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Comparison of efficacy of topical bepotastine besilate and alcaftadine in patients with vernal keratoconjunctivitis

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ABSTRACT

Aim: To compare efficacy of bepotastine besilate (1.5%) versus alcaftadine (0.25%) in patients with vernal keratoconjunctivitis.

Materials and Methods: This comparative, randomized, single-blind and prospective study was conducted on 100 patients diagnosed with VKC, who were allocated to receive either of the two treatment groups. Group A received Alcaftdine eye drops once daily, while Group B received bepotastine besilate twice daily for 8 weeks. The efficacy assessment was done at baseline and then at 4 and 8 weeks post-treatment using following parameters - Primary endpoints included clinical symptoms score and clinical signs score and secondary endpoint included upper tarsal conjunctival brush cytology for eosinophil count.

Results: Intra-group analysis of clinical symptoms and clinical signs score showed statistically significant reduction in both scores and eosionophil count when compared to baseline values with both the drugs. On inter-group analysis, it was found that there was no statistically significant difference between the two groups in reduction in clinical symptoms and clinical signs score and eosinophil count.

Conclusion: This study concluded that both drugs proved equally efficacious in relieving signs and symptoms of VKC. Difference in improvement of signs, symptoms, eosinophil count between both the groups drugs was not statistically significant.

1. Introduction

Vernal keratoconjunctivitis (VKC) is an atopic condition of the external ocular surface and is most common and more severe in hot, dry environments such as the Mediterranean basin, West Africa and the Indian subcontinent.[1] Symptoms include ocular itching, redness, swelling, photophobia and discharge. The most characteristic sign is giant papillae on the upper tarsal conjunctiva (figure 1). The tears of VKC patients contain high levels of IgE and mast cell mediators.[2] Histamine, leukotrienes and prostaglandins may also be found in the tears of VKC patients. Corneal involvement in VKC may vary from superficial punctate keratitis to ulceration of surface known as 'shield ulcers'. Tranta's dots consist of clumps of necrotic eosinophils.[3] These cells collect in crypts, which are formed by invaginations at the junction of the cornea and conjunctiva. Tranta's dots tend to appear when VKC is active and disappear when symptoms abate.[4]

VKC has relapsing and remitting course and hence, it is very important to counsel patients and their parents about the course of disease and the possible complications

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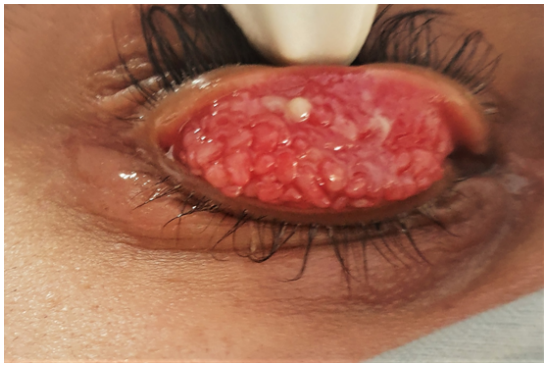

Figure 1: Cobblestone papillae

associated with its severe form. The first line of management is identification and avoidance of allergen by measures like use of protective glasses. Frequent washing of eyes also leads to mechanical dislodging of allergens. Ice fomentation can serve as natural decongestant and can provide symptomatic relief.

Patients of VKC have a tendency itch frequently which causes mast cell degranulation and release of more histamine, which again causes more itching. This leads to a vicious cycle of itching and rubbing. Therefore, patients should be strictly instructed to avoid rubbing. Severe itching can be alleviated by ice fomentation or artificial tear drops.[1]

Artificial tears (carboxymethyl cellulose 0.5%, carboxymethyl cellulose gel 1%) may help to alleviate symptoms like irritation and itching.[5] They also provide relief by washing out the inflammatory mediators pooled inside the conjunctival sac.

