

# Comparative Study of 0.1% Olopatadine vs 0.05% Cyclosporine in Patients of Recalcitrant Vernal Keratoconjunctivitis

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## ABSTRACT

**Introduction:** Vernal keratoconjunctivitis (VKC) is a chronic, recurrent, bilateral inflammatory disease showing exacerbations during the spring and summer seasons, affecting young children. Present study was conducted with the aim of comparing the efficacy of cyclosporine 0.05% with olopatadine 0.1% in recalcitrant patients of VKC.

**Materials and methods:** A prospective randomized controlled trial was performed on 40 eyes (20 patients of recalcitrant VKC) during the period of May 2015 to September 2015. A short course of mild steroid was given for 5 days to all patients as they presented with acute exacerbation of recalcitrant VKC.

Left eye of each patient received topical cyclosporine 0.05%, which is a nonsteroidal immunomodulator, twice daily, and right eye of the same patient received olopatadine 0.1%, which has a dual action, i.e., mast cell stabilizer action as well as antihistaminic activity, twice daily for a period of 3 months. Grading of signs and symptoms was done at the time of presentation and at 2 weeks, 1 month, and 3 months interval.

**Results:** When compared with baseline, scores for signs and symptoms at 2 weeks reduced significantly for both cyclosporine and olopatadine. However, at 3 months, scores as regards signs and symptoms were found to be lower in cyclosporine as compared with olopatadine eyes.

**Conclusion:** Cyclosporine 0.05% was found to be equally effective in treating signs and symptoms as olopatadine in the early phase of the treatment. But, a significant improvement was noted in cyclosporine eyes as compared with olopatadine eyes in the late period.

**Keywords:** Immunomodulator, Mean symptom score, Nonsteroidal, Recalcitrant.

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## INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, recurrent, bilateral inflammatory disease of cornea and conjunctiva affecting young children, mostly in their first decade of life.<sup>1</sup> Signs and symptoms of VKC show exacerbations during spring and summer seasons, but a small percentage of patients have the perennial form.<sup>2</sup>

Diagnosis of this allergic condition is done by the presence of characteristic clinical features which consist of itching, tearing, mucous discharge, conjunctival hyperemia, cobblestone papillae seen over upper tarsal conjunctiva, Tranta's spots over the limbus, and superficial keratitis. Severe corneal involvements in the form of shield ulceration and conjunctival cicatrization are sight threatening.

The pathogenesis of VKC is considered to be multifocal with the involvement of immune, nervous, and endocrine systems.<sup>3-5</sup>

Steroids are being used as the mainstay of treatment for VKC, but a standard treatment protocol is not yet established. Steroids are very effective in controlling the acute exacerbation, but they may cause intraocular pressure elevation in steroid-responders, risk of corneal infection, and cataract. Therefore, they are used for a short period of time.<sup>6</sup> Topical mast cell stabilizers and antihistaminics are also used to reduce the signs and symptoms of the disease. Olopatadine 0.1% acts as a mast cell stabilizer as well as an antihistaminic in treating patients of VKC. Studies have shown that it is more effective than sodium cromoglycate, ketorolac, and levocabastine.<sup>7-9</sup> Cyclosporine 0.05% is a nonsteroidal immunomodulator, used as an effective alternative for the control of ocular inflammation. It inhibits eosinophilic infiltration into the conjunctiva without affecting systemic immune responses.<sup>10</sup>

In the present prospective study, we compared the effects of topical olopatadine 0.1% vs topical cyclosporine 0.05% on the signs and symptoms of patients of recalcitrant VKC, with an aim to earmark the superiority of either of the drugs in the management of VKC.

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## MATERIALS AND METHODS

This was a randomized prospective controlled trial performed on 40 eyes of 20 patients of recalcitrant VKC, who came to the outpatient department (OPD) at Rohilkhand Medical College and Hospital, Bareilly, India, during the period of May 2015 to September 2015.

### Inclusion Criteria

- Age >5 years
- Patients of recalcitrant VKC
- Bilateral symmetrical presentation

### Exclusion Criteria

- Patients who did not give consent
- Patients with other active ocular inflammatory disorders apart from VKC

All patients presenting in the OPD between May 1, 2015 and September 30, 2015, and fulfilling the inclusion criteria were included in the study. A total of 20 patients (40 eyes) were enrolled in the study. An informed consent was taken from them after which each patient was subjected to a detailed slit lamp examination.

