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Original Article

Ophthalmology Section

Efficacy of Bepotastine versus Olopatadine Ophthalmic Solutions in Mild to Moderate Vernal Keratoconjunctivitis as a Sole Therapy

RAHUL DARA[1], VANDANA MAHAUR[2], JAYA DEVENDRA[3], MALHAR VYAS[4], MANISH PRAJAPAT[5], TEJINDER SINGH AHLUWALIA[6]

ABSTRACT

Introduction: Vernal Keratoconjunctivitis (VKC) is a chronic, seasonally exacerbated allergic ocular inflammation of the conjunctiva. It affects predominantly the school going male population and is not so common. There is a paucity of comparative studies on efficacies of dual-action topical agents having both antihistamine and mast cell stabilising properties. These are currently the first line drugs in the management of mild to moderate VKC.

Aim: To compare the efficacy and safety of bepotastine besilate 1.5% and olopatadine Hydrochloride (HCl) 0.1%, ophthalmic solutions in mild to moderate VKC patients.

Materials and Methods: This prospective, comparative study was conducted in the Ophthalmology Department at National Institute of Medical Sciences Hospital, Jaipur, Rajasthan, India, from January 2020 to January 2021. It included 76 patients having mild to moderate VKC who were randomised into two groups of 38 patients each. Each group was assigned to be treated with one of the two treatment options namely bepotastine besilate 1.5% and olopatadine HCl 0.1% ophthalmic solutions. Typical symptoms and signs of VKC like ocular itching, watering, mucoid discharge, conjunctival hyperaemia and tarsal papillary hypertrophy were recorded at baseline and at the time of follow-up on 7th, 15th and 30th day using simplified scoring 4-point scales ranging from 0-3. Safety assessment was also done. Friedman's test and Mann-Whitney's U test were performed for intra-arm and inter-arm analysis of continuous variables respectively. Nominal categorical data between the groups were compared using the Chi-square test. The p-value <0.05 was considered as statistically significant.

Results: The mean age of the participants was 10.49±2.95 years and the male to female ratio (M:F) was 1.7:1. After 30 days of drug therapy, patients in both arms showed significant improvement in the symptoms and signs scoring of VKC. There was no statistically significant difference in efficacy on inter-arm analysis at baseline and subsequent follow-ups. Almost all patients became free from their symptoms and signs at the end of the study. However, 25 of 38 (65.8%) patients in bepotastine treated group and 23 of 38 (60.5%) patients in olopatadine treated group had residual tarsal papillae. None of the patients in either group reported any significant adverse effects.

Conclusion: Both bepotastine besilate 1.5% and olopatadine HCl 0.1% ophthalmic solutions are safe and equally effective in alleviating the clinical symptoms and signs of mild to moderate VKC.

Keywords: Allergic conjunctivitis, Antihistamines, Mast cell stabilisers, Topical, Treatment

INTRODUCTION

Ocular allergic diseases are common worldwide and mainly consist of conjunctivitis with or without involvement of cornea. Allergic Conjunctivitis (AC) is the most common type of ocular allergy and affects 6-30 % of the general population and up to 30% of children and adolescents [1]. Eye allergies can be seasonal, perennial, or chronic; and, are a part of generalised allergic syndromes like seasonal or perennial keratoconjunctivitis which are directly related to allergic diseases like rhinitis, asthma, or other atopic conditions [2]. Ocular surface diseases are classified into Seasonal Allergic Conjunctivitis (SAC), Perennial Allergic Conjunctivitis (PAC), Vernal Keratoconjunctivitis (VKC), Atopic Keratoconjunctivitis (AKC), contact blepharoconjunctivitis; and non allergic hypersensitivity ailments like Giant Papillary Conjunctivitis (GPC) [3].

The VKC is a chronic, recurrent, bilateral inflammation of the conjunctiva mainly occurring in kids and adolescents with a male predominance. It is a seasonal allergic disease, but in severe cases, it may turn into a perennial one. It includes a wide spectrum of manifestations like intense itching, tearing, red eye, foreign body sensation, mucus discharge, photophobia, lid oedema, chemosis, papillae hypertrophy in tarsal and/or limbal areas, giant papillae, Horner-Trantas dots, and corneal epitheliopathy [4,5].