Pharmacologic therapy for VKC includes antihistaminics, mast cell stabilizers, corticosteroids and immunomodulaters.. In recent years, multiple new anti-allergic drugs have been introduced such as olopatadine, Alcaftadine, ketotifen, azelastine, Bepotastine and epinastine that exert multiple anti allergic effects such as histamine receptor antagonism, stabilization of mast-cell degranulation and suppression of activation and infiltration of eosinophils.

Bepotastine besilate (0.15%) is an anti-allergic agent with multiple mechanisms of action. It is a 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.[6]

Alcaftadine is a new chemical entity developed as an antiallergic agent. It is potent H_1, H_2 receptor antagonist and has moderate affinity for H4 receptor.[7] This molecule also possess low affinity for various other receptors like human serotonin 5HT1A, human α2A adrenergic, human melanocortin receptor MC4. Alcaftadine treatment significantly lowers eosinophil recruitment and thus prevents the disruption of tight junction proteins.[8] Alcaftadine also has H4 receptor inverse agonistic action which can inhibit H4 receptor mediated allergic response of conjunctiva.[9–11] This drug prevents binding of histamine to its receptors located on conjunctival goblet cells, conjunctival nerve fibres, conjunctival epithelial cells, eosinophils, mast cells and vascular endothelial cells.

Allergic conjunctivitis is quite prevalent in our country and often underdiagnosed and mistreated. Lack of a defined gold standard treatment leads to mismanagement and irrational use of steroids. Newer anti-histaminics have emerged as an alternative to conventional drugs being used in treatment of VKC.

2. Materials and Methods

This prospective, randomized, comparative study was carried out on patients presenting to the outpatient department of Regional Institute of Ophthalmology(RIO), Pt. B.D. Sharma PGIMS, Rohtak, after approval from institutional ethics committee for a period of about one year.

Patients who presented with signs and symptoms of VKC in RIO, PGIMS, Rohtak were included in study after written consent. Exclusion criteria were contact lens wearers, other ocular diseases, systemic or topical corticosteroid therapy.

Diagnosis of VKC was made based on clinical signs and symptoms and severity was graded. Patients with mild and moderate VKC were divided into two study groups after randomization with 50 patients in each group. One group (group A) received alcaftadine(0.25%) eye drops once daily and other (group B) received bepotatsine besilate (1.5%) eye drops twice daily for 8 weeks.

A detailed ophthalmological 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 weeks 8. Secondary parameters were recorded using upper tarsal conjunctival brush cytology to see for eosinophil count. (Figure 2)

2.1. Clinical grading system

The clinical improvement was assessed based on clinical parameters for evaluation of symptoms of VKC, which were itching, tearing, redness, visual disturbance, photophobia and mucus discharge while signs of VKC conjunctival hyperemia, tarsal papillae, limbal tranta's 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.

2.2. 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.

Table 1: Alcaftadine intra group symptom score analysis

Alcaftadine	Week 1	Week 4	Week 8	p-value	
	1	2	3	1 vs 2	1 vs 3
Itching	2.08 ± 0.56	1.24 ± 0.59	0.52 ± 0.50	0.0001*	0.0001*
Tearing	2.06 ± 0.65	1.06 ± 0.55	0.36 ± 0.48	0.0001*	0.0001*
Redness	1.90 ± 0.65	1.20 ± 0.53	0.50 ± 0.54	0.0001*	0.0001*
Discomfort	1.68 ± 0.87	0.98 ± 0.68	0.24 ± 0.43	0.0001*	0.0001*
VD	0.36 ± 0.66	0.34 ± 0.63	0.12 ± 0.33	0.709	0.002*
	0.64 ± 0.72	0.34 ± 0.63	0.22 ± 0.42	0.001*	0.0001*

Intra-group sign scoring of patients on alcaftadine showed that baseline discharge score was 1.64 ± 0.94 at baseline and reduced to 0.62 ± 0.57 at 4 weeks and 0.22 ± 0.42 at 8 weeks. Hyperemia scoring reduced from 1.96 ± 0.60 at baseline, to 1.10 ± 0.36 at 4 weeks and 0.64 ± 0.52 at 8 weeks.