Symptoms like itching, tearing, foreign body sensation, and discharge were graded on a scale of 0 to 3 on the basis of grading system adopted from Ozcan et al<sup>11</sup> (Table 1).

Signs like limbal hypertrophy, bulbar conjunctival hyperemia, and tarsal conjunctival hypertrophy were noted and graded on a scale of 0 to 3. Grading system is shown in Table 2.

After grading of signs and symptoms, treatment was initiated. All patients received a short course of topical fluorometholone thrice daily, in both eyes for a period of 5 days. Along with this, right eye of each patient received topical olopatadine 0.1%, twice a day and left eye of same patient received topical cyclosporine 0.05% (Imudrops), twice daily. Patients were followed up for a period of

3 months, and scoring of signs and symptoms was done at 2 weeks, 1 month, and 3 months intervals.

### Statistical Analysis

Statistical analysis of data was done using Statistical Package for the Social Sciences software version 22.0 and unpaired t-test was applied. A p-value of <0.05 was considered statistically significant.

## RESULTS

The present study was done on 40 eyes of 20 patients of VKC in whom majority were male (70%) as compared with females (30%).

Mean age of the patients was 9.4 years, with minimum and maximum age being 7 and 14 years respectively.

Mean scores for signs and symptoms of both olopatadine-treated eyes and cyclosporine-treated eyes are given in Table 3. At 2 weeks posttreatment, olopatadine-treated eyes showed a significant reduction in mean symptom score ( $p < 0.01$ ). Similarly, in cyclosporine-treated eyes, a highly significant reduction was seen ( $p < 0.001$ ). Both drugs were individually effective in lowering the mean symptom and sign score posttreatment at 1 and 3 months intervals when compared with mean baseline symptom and sign scores.

On comparative analysis of mean symptom and sign score between olopatadine- and cyclosporine-treated eyes, the response noted was not statistically significant at 2 weeks ( $p > 0.05$ ). At 1 and 3 months, a highly significant difference was noted ( $p < 0.001$ ) (Table 4).

## DISCUSSION

Vernal keratoconjunctivitis is a chronic allergic inflammation, which is characterized by recurrent, mostly symmetrical involvement of both eyes.<sup>12</sup> Disease shows seasonal exacerbations, but occasional perennial forms are also encountered.

**Table 1:** Grading of symptoms

Symptoms	Grade			
	0	1	2	3
Itching	No	Occasional	Frequent	Constant
Tearing	Normal	Sensation of fullness in sac	Infrequent spilling of tears over lid margin	Constant spilling of tears over lid margins
Foreign body sensation	Absent	Mild	Moderate	Severe
Discharge	No	Small amount of mucoid discharge	Moderate amount of mucoid discharge	Eyelids matted together on awakening

**Table 2:** Grading of signs

Signs	Grade			
	0	1	2	3
Limbal hypertrophy	No	One quadrant	Two quadrant	>2 quadrants
Bulbar conjunctival hyperemia	No	Mild	Moderate	Severe
Tarsal conjunctival papillary hypertrophy	No	Mild	Moderate	Severe

**Table 3:** Mean symptom and sign score of patients

Treatment period		Olopatadine				Cyclosporine			
		Mean	SD	t	p-value	Mean	SD	t	p-value
At presentation	Symptom	6.9	1.34	–	–	6.9	1.34	–	–
	Sign	4.5	1.15	–	–	4.5	1.15	–	–
2 weeks	Symptom	5.5	0.83	2.74	0.006	5.1	0.73	3.66	<0.001
	Sign	3.4	0.84	2.4	0.013	2.9	1.10	3.13	0.003
1 month	Symptom	3.5	1.08	6.16	<0.001	2.2	0.63	9.84	<0.001
	Sign	2.4	0.70	4.85	<0.001	1.7	0.48	6.95	<0.001
3 months	Symptom	1.8	0.42	11.24	<0.001	0.7	0.48	13.49	<0.001
	Sign	1.3	0.45	7.95	<0.001	0.3	0.48	10.42	<0.001

SD: Standard deviation

**Table 4:** Comparative analysis between olopatadine and cyclosporine

Treatment period		Olopatadine		Cyclosporine		t	p-value
		Mean	SD	Mean	SD		
2 weeks	Symptom	5.5	0.83	5.1	0.73	1.12	0.13
	Sign	3.4	0.84	2.9	1.10	1.14	0.13
1 month	Symptom	3.5	1.08	2.2	0.63	3.28	0.002
	Sign	2.4	0.70	1.7	0.48	2.60	0.008
3 months	Symptom	1.8	0.42	0.7	0.48	5.42	<0.001
	Sign	1.3	0.45	0.3	0.48	4.63	<0.001

SD: Standard deviation

Male pediatric population is typically more affected than female,<sup>1,5,13</sup> and similar observation was noted in the present study, with male:female ratio of 2.3:1.