Vernal Keratoconjunctivitis has a worldwide occurrence, usually affects young males in dry and hot climatic regions. In western Europe in a survey, the prevalence of the disease ranged from 1.16 to 10.55 per 10,000 population. The disease is common in temperate zones of Mediterranean areas, Central and West Africa, the Middle East, Japan, the Indian subcontinent and South America. In regions of Cameroon, Turkey, India, and Israel, prevalence ranges from 3% to 10% in younger population [6]. Two studies from northern and southern parts of India also reported the prevalence of VKC to be 5.1% and 18% in school going children [7,8].

In VKC, avoidance of allergens/triggers along with basic eye hygienic practices should be advocated in all patients. Topical agents having dual antihistaminic and mast cell stabilising activity are first line measures in in mild to moderate cases; in refractory, complicated and severe cases, additional treatment options are corticosteroids and immunomodulators. Surgical treatment may be required in complications like shield ulcers, corneal opacities, refractory giant papillae [6,9].

Olopatadine was the first dual-action topical agent approved for the treatment of AC, with the convenience of once or twice daily preparations, and was more effective than second-generation oral or topical antihistamines. In addition, when compared to ketotifen, epinastine, and azelastine, it had a better efficacy and was more comforting for patients [10]. Bepotastine is the last to be approved among dual-action topical agents; and has demonstrated superior

efficacy in controlling the allergic symptoms in AC when compared with other drugs having similar properties [11,12].

Olopatadine is an effective, freely available, cheaper, and with the option of once daily dosing, it is a reasonable alternative to bepotastine for a rural population with limited resources. There is a dearth of comparative studies in VKC, hence, it was thought prudent to compare the efficacy and safety of olopatadine and bepotastine mild to moderate VKC.

MATERIALS AND METHODS

This prospective comparative study was conducted in the Ophthalmology Outpatient Department (OPD) at National Institute of Medical Sciences Hospital, Jaipur, Rajasthan, India, from January 2020 to January 2021. The study was approved by the Institutional Ethics Committee (vide letter no. NIMSUNI/IEC/2019/118, dated 9th December 2019). It was conducted in accordance with the principles of good clinical practice and the declaration of Helsinki. Patients (or their parents when aged <18 years) were explained the procedures and written informed consent was obtained in the local language; for illiterate people, left thumb marks were taken.

Diagnosing VKC: As VKC is common in school going children and mostly resolves after puberty, all consecutive patients of 5 to 18 years of age presenting in OPD with symptoms of AC during the said period were screened for the disease. Screened patients underwent a detailed history and ocular examination by an Ophthalmologist. Patients with bilateral chronic, recurrent or persistent symptoms, complaining predominantly of pruritus, watering, mucoid discharge, foreign body sensation, photophobia; having conjunctival hyperaemia and papillary hypertrophy in the upper tarsal conjunctiva with or without the presence of limbal papilla were diagnosed as VKC. All patients selected for the study had the tarsal form of VKC [13,14].

Inclusion criteria: Patients of either sex of 5 to 18 years of age having diagnosed with mild and moderate VKC with tarsal involvement and willing to give written informed consent for enrollment and follow-up were included in the study.

Exclusion criteria: Patients having severe forms of VKC, those requiring topical steroids or topical immunosuppressive agents or any systemic therapy, patients with large tarsal papillae (>3 mm size) or severe limbal involvement including Horner-Trantas dots, patients with corneal involvement or, with conjunctival or lid scarring, patients having hypersensitivity or contraindication to either agent, single-eyed patients, contact lens wearers, those planning surgery during the study period, patients having history of ocular trauma or ocular surgery, or any active ocular inflammatory or pathological conditions, those who received topical or systemic confounding drugs (antihistamines, steroids and immune-modulators) in last seven days before enrollment and patients unwilling for giving consent or follow-up for 30 days were excluded from the study.