Table 2: Alcaftadine intra group sign score analysis

Alcaftadine	Week 0	Week 4	Week 8	p-value	
	1	2	3	Week 0 vs week 1	Week 1 vs week 8
Discharge	1.64 ± 0.94	0.62 ± 0.57	0.22 ± 0.42	0.0001*	0.0001*
Hyperemia	1.96 ± 0.60	1.10 ± 0.36	0.64 ± 0.52	0.0001*	0.0001*
Papillae	0.96 ± 0.97	0.46 ± 0.61	0.20 ± 0.49	0.0001*	0.0001*
Tranta spots	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	-	-
Cornea inv	0.02 ± 0.14	0.02 ± 0.14	0.00 ± 0.00	1.000	0.322

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 3: Bepotastine intra group analysis

Bepotastine	Week 1	Week 4	Week 8	p-value	
	1	2	3	1 vs 2	1 vs 3
Itching	1.82 ± 0.77	1.36 ± 0.72	0.70 ± 0.71	0.0001*	0.0001*
Tearing	1.44 ± 0.79	0.90 ± 0.65	0.42 ± 0.50	0.0001*	0.0001*
Redness	1.62 ± 0.67	1.00 ± 0.70	0.38 ± 0.57	0.0001*	0.0001*
Discomfort	1.64 ± 0.69	0.84 ± 0.68	0.26 ± 0.49	0.0001*	0.0001*
VD	0.54 ± 064	0.46 ± 0.61	0.32 ± 0.51	0.420	0.026*
	0.72 ± 0.83	0.38 ± 0.78	0.18 ± 0.48	0.018*	0.0001*

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 4: Bepotastine intra group sign score

Bepotastine	Week 0	Week 4	Week 8	p-value	
	1	2	3	1 vs 2	1 vs 3
Discharge	1.36 ± 1.02	0.54 ± 0.61	0.30 ± 0.46	0.0001*	0.0001*
Hyperemia	1.82 ± 0.75	1.04 ± 0.45	0.56 ± 0.54	0.0001*	0.0001*
Papillae	0.70 ± 0.76	0.38 ± 0.53	0.10 ± 0.36	0.003*	0.0001*
Tranta spots	0.02 ± 0.14	0.00 ± 0.00	0.00 ± 0.00	0.322	0.322
Cornea inv	0.04 ± 0.20	0.02 ± 0.14	0.00 ± 0.00	0.322	0.159

3. Results

3.1. Following observations were made

1. On intra-group analysis of clinical symptoms score in VKC patients, it was noted that there was statistically significant reduction in clinical symptoms score when compared to baseline values at the end of 4 and 8 weeks with both the drugs. In Group A, baseline mean symptom score was 7.04 ± 0.56 which reduced to 1.72 ± 0.50 at 8 weeks. Similarly, in Group B, the baseline clinical symptom score was 7.78 ± 0.39. The clinical symptoms score reduced to 2.26 ± 0.19 at 8 weeks. (Tables 2 and 3)
2. On intra-group analysis of clinical signs score in VKC patients, it was noted that there was statistically significant decrease in clinical signs score when compared to baseline values at the end of 4^{th} and 8^{th} weeks. In Group A, baseline score was 4.58 ± 0.21 which reduced to 1.06 ± 0.15 at 4 weeks and 1.06±0.11 at 8 weeks. Similarly, in Group B, baseline score was 3.94 ± 0.22 which was reduced to 0.96 ± 0.15 at 4 weeks and 0.92±0.09 at 8 weeks. (Tables 4 and 5)