Rarely seen in adults, VKC affects young children in the first decade of life.<sup>14,15</sup> Leonardi et al<sup>16</sup> conducted a study on 406 VKC patients and reported that 83% of the patients were less than 10 years of age at the time of presentation and same age distribution was seen in this study.

Vernal keratoconjunctivitis is a multifactorial disease with immune-mediated processes. T-helper 2 (Th2) lymphocytes, eosinophils, immunoglobulin E (IgE), mast cells, interleukins, and other cell mediators are known to play a major role.<sup>11</sup> Few authors have reported that neural factors and sex hormones also contribute to the pathogenesis of VKC.<sup>3,12,14</sup>

As for other allergic conditions, the main aim of treatment in VKC is blockage of release of allergic mediators and control of allergic inflammatory cascade and, in turn, protection of ocular structures. Various treatment modalities of VKC are topical mast cell stabilizers, anti-histaminics, corticosteroids, and immunomodulators.

Cyclosporine is an immunomodulator, which acts as an anti-inflammatory agent by blocking histamine release from mast cells through inhibition of calcineurin essential for IgE receptor mediated exocytosis of preformed mediators from mast cells. It also acts by inhibiting Th2 lymphocyte proliferation and interleukin (IL)-2 and IL-5 production and, thus, prevents eosinophil infiltration.<sup>17</sup>

Various studies have reported the benefit of cyclosporine in reducing the ocular signs and symptoms in patients of VKC with different grades of severity.<sup>18-21</sup> In the present study, a comparison of efficacy of both cyclosporine and olopatadine with regard to objective symptoms like itching, tearing, foreign body sensation, discharge, and signs like limbal hypertrophy, hyperemia of bulbar conjunctiva, and papillary hypertrophy over the palpebral conjunctiva was done.

A significant improvement in symptoms and signs was noted at 2 weeks in eyes treated with cyclosporine as well as those treated with olopatadine, but the results were highly significant in the eyes treated with cyclosporine.

At 2 weeks, when we compared both, no statistically significant results were seen. Then after a period of 1 month, improvement in the cyclosporine eyes was statistically significant with a  $p < 0.01$  for symptoms and  $p < 0.01$  for signs. After 3-month interval, highly significant difference was noted in the cyclosporine-treated eyes for both symptoms and signs ( $p < 0.001$ ).

Limitations of the study were a small sample size and a short follow-up period. Further studies are required to establish the efficacy of cyclosporine as a prophylactic measure for the acute exacerbations in patients of recalcitrant VKC.

## CONCLUSION

In early phase of the treatment, both cyclosporine 0.05% and olopatadine 0.1% were found to be equally effective

in alleviating signs and symptoms of VKC. But, in the late period, a clinical and statistical significant improvement was noted in cyclosporine-treated eyes as compared with olopatadine-treated eyes.