Total 76 consecutive patients of mild to moderate VKC, fulfilling inclusion and exclusion criteria, who visited OPD during the study period constituted the sample size and were randomised. The patients were randomly assigned into two groups by the chit and box method.

- Group 1 (n=38) received Bepotastine Besilate (1.5%) 1 drop twice daily in both eyes for 30 days.
- Group 2 (n=38) received Olopatadine HCl (0.1%), 1 drop twice daily in both eyes for 30 days.

Procedure

Objective symptoms such as itching, watering, mucoid discharge; and signs such as conjunctival hyperaemia, and tarsal papillae hypertrophy were observed and recorded in a standardised proforma at baseline and follow-ups. For simplified, easy to perform and uniform grading of each symptom and sign at every visit, 4-point scoring scales (0-3) were used [12,13,15].

Scales used by Muller GG et al., were followed for grading of symptoms [13].

Itching:

- Grade 0 indicated no itching.
- Grade 1 indicated occasional desire to scratch.
- Grade 2 indicated frequent desire to scratch.
- Grade 3 indicated a constant desire to itch interfering with daily activities.

Watering (tearing):

- Grade 0 indicated no watering.
- Grade 1 indicated occasional tearing.
- Grade 2 indicated intermittent tearing.
- Grade 3 indicated constant watering disrupting daily activities.

Mucoid discharge:

- Grade 0 indicated no discharge.
- Grade 1 indicated little discharge in the fornix.
- Grade 2 indicated moderate discharge in the fornix, with crusting on eyelashes.
- Grade 3 indicated daily abundant discharge with eyes sticking on waking, or needed washing several times a day.

Hyperaemia: Scale used by Ayyappanavar S et al., was followed for grading of hyperaemia [12].

- Grade 0 indicated absence of conjunctival hyperaemia.
- Grade 1 indicated mild reddish colour.
- Grade 2 indicated moderate bright red colour.
- Grade 3 indicated a bright and intense diffuse hyperaemia.

Tarsal papillae: Scale used by Bonini S et al., was followed for grading of tarsal papillae [15].

- Grade 0 indicated no tarsal papillae.
- Grade 1 indicated few small papillae <0.3 mm.
- Grade 2 indicated papillae of 0.3 to 1 mm over the tarsal conjunctiva.
- Grade 3 indicated papillae of 1 to 3 mm all over the tarsal conjunctiva.

Patients were examined on day 0 (before treatment) and later on the 7th day, 15th day, and 30th day after initiation of treatment. Side effects were noted as per adverse drug reaction forms. During the study period, no patient was lost to follow-up.

STATISTICAL ANALYSIS

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 20.0, IBM, Chicago, IL, USA. Continuous variables were expressed as mean±SD and categorical variables were expressed as absolute numbers and percentages. The comparison of non normally distributed continuous variables within the study group (intra-arm analysis) was performed using the Friedman's test. The comparison between non normally distributed continuous variables among the study groups (inter-arm analysis) was performed using Mann-Whitney's U test. Nominal categorical data between the groups were compared using the Chi-square test. The p-value <0.05 was considered to be statistically significant.

RESULTS

Both the groups were matched at baseline for age and gender. The overall age of the participants was 10.49±2.95 years and the Male to Female ratio (M:F) was 1.7:1.

In overall 76 patients of VKC, three characteristic complaints were analysed; these were itching in 75 (98.6%), watering in 75 (98.6%), and ropy mucoid discharge in 65 (85.5%) patients. Mean symptom scores of itching, watering and eye discharge on presentation (day 0), and on subsequent follow-ups in both groups are shown in [Table/Fig-1-3] respectively.

