Safety assessment

Safety of both study medications were assessed by expert clinician. Following test were applied (Schirmer II test, tear breakup time, tear meniscus height, visual blur).[30] Any deviation from normal value of the test during the study period was noted. Patients were assessed on receiving bepotastine (1.5%) eye drops (arm A) versus olopatadine (0.1%) eye drops (arm 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. If any adverse drug reactions are noted, then the causality assessment is done by World health organisation uppsala monitoring centre (WHO-UMC) scale.[31]

Table 1: Scoring of clinical symptoms of VKC.

Symptoms	Score 3	Score 2	Score 1	Score 0
Ocular itch	Severe/constant/present all day (>10 times)	Moderate/frequent/most of the day (>5 times)	Mild/occasional in a day (2-3 times)	No symptom
Photophobia	Severe/even present in the room	Moderate/during outdoor	Mild/occasionally during outdoor	No symptom
Foreign body sensation/discomfort	Severe/present all day	Moderate/most of the day	Mild/occasional in a day	No symptom
Tearing	Constant tears on the face	Intermittent tears on the face	Impression of wet eyes, without tears on the face	None
Mucoid discharge	Constant	Moderate amount	Small amount	No symptom

Statistical analysis

Continuous variables are presented as mean±SD and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables within the study arm was performed using Friedman test. The comparison between two study arm were analyzed using Mann Whitney U test. Nominal categorical data between the two arms were compared using chi-square test. Significance level was set at <0.05. All the above statistical tests are processed by SPSS 20 version.

Table 2: Scoring of sign in VKC.

| Signs	None (score 0)	Mild (score 1)	Moderate (score 2)	Marked (score 3)
Lid edema	None	Minimal (Palpebral conjunctiva/lower lid involved)	Moderate (both lids involved)	Inter-palpebral fissure decreased
Conjunctival chemosis	None	No obvious	Focal area of chemosis	Frank chemosis
Conjunctival injection	None	Focal redness	Obvious but not diffuse	Diffuse redness
Conjunctival mucous	None	Mucous strands only in conjunctival sac	Few mucous strands	Diffuse mucous strands
Papillary hypertrophy	None	Mosaic flat appearance	Elevated with definite	Cobblestone papillae depression
Limbal changes	None	Upto one quandrant	Upto 2 quandrants	>2 quadrants
Keratitis	None	Fine erosions	Macro-erosion	Vernal ulcer
Trantas	None	1-2 dots	3-4	>4