## REFERENCES

1. Keklikci U, Dursun B, Cingu AK. Topical cyclosporine 0.05% eyedrops in the treatment of vernal keratoconjunctivitis – randomized placebo-controlled trial. *Adv Clin Exp Med* 2014 May-Jun;23(3):455-461.
2. Akpek EK, Hasiripi H, Christen WG, Kalayci D. A randomized trial of low dose mitomycin C in treatment of severe vernal keratoconjunctivitis. *Ophthalmology* 2000 Feb;107:263-269.
3. Spadavecchia L, Fanelli P, Tesse R, Brunetti L, Cardinale F, Bellizzi M, Rizzo G, Procoli U, Bellizzi G, Armenio L. Efficacy of 1.25% and 1% topical cyclosporine in the treatment of severe vernal keratoconjunctivitis in childhood. *Pediatr Allergy Immunol* 2006 Nov;17(7):527-532.
4. Bozkurt B, Artac H, Arslan N, Gokturk B, Bozkurt MK, Reisli I, Irkec M. Systemic atopy and immunoglobulin deficiency in Turkish patients with vernal keratoconjunctivitis. *Ocul Immunol Inflamm* 2013;21(1):28-33.
5. Labcharoenwongs P, Jirapongsananuruk O, Visitsunthorn N, Kosrirukvongs P, Saengin P, Vichyanond P. A double-masked comparison of 0.1% tacrolimus ointment and 2% cyclosporine eye drops in the treatment of vernal keratoconjunctivitis in children. *Asian Pac J Allergy Immunol* 2012 Sep;30(3):177-184.
6. Carnahan MC, Goldstein DA. Ocular complications of topical peri-ocular, and systemic corticosteroids. *Curr Opin Ophthalmol* 2000 Dec;11(6):478-483.
7. Ketelaris CH, Ciprandi G, Missotten L, Turner FD, Bertin D, Berdeaux G, International Olopatadine Study Group. A comparison of efficacy and tolerability of olopatadine hydrochloride 0.1% ophthalmic solution and cromolyn sodium 2% ophthalmic solution in seasonal allergic conjunctivitis. *Clin Ther* 2002 Oct;24(10):1561-1575.
8. Abelson MB, Greiner JV. Comparative efficacy of olopatadine 0.1% ophthalmic solution versus levocabastine 0.05% ophthalmic suspension using the conjunctival allergen challenge model. *Curr Med Opin* 2004 Dec;20(12):1953-1958.
9. Deschenes J, Discepolo M, Abelson MB. Comparative evaluation of olopatadine ophthalmic solution (0.1%) versus ketorolac ophthalmic suspension (0.5%) using the provocative antigen challenge model. *Acta Ophthalmol Scand* 1999;(228):47-52.
10. Fukushima A, Yamaguchi T, Ishida W, Fukata K, Liu FT, Ueno H. Cyclosporin A inhibits eosinophilic infiltration into the conjunctiva mediated by type IV allergic reactions. *Clin Exp Ophthalmol* 2006 May-Jun;34(4):347-353.
11. Ozcan AA, Ersoz TR, Dulger E. Management of severe allergic conjunctivitis with topical cyclosporin 0.05% eyedrops. *Cornea* 2007 Oct;26(9):1035-1038.
12. Abelson MB, Gomes PJ. Olopatadine 0.2% ophthalmic solution: the first ophthalmic antiallergy agent with once-daily dosing. *Exp Opin Drug Metab Toxicol* 2008 Apr;4(4):453-461.
13. Bonini S, Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, Rama P, Magrini L, Juhas T, Bucci MG. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term followup. *Ophthalmology* 2000 Jun;107(6):1157-1163.
14. Bonini S, Bonini S. Vernal Keratoconjunctivitis. *Ocul Immunol Inflamm* 1993;1(1-2):13-17.
15. Gupta V, Sahu PK. Topical cyclosporin A in the management of vernal keratoconjunctivitis. *Eye (Lond)* 2001 Feb;15(Pt 1):39-41.
16. Leonardi A, Busca F, Motterle L, Cavarzeran F, Fregona IA, Plebani M, Secchi AG. Case series of 406 vernal keratoconjunctivitis patients: a demographic and epidemiological study. *Acta Ophthalmol Scand* 2006 Jun;84(3):406-410.
17. Daniell M, Constantinou M, Vu HT, Taylor HR. Randomised controlled trial of topical cyclosporin A in steroid dependent allergic conjunctivitis. *Br J Ophthalmol* 2006 Apr;90(4):461-464.
18. Pucci N, Novembre E, Cianferoni A, Lombardi E, Bernardini R, Caputo R, Campa L, Vierucci A. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol* 2002 Sep;89(3):298-303.
19. Bleik JH, Tabbara KF. Topical cyclosporine in vernal keratoconjunctivitis. *Ophthalmology* 1991 Nov;98(11):1679-1684.
20. Takamura E, Uchio E, Ebihara N, Okamoto S, Kumagai N, Shoji J, Nakagawa Y, Namba K, Fukushima A, Fujishima H, et al. A prospective, observational, all-prescribed-patients study of cyclosporine 0.1% ophthalmic solution in the treatment of vernal keratoconjunctivitis. *Nihon Ganka Gakkai Zasshi* 2011 Jun;115(6):508-515.
21. Tesse R, Spadavecchia L, Fanelli P, Rizzo G, Procoli U, Brunetti L, Cardinale F, Miniello VL, Bellizzi M, Armenio L. Treatment of severe vernal keratoconjunctivitis with 1% topical cyclosporine in an Italian cohort of 197 children. *Pediatr Allergy Immunol* 2010 Mar;21(2 Pt 1):330-335.