Time	Itching score (Mean±SD)		p-value
	Group 1	Group 2	
Day 0	2.01±0.75	2.18±0.75	0.40
Day 7	1.36±0.74	1.45±0.71	0.62
Day 15	0.79±0.60	0.75±0.68	0.75
Day 30	0.14±0.33	0.21±0.34	0.24
p-value	<0.001*	<0.001*	-

[Table/Fig-1]: Comparison of group 1 and group 2 in mean itching scores before treatment (day 0); at day 7, day 15, and 1 month on treatment with bepotastine besilate 1.5% or olopatadine HCl 0.1% ophthalmic solution.
Inter-arm analysis was performed using the Mann-Whitney's U test. Intra-arm analysis was performed using the Friedman's test. *p-value <0.05 was considered to be statistically significant

Time	Watering score (Mean±SD)		p-value
	Group 1	Group 2	
Day 0	2.05±0.71	2.08±0.74	0.68
Day 7	1.21±0.76	1.34±0.72	0.44
Day 15	0.49±0.66	0.67±0.66	0.16
Day 30	0.12±0.32	0.13±0.32	0.78
p-value	<0.001*	<0.001*	-

[Table/Fig-2]: Comparison of group 1 and group 2 in mean watering scores before treatment (day 0); at day 7, day 15, and 1 month on treatment with bepotastine besilate 1.5% or olopatadine HCl 0.1%.
Inter-arm analysis was performed using the Mann-Whitney's U test. Intra-arm analysis was performed using the Friedman's test. *p-value <0.05 was considered to be statistically significant

Time	Mucoid discharge score (Mean±SD)		p-value
	Group 1	Group 2	
Day 0	1.50±0.95	1.76±0.79	0.16
Day 7	0.74±0.68	0.93±0.57	0.12
Day 15	0.45±0.46	0.53±0.48	0.48
Day 30	0.12±0.29	0.14±0.30	0.58
p-value	<0.001*	<0.001*	-

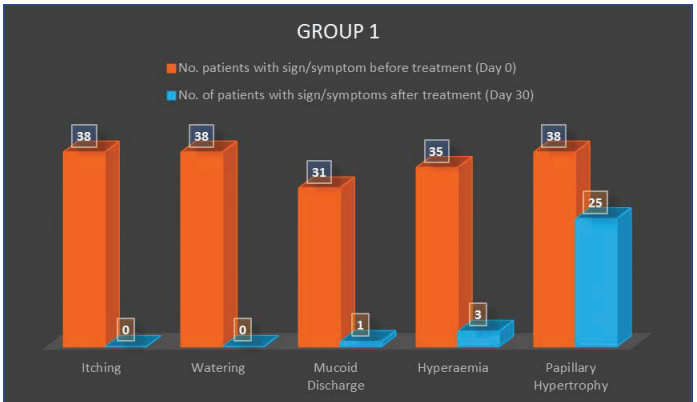
[Table/Fig-3]: Comparison of Group 1 and Group 2 in mean mucoid discharge scores before treatment (day 0); at day 7, day 15, and 1 month on treatment with bepotastine besilate 1.5% or Olopatadine HCl 0.1%.
Inter-arm analysis was performed using the Mann-Whitney's U test. Intra-arm analysis was performed using the Friedman's test. *p-value <0.05 was considered to be statistically significant

Mean symptoms scores of itching, watering, and discharge were comparable in both the treatment groups at baseline. There was no significant difference in reduction of any mean symptoms scores when the drug effects were compared between group 1 and group 2 patients in all subsequent visits [Table/Fig-1,2,3]. This showed that both bepotastine and olopatadine were equally efficacious in controlling itching, watering, and mucoid discharge in patients having mild to moderate VKC.