RESULTS

This study was planned to compare the efficacy of two topical dual acting agents, one being bepotastine besilate (arm A) and another being olopatadine (arm B) received twice daily for 21 days. Total 65 subjects were randomized to the study. 5 subjects (3 subjects from arm A and 2 from arm B) were discontinued from the study due to lost to follow up (Figure 1). No subject terminated from the study due to adverse event.
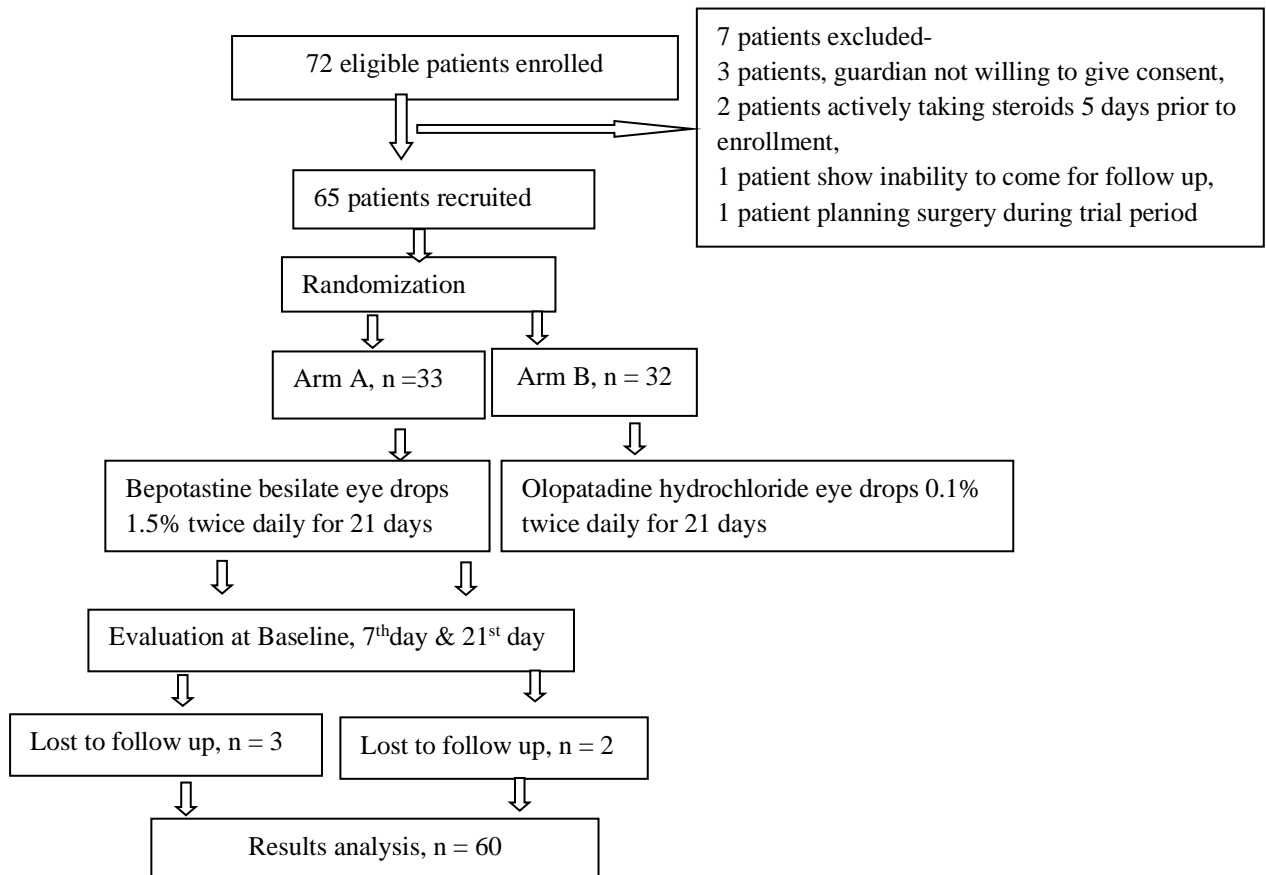
Figure 1: Study flowchart.
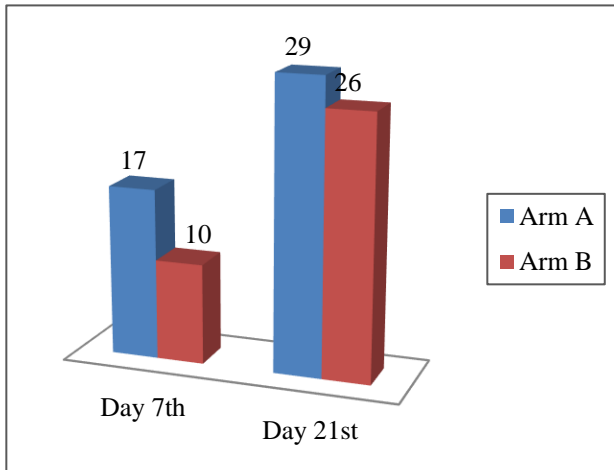
Figure 2: Relievers from ocular itch (score 0).

The efficacy assessment was done at baseline and subsequently the patients of VKC were followed on 7th day and 21st day for the following parameters like 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 ocular itch, photophobia, foreign body sensation/discomfort, tearing, mucoid discharge while signs of VKC include degree of lid edema, conjunctival chemosis, conjunctival injection, conjunctival mucous, papillary hypertrophy, limbal changes, keratitis, trantas. These parameters were assessed on a 3-grade score system (0 corresponding to no sign/symptom at all, 1 to mild and 2 to moderate and 3 to marked sign/symptom).

Table 3: Clinical symptoms score in intraarm/interarm analysis.

Clinical symptom score	Arm A	Arm B	Mann Whitney U test
Visit	Mean±SD	Mean±SD	P value
Baseline	7.77 ±1.77	7.00 ±1.76	0.864
7th day	1.70 ±1.31	1.97 ±1.54	0.440
21st day	0.23 ±0.67	0.30 ±0.75	0.50
Friedman test	0.000*	0.000*	

All values are expressed as mean±SD; *intraarm/within two study arm comparison of values on 7th day and 21st day from baseline values is statistically significant (p<0.05); however, in interarm/between two study arm comparison of values on 7th day and 21st day baseline values is statistically insignificant (p>0.05).