Table 5: Inter-group analysis

Clinical subjective score	Study group		p-value
	Alcaftadine (Group A) N=50 (%)	Bepotastine (Group B) N=50 (%)	
Week 0			
Itching	2.08 ± 0.56	1.82 ± 0.77	0.058
Tearing	2.06 ± 0.65	1.44 ± 0.79	0.0001*
Redness	1.90 ± 0.65	1.62 ± 0.67	0.036*
Discomfort	1.68 ± 0.87	1.64 ± 0.69	0.799
VD	0.36 ± 0.66	0.54 ± 064	0.075
	0.64 ± 0.72	0.72 ± 0.83	0.763
Week 4			
Itching	1.24 ± 0.59	1.36 ± 0.72	0.365
Tearing	1.06 ± 0.55	0.90 ± 0.65	0.186
Hyperemia	1.20 ± 0.53	1.00 ± 0.70	0.112
Discomfort	0.98 ± 0.68	0.84 ± 0.68	0.332
VD	0.34 ± 0.63	0.46 ± 0.61	0.197
	0.34 ± 0.63	0.38 ± 0.78	0.805
Week 8			
Itching	0.52 ± 0.50	0.70 ± 0.71	0.276
Tearing	0.36 ± 0.48	0.42 ± 0.50	0.541
Hyperemia	0.50 ± 0.54	0.38 ± 0.57	0.201
Discomfort	0.24 ± 0.43	0.26 ± 0.49	0.955
VD	0.12 ± 0.33	0.32 ± 0.51	0.026
	0.22 ± 0.42	0.18 ± 0.48	0.357

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 ($p<0.001$)

Table 6: Intergroup comparison of clinical signs score in group A and group B (N=50 in each group)

Clinical Sign Score	Study Group		P-Value
	Alcaftadine (Group A) N=50 (%)	Bepotastine (Group B) N=50 (%)	
Week 0			
Discharge	1.64 ± 0.94	1.36 ± 1.02	0.158
Hyperemia	1.96 ± 0.60	1.82 ± 0.75	0.310
Papillae	0.96 ± 0.97	0.70 ± 0.76	0.223
Tranta spots	0.00 ± 0.00	0.02 ± 0.14	0.317
Cornea inv	0.02 ± 0.14	0.04 ± 0.20	0.560
Week 4			
Discharge	0.62 ± 0.57	0.54 ± 0.61	0.41
Hyperemia	1.10 ± 0.36	1.04 ± 0.45	0.486
Papillae	0.46 ± 0.61	0.38 ± 0.53	0.587
Tranta spots	0.00 ± 0.00	0.00 ± 0.00	1.000
Cornea inv	0.02 ± 0.14	0.02 ± 0.14	1.000
Week 8			
Discharge	0.22 ± 0.42	0.30 ± 0.46	0.364
Hyperemia	0.64 ± 0.52	0.56 ± 0.54	0.435
Papillae	0.20 ± 0.49	0.10 ± 0.36	0.221
Tranta spots	0.00 ± 0.00	0.00 ± 0.00	1.000
Cornea inv	0.00 ± 0.00	0.00 ± 0.00	1.000

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.