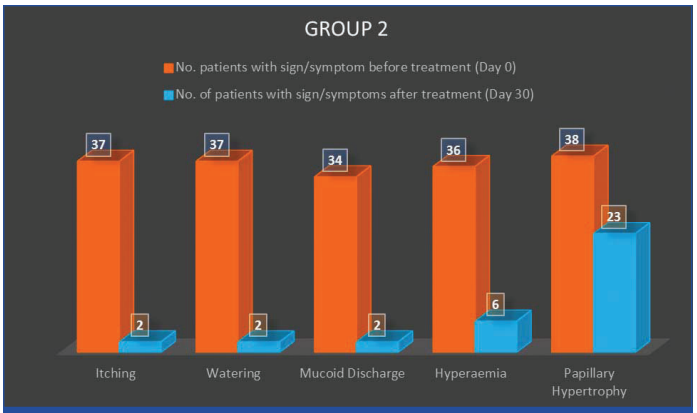
All mean symptom scores showed a significant decrease at end of the study (30th day) in each treatment arm when compared from baseline suggesting that both Bepostatine and Olopatadine were efficacious in controlling the cardinal symptoms of VKC. Almost all patients were relieved of ocular itching, watering and mucoid discharge at the end of the study (defined as a reduction of atleast 2 points in symptom score from baseline, or a symptom score of 0) in both treatment arms; their efficacies were comparable (p-value >0.05, NS, Chi-square test) [Table/Fig-4,5].

Efficacy of bepotastine and olopatadine was also studied on mucosal hyperaemia and tarsal papillary hypertrophy. There was a significant reduction in mean hyperaemia and papillary scores in study groups at follow-up visits, suggesting that both drugs were effective in relieving these signs in mild to moderate VKC. The efficacy of both drugs in reducing mucosal hyperaemia and papillary hypertrophy was comparable at each follow-up [Table/Fig-6,7].

Mucosal hyperaemia was relieved in 32 of 35 (91.4%) patients in bepotastine group, and 30 of 36 (83.3%) patients in olopatadine group at the end of the study. Although there was a significant



[Table/Fig-4]: Relief* of symptoms and signs after topical bepotastine besilate 1.5% in VKC patients (Group 1).
*Relief from symptom/sign at 30 days was considered as at least 2 points reduction in mean score or a score of 0



[Table/Fig-5]: Relief* of symptoms and signs after topical olopatadine HCl 0.1% in VKC patients (Group 2).
*Relief from symptom/sign at 30 days was considered as at least 2 points reduction in mean score or a score of 0

Time	Hyperaemia score (Mean±SD)		p-value
	Group 1	Group 2	
Day 0	1.77±0.77	1.80±0.69	0.62
Day 7	0.91±0.55	1.13±0.65	0.08
Day 15	0.62±0.63	0.66±0.65	0.96
Day 30	0.15±0.32	0.16±0.34	0.97
p-value	<0.001*	<0.001*	-

[Table/Fig-6]: Comparison of Group 1 and Group 2 in mean hyperaemia scores before treatment (day 0); at day 7, day 15, and 1 month on treatment with bepotastine besilate 1.5% or olopatadine HCl 0.1%.
Inter-arm analysis was performed using the Mann-Whitney's U test. Intra-arm analysis was performed using the Friedman's test. *p-value <0.05 was considered to be statistically significant

Time	Papillary hypertrophy score (Mean±SD)		p-value
	Group 1	Group 2	
Day 0	1.68±0.65	1.73±0.63	0.52
Day 7	1.60±0.69	1.63±0.75	0.72
Day 15	1.08±0.47	0.95±0.63	0.49
Day 30	0.75±0.49	0.70±0.57	0.54
p-value	<0.001*	<0.001*	-

[Table/Fig-7]: Comparison of Group 1 and Group 2 in mean papillary hypertrophy scores before treatment (day 0); at day 7, day 15, and 1 month on treatment with bepotastine besilate 1.5% or olopatadine HCl 0.1%.
Inter-arm analysis was performed using the Mann-Whitney's U test. Intra-arm analysis was performed using the Friedman's test. *p-value <0.05 was considered to be statistically significant

improvement in mean papillary scores with bepotastine and olopatadine on all subsequent visits, 25 of 38 (65.8%) patients in bepotastine group and 23 of 38 (60.5%) patients in olopatadine group had residual tarsal papillae [Table/Fig-4,5]. The effect of drugs was again comparable in relieving mucosal hyperaemia and papillary hypertrophy (p-value >0.05, NS, Chi-square test). None of the patients in either group reported any significant side effects. No

patient worsened during the treatment period and none dropped out during the study period.