Table 4: Ocular itch score in intraarm/interarm analysis.

Ocular itch	Arm A	Arm B	Mann Whitney U test
Visit	Mean±SD	Mean±SD	P value
Baseline	2.78±0.50	1.88±0.64	0.075
7th day	0.53±0.68	0.80±0.66	0.032**
21st day	0.08±0.18	0.27±0.34	0.011**
Friedman test	0.000*	0.000*	

All values are expressed as mean± SD; *intraarm/within two study arm comparison of values on 7th day and 21st day from baseline values is statistically significant (p<0.05); **interarm/between two study arm comparison of values on 7th day and 21st day baseline values is statistically significant (p<0.05).

Table 5: Clinical signs score in intraarm/interarm analysis.

Clinical sign score	Arm A	Arm B	Mann Whitney U test
Visit	Mean±SD	Mean±SD	P value
Baseline	5.67±2.171	6.53±2.78	0.184
7th day	1.27±1.11	1.40±1.69	0.73
21st day	0.30±0.65	0.40±0.89	0.247
Friedman test	0.000*	0.000*	

All values are expressed as mean±SD; *intraarm/within two study arm comparison of values on 7th day and 21st day from baseline values is statistically significant (p<0.05); however, in interarm/between two study arm comparison of values on 7th day and 21st day baseline values is statistically insignificant (p>0.05).

Clinical symptoms score

The subjective score was calculated in all the patients of either arm before drug administration at baseline and further re-assessed at the end of 7th day and on 21st day.

Clinical symptoms score in arm A/intraarm analysis (Table 3). In arm A, the baseline clinical symptom score was 7.77±1.77 which reduced to 1.70±1.31 by 7th day and 0.23±0.67 by 21st day. There was statistically significant reduction in clinical symptoms score when compared to

baseline on 21st day. Clinical symptoms score in arm B/intraarm analysis (Table 3). In Arm B, the baseline clinical symptom score was 7.00±1.76 which reduced to 1.97±1.54 by 7th day and 0.30±0.75 by 21st day. There was statistically significant reduction in clinical symptoms score when compared to baseline on 21st day.

Clinical symptoms score between both arm A and B/interarm analysis (Table 3). On interarm analysis, at the end of 7th day and 21st day there was no statistically significant difference in reduction in clinical symptoms score. The results were equivocal in both the study arm. However, ocular itch which is the main complaint of VKC patients, comparing both arms on 7th day, score was (arm A 0.53±0.68; arm B 0.80±0.66, p value 0.032) and on 21st day score was (arm A 0.08±.18; arm B 0.27±0.34, p value 0.011). So, there was significant difference statistically in reduction in ocular itching score at 7th day and 21st day (Table 4). P value was <0.05.

Table 6: Grading of symptoms of VKC based on ARIA criteria.

	Arm A			Arm B			Chi square (p value)
	Persistent	Intermediate	None	Persistent	Intermediate	None	
Baseline	29	1	0	28	2	0	0.000*
7th Day	1	29	0	0	28	2	
21st Day	0	3	27	0	2	28	

*p<0.05 statistically significant.

Table 7: Grading of severity of VKC based on ARIA criteria.

Grading	Arm A	Arm B	Chi-square test (p value)
Mild	4	2	0.613
Moderate	21	24	
Severe	5	4	

Table 8: Adverse incidence.

Arm	Total	Present	Absent	Chi-square (p value)
Arm A	30	8	22	0.580
Arm B	30	11	19	

Clinical signs score

The clinical signs score was calculated in all the patients of either arm before drug administration at baseline and further re-assessed on 7th day and on 21st day after drug administration.

Clinical signs score in arm/intraarm analysis (Table 5). In arm A, the baseline clinical sign score was 5.67±2.171 which reduced to 1.27±1.11 by 7th day and 0.30±0.65 by 21st day. There was statistically significant reduction in clinical sign score when compared to baseline on 21st day.