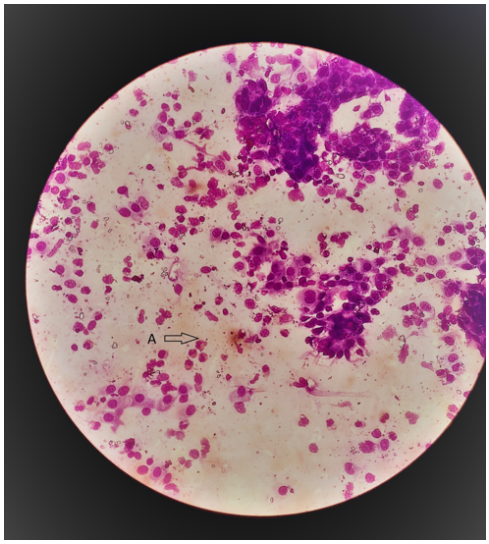

Figure 2: Histopathology slide showing eosinophil

3. On inter-group analysis of clinical symptoms score in VKC patients, it was found that there was no statistically significant difference between the two groups at the end of 4 and 8 weeks in reduction in clinical symptoms score. The results were equivocal in both the groups when compared to baseline values. On analysis of clinical signs score, it was noted that there was no statistically significant difference at the end of 4 and 8 weeks in reduction in clinical signs score. The results were equivocal in both the groups when compared to baseline values. Table 6)
4. On evaluating the secondary efficacy parameter i.e upper tarsal conjunctival brush cytology, it was found that eosinophil count reduced significantly both in Group-A and Group-B at 8 weeks post-treatment. Both the treatments were found to be equally effective with regard to improvement in eosinophil count. Difference in reduction in eosinophil count amongst the two groups was statistically insignificant.

4. Discussion

VKC remains a disease of concern, especially in tropical countries. Management is challenging and thus requires continuous research and advancements. Our study findings are on similar lines as the studies conducted using these two drugs previously.

A very few studies have been conducted to study the cytological parameters in VKC. Abelson et al.[15] conducted a study and found that 63% patients had eosinophils in conjunctival scrapings. Kari et al. concluded that 53% patients of patients with allergic conjunctivitis had eosinophilia. Results of these studies are in accordance with our findings as eosinophils were found in conjunctival scraping of 72% patients in both study groups. Our study concluded that both drugs showed significant reduction in eosinophil count after treatment for 8 weeks. However, the difference in reduction in both study groups was not statistically significant.

Table 7:

Study	Year	Result
1. Dudeja et al.[12]	2019	• Olopatadine, Bepotastine and Alcaftadine provided similar relief in symptoms of VKC
2. Kothai et al.[13]	2021	• Both Alcaftadine and Bepotastine were equally efficacious in ameliorating the symptoms of VKC. • Alcaftadine provided statistically significant results in relieving the itching and redness compared to bepotastine.
3. Ayyappanavar S et al.[14]	2021	• Bepotastine and Alcaftadine had superior efficacy than Olopatadine. • Efficacy of Alcaftadine was comparable to Bepotastine in overall relief of symptoms and signs. • Alcaftadine had better results than Bepotastine in reducing itching and conjunctival redness.
4. Present study	2020-21	• Alcaftadine and Bepotastine have similar efficacy in alleviating signs and symptoms of mid and moderate VKC. The comparision of relief in symptoms and signs score was found to be statistically insignificant for all parameters.

We assessed quality of life in our study by QUICK questionnaire which was designed and tested by Sacchetti et al.[16] With extensive literature research, we found only one study on similar lines in which Bremond-Gignac D et al.[17] conducted a multicenter randomized control trial to assess efficacy and safety of Cyclosporine A and observed significant improvement in QoL (quality of life) in VKC patients.

In our study, both groups showed statistically significant improvement in QoL by QUICK questionnaire at 8 weeks. The two groups were comparable regarding the

improvement in QOL in patients of VKC. The findings of the present study are similar to above mentioned study as statistically significant improvement in response to QUICK questionnaire.

5. Conclusion

This comparative study conducted on patients of VKC showed that both drugs i.e. Alcaftadine (0.25%) and Bepotastine besilate (1.5%) were equally efficacious in relieving signs and symptoms of VKC. Response of both drugs was statistically significant ($p<0.0001$). Difference in improvement of signs, symptoms, eosinophil count and quality of life between both the groups drugs was not statistically significant. Both the drugs proved equally efficacious in alleviating signs and symptoms of VKC at 4 weeks and 8 weeks post treatment. Both drugs proved equally safe during the course of treatment. Our study was not only subjective but objective parameters like eosiophil count showed that both the drugs are efficacious in reducing signs and symptoms of VKC.