DISCUSSION

The VKC is a relatively uncommon, chronic, allergic disease of the conjunctiva, characterised by severe itching, sticky ropy mucous discharge, conjunctival hyperaemia, and large papillae in the upper tarsal and/or limbus with corneal involvement in some [15,16].

In present study, mean age of the patients was 10.49±2.95 years and the M:F was 1.7:1. Studies from India have shown a similar age and male predominance. Saboo US et al., showed that the mean age at presentation was 12 years±6.63 years and M:F was 6.4:1 in patients of VKC [17]. Nagpal H et al., reported that among 150 patients of VKC, 110 (73.33%) were males and 40 (26.67%) were females, the highest incidence occurred in the age group 11-15 years [18]. Leonardi A et al., in one of the largest case series of 406 VKC patients from Italy showed a M:F of 3.3:1; 83% of patients were under 10 years of age, only 4% were aged 20 years or above [14].

Basic eye care, avoidance of allergens or provocative stimuli, and dual-acting topical drugs with antihistamine and mast cell stabilising properties are corner stones of management of mild to moderate cases of VKC [6,9,16].

Olopatadine is one such topical agent and is shown to be efficacious in reducing symptoms of AC; scores better than antihistamines [10]. It is a low-cost, effective, widely available therapy in India and without significant adverse effects [12,19,20]. Bepotastine, is also a similar drug, however it is less freely available and relatively costlier. It has been compared with olopatadine and other dual-action topical agents like alcaftadine in AC and was found to be more effective in controlling allergic symptoms, reducing ocular discomfort, and was preferred by patients in a few studies [11,12,19].

In Indian regions having a dry and hot climate during spring and summers, VKC is relatively common in the younger population [7,8,17,18]. There is a lack of well-conducted, good-quality studies comparing the efficacy of olopatadine with bepotastine in VKC. In a study of 50 patients of VKC, Shruti V et al., demonstrated that Bepotastine 1.5% eye drops provided better and quicker relief of watering, ocular discomfort, and conjunctival hyperaemia after 8 weeks of follow-up; olopatadine 0.1% eye drops provided faster improvement in papillary hypertrophy. However, both drugs were equally effective in reducing itching [21]. In another comparative study from north India, Gupta P et al., randomised 65 patients of VKC aged 5-15 years in two study arms. Patients in arm A were given Bepotastine 1.5% and those in arm B were given Olopatadine 0.1% twice daily. After three weeks of therapy, patients in both arms showed similar improvement in the composite symptoms and signs severity scores. In contrast to Shruti V et al., they have shown that reduction in ocular itching score was more in the bepotastine arm as compared to the olopatadine arm [22]. Both the studies, however, didn't mention whether they have excluded severe cases of VKC who would have required other pharmacological interventions in addition to topical dual-action agents. In a recent Indian study, Malahat AR et al., studied 50 patients of VKC without severe symptoms who did not require topical steroids or immunosuppressive agents for three months. They demonstrated that both olopatadine and bepotastine were equally efficacious in improving itching and foreign body sensation scores, and for the reduction in papillary hypertrophy scores. Although the reduction in watering and conjunctival hyperaemia scores was more in the bepotastine group at one week and one month, at further follow-up at three months, there was no significant difference in the two study groups [23]. However, the authors have not elaborated whether, the reduction in signs and symptoms scores in each treatment arm was statistically significant at the end of the study when compared from baseline [23].

Present study comprised of 76 patients, in which the efficacy of bepotastine 1.5% ophthalmic solution and olopatadine 0.1% ophthalmic solution in controlling major symptoms and signs of mild to moderate VKC patients was compared. Patients with severe manifestations of VKC were excluded as they often need other topical and systemic agents. The study demonstrated that, both agents were very efficacious in reducing symptoms of itching, tearing, mucosal discharge; and in reduction of conjunctival hyperaemia at the end of the study period. There was no statistical difference in mean symptoms/sign scores among both agents at any follow-up or the end of the study. This suggested that both the drugs had equal efficacy in reducing common discomforting symptoms and signs of VKC.