Clinical signs score in arm/intraarm analysis (Table 5). In arm B, the baseline clinical sign score was 6.53±2.78 which reduced to 1.40±1.69 by 7th day and 0.40±0.89 by 21st day. There was statistically significant reduction in clinical sign score when compared to baseline on 21st day.

Clinical signs score between both arm A and B/interarm analysis (Table 5). On interarm analysis, on assessment on 7th day and on 21st day, there was no statistically significant difference in reduction in clinical signs score. The results were equivocal in both the study arms which is indicative of the fact that both the drugs were equally effective in improving the VKC signs.

Grading of symptoms of VKC Based on ARIA criteria (Table 6). Based on ARIA criteria, grading of symptoms was done. At baseline visit, 29 patients in arm A and 28 patients in arm B had persistent symptoms. During 7th day, symptoms decreased in both the study arm with patients having intermittent symptoms. At 21st day, 27 patients in arm A and 28 patients in arm B, were symptom free. p value was significant.

Grading of severity of VKC based on ARIA criteria (Table 7). It shows that 4 patients in arm A and 2 patients in arm B have mild symptoms. 21 patients in arm A and 24 patients in arm B are suffering from moderate symptoms and 5 patients in arm A and 4 patients in arm B have severe symptoms according to ARIA criteria.

Safety assessment

Various parameters (Schirmer test II, tear break up time, tear meniscus height, visual blur) regarding drug safety was observed (Table 8). In both the study arm, all the parameters come normal. No deviation of the test from normal value during the study period was seen.

The patients were observed for the side effects like headache, eye irritation, blurred vision, pharyngitis, dry

eye, rhinitis, taste perversions, sore throat. Patients were also enquired for any other side effects. A total of 19 patients out of 60 showed adverse drug reactions. 8 patients in arm A and 11 patients in arm B had mild adverse event. In arm A, 5 patients had headache, 1 patient had eye irritation, 1 patient had nasopharyngitis, 1 had runny nose. In arm B, 6 patients had headache, 2 patients had eye irritation, and 3 patients had sore throat. There was no significant difference between the arm A and arm B statistically on adverse effect occurrence (p>0.05). No patient discontinued the study medication due to adverse drug reactions in any of the study arm.

DISCUSSION

The analysis of clinical symptoms score and clinical signs score in the present study showed that both the study arm had statistically significant reduction in the individual score during subsequent visit. In both the study arm, statistically significant reduction in scores occurred at visit 1, that is at 7th day, indicating a similar onset of action and clinical improvement with the two drug arms. During subsequent visits, there was a further gradual decrease in the symptom and sign score indicating that the improvement was sustained throughout the study period without loss of efficacy. Individually, drugs in each arm was effective in reducing symptoms and signs score but there was no statistically significant difference in inter arm comparison. However, ocular itch score, which is the main symptomatic presentation of VKC patient, during inter arm comparison, bepotastine performed better then olopatadine on 7th day and 21st day follow up visit. Similar findings was shown by Shailesh et al in their and McCabe et al in their study also showed that 63.3% and 66.7% of patients preferred bepotastine 1.5% for all-day relief of ocular itching and all-day relief of itchy/runny nose, respectively.[32,33] Sharma et al in their study showed that topical bepotasine 1.5% given to the patients of allergic conjunctivitis effectively relieve an intense ocular itching within 7 days of treatment.[34] Although patients reported that even within 5 minutes of instillation of medication itching started relieving. Malahat AR et al in their study also showed that both olopatadine and bepotastine are equally efficacious in improving symptoms and signs score of patients with VKC.[35] However, bepotastine provided quicker relief to symptoms of watering, ocular discomfort and conjunctival hyperaemia.

In this study, grading of symptoms based on ARIA criteria also showed statistically significant improvement in subjects with treatment in both arms during follow-ups. Bepotastine showed better response than olopatadine regarding rest of the clinical symptomatic parameters, although the difference was not statistically significant. The improvement is on the expected lines of dual acting drugs that combine mast cell stabilizing properties and histamine receptor antagonism. 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.

In the year September 2009, the US food and drug administration (FDA) approved the bepotastine 1.5% for the treatment of itching associated with allergic conjunctivitis on the basis of results of CAC based trials. In this study we found that bepotastine is more superior in relieving ocular itching than olopatadine. Although olopatadine is also an antihistamine with dual action of selective H1 receptor antagonist and mast cells stabilizer like bepotastine.