Hence, we conclude that both Alcaftadine and Bepotastine are equally efficacious and both can be used in management of VKC. The benefit of Alcaftadine over Bepotastine is in its once daily schedule, but it is slightly more expensive than Bepotastine, hence both may be used according to the scenario and considering patient's affordability.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Kumar S. Vernal keratoconjunctivitis: a major review. *Acta Ophthalmol*. 2009;87(2):133–47.
2. Irani AM, Butrus SI, Tabbara KF, Schwartz LB. Human comjunctival mast cells: distribution of MCT and MCTC in vernal keratoconjunctivitis and giant papillary conjunctivitis. *J Allergy Clin Immunol*. 1990;86(1):34–40.
3. Leonardi A. Management of vernal keratoconjunctivitis. *Ophthalmol Ther*. 2013;2(2):73–88.
4. Friedlaender MH. Ocular allergy. *Curr Opin Allergy Clin Immunol*. 2011;11(5):477–82.
5. Pucci N, Caputo R, Mori F, De Libero C, Grande LD, Massai C, et al. Long-term safety and efficacy of topical cyclosporine in 156 children with vernal keratoconjunctivitis. *Int J Immunopathol Pharmacol*. 2010;23(3):865–71.
6. Kawana S, Niimi Y, Higashi N. Efficacy and safety investigation of Bepotastine besilate in patients with atopic dermatitis. *J New Rem Clin*. 2005;54:1325–31.
7. Greiner JV, Edwards-Swanson K, Ingerman A. Evaluation of Alcaftadine 0.25% ophthalmic solution in acute allergic conjunctivitis at 15 minutes and 16 hours after instillation versus placebo and olopatadine 0.1%. *Clin Ophthalmol*. 2011;5:87–93.
8. Ono SJ, Lane K. Comparison of effects of Alcaftadine and olopatadine on conjunctival epithelium and eosinophil recruitment in a murine model of allergic conjunctivitis. *Drug Des Devel Ther*. 2011;5:77–84.
9. Amaral MM, Davio C, Ceballos A, Salamone G, Cañones C, Geffner J, et al. Histamine improves antigen uptake and cross-presentation by dendritic cells. *J Immunol*. 2007;179(6):3425–33.
10. Smuda C, Bryce PJ. New developments in the use of histamine and histamine receptors. *Curr Allergy Asthma Rep*. 2011;11(2):94–100.
11. Kmiecik T, Otocka-Kmiecik A, Gorska-Ciebiada M, Ciebiada M. T lymphocytes as a target of histamine action. *Arch Med Sci*. 2012;8(1):154–61.
12. Dudeja L, Janakiraman A, Dudeja I, Sane K, Babu M. Observer-masked trial comparing the efficacy of topical olopatadine(0.1%), Bepotastine (1.5%) and Alcaftadine (0.25%) in mild to moderate allergic conjunctivitis. *Indian J Ophthalmol*. 2019;67(9):1400–4.
13. Kothai R, Jeyprakash B, John AM, Reji AV, Benny A. Retrospective analysis on the efficacy of Alcaftadine 0.25% and Bepotastine besilate 1.5% ophthalmic solutions in the management of allergic conjunctivitis. *Pharmacologyonline*. 2021;3:443–9.
14. Ayyappanavar S, Sridhar S, Kumar K, Jayanthi CR, Gangasagara SB, Rathod BL, et al. Comparative analysis of safety and efficacy of Alcaftadine 0.25%, olopatadine hydrochloride 0.2% and Bepotastine besilate 1.5% in allergic conjunctivitis. *Indian J Ophthalmol*. 2021;69(2):257–61.
15. Abelson MB, Madiwale N, Weston JH. Conjunctival eosinophils in allergic ocular disease. *Arch Ophthalmol*. 1983;101(4):555–6.
16. Sacchetti M, Baiardini I, Lambiase A, Aronni S, Fassio O. Development and testing of the quality of life in children with Vernal keratoconjunctivitis questionnaire. *Am J Ophthalmol*. 2007;144(4):557–63.
17. Bremond-Gignac D, Doan S, Amrane M, Ismail D, Montero J. Twelve months results of Cycloporin A Cationic emulsion in a randomized study in patients with pediatric Vernal Keratoconjunctivitis. *Am J Ophthalmol*. 2020;212:116–26.

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