Bepotastine and olopatadine were also equally effective in reducing papillary hypertrophy. This finding is different from that reported by Gupta P et al., wherein olopatadine was more effective than Bepotastine in reducing papillary hypertrophy in VKC patients [22]. Mahalat et al., have shown that the efficacy of both the topical agents was comparable in reducing papillary hypertrophy in VKC cases, however, they did not mention whether the reduction in each group was statistically significant [23]. On the contrary, Dudeja L et al., have demonstrated that topical dual-action agents were ineffective in the reduction of tarsal papillary hypertrophy, although their study groups comprised of mild to moderate cases of AC instead of VKC [19]. In present study also, it was observed that despite significant improvement in papillary scores in both groups, a considerable number of patients had persistent albeit smaller lesions at the end of follow-up. This suggests that agents having antihistamine and mast cell stabilising properties, predominantly offer symptomatic relief of allergic symptoms as well as reduction in papillary inflammation and size; however, treatment with more potent agents like topical or systemic steroids/immuno-modulators should be considered in VKC patients having residual papillae or severe disease.

Bepotastine 1.5% eye drops and olopatadine 0.1% eye drops are very safe and devoid of significant adverse effects, none of the patients reported any adverse event, and none dropped out during the study period. Other studies nevertheless reported few, mild and transient adverse effects of topical bepotastine and olopatadine in the management of AC and VKC patients; however, none of the patients enrolled in these studies discontinued treatment because of significant adverse effects. Adverse effects that were reported in these studies were headache, mild taste impairment, mild redness or irritation of eyes, and sore throat [11,12,19,21,22].

Limitation(s)

There were several limitations of the present study. As the present study, was a single centre study, the sample size was small; and the efficacy of treatment could be ascertained only against regional allergens. Severe cases of VKC were excluded, hence the effects of bepotastine or olopatadine as an adjunct to other pharmacological agents could not be studied. The effect of bepotastine and olopatadine on signs and symptoms associated with severe VKC like photophobia, chemosis, severe limbal involvement including Horner Trantas dots and corneal involvement could not be studied. This was an open-labelled study, so, there is a possibility of influence of product marketing and previous experiences of the patients.

CONCLUSION(S)

In current study, both topical bepotastine and olopatadine ophthalmic solutions significantly reduced typical signs/symptoms of VKC like itching, watering, mucoid discharge, conjunctival hyperaemia and papillary hypertrophy in mild to moderate disease. The inter-arm analysis also suggested both the agents were equally efficacious in reducing these common signs and symptoms. Olopatadine use in mild to moderate VKC is efficacious, safe, less costly, and readily available treatment. It is, thus, more commonly prescribed than

bepotastine in general practice and seems to be more suitable for improving compliance and effectively managing less severe VKC in underprivileged patients of rural and remote areas of India. In future, studies comparing olopatadine and bepotastine with other topical agents with dual antihistamine and mast cell stabilising effects like alcaftadine can be conducted in VKC similar to other studies done on AC. It is also recommended to perform a randomised, double-masked, crossover studies with adequate sample size during all seasons over couple of years, and at different geographical locations to better define the best initial topical therapy for patients with mild to moderate VKC.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Resident, Department of Ophthalmology, National Institute of Medical Sciences Hospital, Jaipur, Rajasthan, India.
2. Associate Professor, Department of Ophthalmology, National Institute of Medical Sciences Hospital, Jaipur, Rajasthan, India.
3. Professor, Department of Ophthalmology, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India.
4. Assistant Professor, Department of Ophthalmology, National Institute of Medical Sciences Hospital, Jaipur, Rajasthan, India.
5. Assistant Professor, Department of Ophthalmology, National Institute of Medical Sciences Hospital, Jaipur, Rajasthan, India.
6. Professor, Department of Ophthalmology, National Institute of Medical Sciences Hospital, Jaipur, Rajasthan, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Vandana Mahaur,
Associate Professor, Department of Ophthalmology, NIMS Medical College and Hospital, NIMS University, NH-11C, Delhi-Jaipur Expressway,
Jaipur-303121, Rajasthan, India.
E-mail: vandanarai10@gmail.com

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