Moreover, as per the safety assessment, there was no drop out in this study as account of any adverse effect. Most events were reported as mild and transient, with no patients discontinuing therapy during the study period. On safety parameters assessment, all the parameters were in normal range at baseline. Even during the course of treatment, none of the parameters got derranged in both the study arms.

CONCLUSION

There was statistically significant reduction in clinical symptoms and signs score of VKC, which were the primary efficacy parameters in both the study arm. Both bepotastine and olopatadine one drop twice daily are effective in reducing symptoms and signs of mild and moderate grade of VKC by 7th day and 21st day of treatment. No patient discontinued the study medication due to adverse drug reactions in any of the study arm. There was no deviation of the safety parameters test from normal value during the study period. Both drugs show good patient tolerability and safety profile. However, bepotastine 1.5% twice daily ocular drops was found to be more effective than olopatadine 0.1% twice daily in reducing itching scores on 7th day and 21st day of follow ups. So, from present study it can be concluded that bepotastine possesses similar efficacy and comparable safety profile with olopatadine. However, the improvement in clinical parameters particularly ocular itching, which is the main complaint of patients with VKC was more in bepotastine treated arm as compared to olopatadine treated arm. 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.

REFERENCES

1. Rigoli L, Briuglia S, Caimmi S, Ferrau V, Gallizzi R, Leonardi S, et al. Gene-environment interactions in childhood asthma. Int J Immunopathol Pharmacol. 2011;24:41-7.

2. Maziak W, Behrens T, Brasky TM, Duhme H, Rzehak P, Weiland SK, et al. Are asthma and allergies in children and adolescents increasing. Results from ISAAC phase I and phase III surveys in Munster, Germany. Allergy. 2003;58(7):572-9.

3. Pawankar R, Canonica GW, Holgate ST, Lockey RF, Blaiss MS. WAO white book on allergy. Milwaukee: World Allergy Organization; 2013.

4. Akhil H, Celik F, Ulas F, Kara IS. Dry eye syndrome and allergic conjunctivitis in the pediatric population. Midd East Afr J Ophthalmol 2015;22(4):467-1.

5. Doğan, Ü, Ağca S. Investigation of possible risk factors in the development of seasonal allergic conjunctivitis. Int J Ophthalmol. 2018;11(9):508-13.

6. Abelson MB, Shetty S, Korchak M, Butrus SI, Smith LM. Advances in pharmacotherapy for allergic conjunctivitis. Expert Opin Pharmacother. 2015;16(8):1219-31.

7. Chakraborti C, Mallik S, Choudhury KP, Das J. Childhood ocular morbidity in Eastern India: a tertiary hospital study. Sudanese J Public Health. 2012;7(4):126-30.

8. Kamath PBT, Prasad BS, Deepthi R, Muninrayana C. Prevalence of ocular morbidity among schoolgoing children (6-15years) in rural area of Karnataka, South India. Int J Pharm Biomed Res. 2012;3(4):209-12.

9. Mishra GP, Tamboli V, Jwala J and Mitra AK. Recent patents and emerging therapeutics in the treatment of allergic conjunctivitis. Recent Pat Inflamm Allergy Drug Discov. 2011;5(1):26-36.

10. Kanski J. Clinical ophthalmology. 4th ed. Windsor: Butterworth-Heinemann; 1999: 66-78.

11. Swamy BN, Chilov M, McClellan K, Petsoglou C. Topical non-steroidal anti-inflammatory drugs in allergic conjunctivitis: meta-analysis of randomized trial data. Ophthalmic Epidemiol. 2007;14(5):311-9.

12. Bielory L, Frohman L. Allergic and immunologic disorders of the eye. J Allergy Clin Immunol. 1992;86:1-20.

13. Keklikci U, Dursun B, Cingu AK. Topical cyclosporine a 0.05% eyedrops in treatment of vernal keratoconjunctivitis-randomized placebo-controlled trial. Adv Clin Exp Med. 2014;23(3):455-61.

14. Allansmith MR, Baird RS, Greiner JV. Vernal conjunctivitis and contact lens-associated giant papillary conjunctivitis compared and contrasted. Am J Ophthalmol. 1979;87(4):544-55.

15. Buckley RJ. Long-term experience with sodium cromoglycate in the management of vernal keratoconjunctivitis. In: Pepys J, Edward AM, eds. The mast cell, London: Pitman Medical; 1980.

16. Ukponmwan CU. Vernal conjunctivitis in Nigerians: 109 consecutive cases. Trop Doct. 2003;33(4):242-5.

17. Katelaris CH. Ocular allergy in the Asia Pacific region. Asia Pac Allergy. 2011;1(3):108-14.

18. Kumar S. Vernal keratoconjunctivitis: a major review. Acta Ophthalmol. 2009;87(2):133-47.

19. Bremond-Gignac D, Donadieu J, Leonardi A, Pouliquen P, Doan S, Chiambarretta F, et al. Prevalence of vernal keratoconjunctivitis: a rare disease? Br J Ophthalmol. 2008;92(2):1097-102.

20. Bonini S, Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, et al. Vernal keratoconjunctivitis revisited: A case series of 195 patients with long-term followup. Ophthalmology 2000;107(6):1157-63.

21. Buckley RJ. Vernal keratoconjunctivitis. Int Ophthalmol Clin. 1988;28(4): 303-8.

22. Saboo US, Jain M, Reddy JC, Sangwan VS. Demographic and clinical profile of vernal keratoconjunctivitis at a tertiary eye care center in India. Ind J Ophthalmol. 2013;61(9):486-9.

23. Akpek EK, Hasiripi H, Christen WG, Kalayci D. A randomized trial of low dose mitomycin C in treatment of severe vernal keratoconjunctivitis. Opthalmology. 2010;107:263-9.

24. Sacchetti M, Baiardini I, Lambiase A, Aronni S, Fassio O, Gramiccioni C, et al. Development and testing of the quality of life in children with vernal keratoconjunctivitis questionnaire. Am J Ophthalmol. 2007;144(4):557-63.

25. Kubaisi B, Samra KA, Syeda S, Schmidt A, Foster SC. Ocular Allergy: an updated review. J Allergy Immunol. 2017;1:2.

26. Ackerman S, Smith LM, Gomes PJ. Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management. Ther Adv Chronic Dis. 2016;7(1):52-67.

27. Bilkhu PS, Wolffsohn JS, Naroo SA, Robertson L, Kennedy R. Effectiveness of nonpharmacologic treatments for acute seasonal allergic conjunctivitis. Ophthalmology. 2014;121(1):72-8.

28. Berger WE, Granet DB, Kabat AG. Diagnosis and management of allergic conjunctivitis in pediatric patients. Allergy Asthma Proc. 2017;38(1):16-27.

29. Riggioni VS, Riggioni VC, Ribó GP. Diagnosis and management of allergic conjunctivitis. Curr Treat Options Allergy. 2018;5:256-65.

30. Kallarackal GU, Ansari EA, Amos N, Martin JC, Lane C, Camilleri JP. A comparative study to assess the clinical use of Fluorescein Meniscus Time (FMT) with Tear Break up Time (TBUT) and Schirmer's tests (ST) in the diagnosis of dry eyes. Eye (Lond). 2002;16(5):594-600.

31. Zaki SA. Adverse drug reaction and causality assessment scales. Lung India. 2011;28(2):152-3.

32. Singh S, Mote R, Shukla S, Mali A, Khatri K. A comparative, randomized, double blind, parallel group and non-crossover multicentric study with bepotastine besilate ophthalmic solution vs. olopatidine hydrochloride ophthalmic solution in subjects suffering from allergic conjunctivitis. Euro J Biomed Pharm Sci. 2017;4(6):671-80.

33. Craig F McCabe, Shannon E McCabe. Comparative efficacy of bepotastine besilate 1.5% ophthalmic solution versus olopatadine hydrochloride 0.2% ophthalmic solution evaluated by patient preference. Clinic Ophthalmol. 2012;6:1731-8.

34. Sharma N, Kedia J. A study on the use of topical bepotastine besilate ophthalmic solution (BBOS)

1.5% in the treatment of allergic conjunctivitis. Ind J Clin Exp Ophthalmol. 2019;5(3):310-3.

35. Malahat AR, Kodudula S, Gali VL. A prospective comparative study to evaluate the efficacy and safety of olopatadine eye drops and bepotastine eye drops in subjects of vernal kerato conjunctivitis. Int J Basic Clin Pharmacol. 2020;9(5):706-11.