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Original Research Article

# Comparison of Effectiveness of Tacrolimus (0.03%) and Cyclosporine (0.05%) as First Line Drugs in Patients of Vernal Kerato Conjunctivitis

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**Conflict of interest: Nil**

**Abstract**

**Background and Objectives:** Vernal keratoconjunctivitis (VKC) is an atopic, chronic condition of external ocularsurface. It is a bilateral recurrent inflammation of the conjunctiva, involving tarsal and/or bulbar conjunctiva. To evaluate clinical efficacy and side effects of the study medications that varies fromindividual to individual.

**Methodology:** Prospective comparative interventional study, Dept of Eye OPD, NRSMCH. **Duration of study:** 1 year 6 months. **Study population:** Patient suffering from vernal keratoconjunctivitis clinicallydiagnosed on 1st visit. **Sample size:** 83 patients. **Case control required or not:** Not required.

**Conclusion:** This study has shown that in treating vernal keratoconjunctivitis, the most important factor in the management is patient's compliance and motivation to continue the medications for longer period of time and thus improving the quality of life in these patients of vernal keratoconjunctivitis.

**Keywords:** Vernal Keratoconjunctivitis, Bulbar Conjunctiva, Tacrolimus, Cyclosporine.



## Introduction

Vernal keratoconjunctivitis (VKC) is an atopic, chronic condition of external ocular surface. [1] It is a bilateral recurrent inflammation of the conjunctiva, involving tarsal and/or bulbar conjunctiva. VKC starts before the age of 10 years and is more common in males. [2] It has male to female ratio varying from 4:1 to 2:1. It is of self-limiting in nature and resolves after puberty. [3] The most common symptoms are itching, photophobia, tearing, foreign body sensation and thick lardaceous yellowish ropy discharge. [4] The most common signs are giant papillae, superficial keratitis and conjunctival hyperaemia. [5]

Palpebral VKC – It is manifested by large cobblestone papillae ranging from 2-8 mm.

Limbal VKC – It is characterised by Horner Trantas spots and gelatinous nodules. This is also known as endemic limbal conjunctivitis.

Mixed VKC – It has features of both palpebral and limbal types. [6] The 4-grade scale used for clinical diagnosis is as follows:

| | |
|---|---|
| Grade 0 | No symptoms |
| Grade 1 | Mild symptoms |
| Grade 2 | Moderate symptoms |
| Grade 3 | Severe symptoms |

It is a chronic form of ocular allergy. It is an Immunoglobulin-E and T cell mediated hypersensitivity reaction leading to chronic inflammation in which eosinophils, lymphocytes and structural cell activation are involved. [7] Treatment of VKC requires multiple approaches that include conservative measures and pharmacological treatment. Patients and parents should be made aware of the chronic evolution, long duration of the disease and its possible complications. Immunomodulators like cyclosporine and tacrolimus are used in the treatment of VKC. Topical cyclosporine in concentrations of 0.05% to 2% has been shown to decrease inflammatory cytokines and the signs and symptoms of treated VKC patients. Tacrolimus 0.1% topically has also shown to improved signs and symptoms of disease. [8-9] Conventional treatment regimens ie topical decongestants, antihistamines, mast cell stabilizing agents and anti-inflammatory agents provide temporary relief with topical steroids being the mainstay of treatment. Chronicity and frequent relapse of VKC warrants use of topical steroids in about 85% patients [10] . But in some cases symptoms and signs persist despite the use of steroids. Also, long term use of steroids comes with its own set of complications like cataract, rise in intra ocular pressure [11]. Immunomodulator drugs show a promising future in controlling signs of refractory VKC. Topical cyclosporine 0.5-2 % have been effective in the treatment of VKC, atopy and other forms of severe allergic disease [12]. Topical tacrolimus which is known to inhibit T- lymphocytes activation, has been used to treat corticosteroid resistant or unresponsive allergic keratoconjunctivitis, VKC and severe case of giant papillary conjunctivitis [6,13].

## Objectives

To study optimal control of symptoms resulting from use of study medications.

To evaluate clinical efficacy and side effects of the study medications that varies fromindividual to individual.

## Material and Methods

Prospective comparative interventional study, Dept of Eye OPD, Nilratan Sircar Medical College & Hospital Kolkata. Duration of study: 1 year 6 months. Study population: Patient suffering from vernal keratoconjunctivitis clinicallydiagnosed on 1st visit. Sample size: 83 patients. Case-control required or not: Not required**.** Ethical approval: The NRS medical college and hospital, institutional ethical committee hasapproved this study.

### Inclusion criteria

Patients clinically diagnosed with vernal keratoconjunctivitis.

### Exclusion criteria

Patients with known hypersensitivity to tacrolimus or cyclosporine A.

Any coexisting conjunctival disorders, Stevens-Johnson syndrome, uveitis and keratitis.

Patients who had undergone any ocular surgery in the past 3 months.

Informed Consent: All study participants were taken through the informed consent process and they willingly agreed to participate.

Outcome definition and parameters: The main outcome measure is the clinical response to the treatment. Cases were selected among the patients attending Eye OPD in NRSMCH, Kolkata. ii)Written informed consent was taken from every

patient and their parents. If the patient is unable to give consent, consent was taken from his parents / guardians.Detailed history of the patient was taken. Ocular examination was conducted. The selected patients was divided into two groups altetnatively. First group received topical cyclosporine A drop (0.05%) q.d.s. and the second group received 0.03% tacrolimus ointment B.D. The study medication was continued inboth the groups for 12 weeks. Parents and patients were instructed not to use anyother ocular medications during the study period.Assessment of the signs and symptoms was done using standard scoring system(both at baseline study entry point and during each subsequent visits.Patient was asked to come in follow up visits after 2 weeks from start of therapy then at 8 weeks, lastly at 12 weeks.At each follow up, patient's clinical response to the treatment was graded and analysed.

**Results**

**Table 1: Showing the age groups involved in the study:**

| Age groups | N | % | p-value |
|---|---|---|---|
| 1-4 years | 4 | 4.8 | 0.003* |
| 5-8 years | 49 | 59.1 | |
| 9-12 years | 20 | 24.1 | |
| 13-16 years | 8 | 9.6 | |
| 17-20 years | 2 | 2.4 | |

**Table 2: Showing Gender distribution among patients**

| Gender | n | % | p- value |
|---|---|---|---|
| Male | 67 | 80.7 | 0.001* |
| Female | 16 | 19.3 | |

**Table 3: Showing assessment of Itching with Tacrolimus**

- In Right eye

| Time | Mean | SD | p value |
|---|---|---|---|
| Baseline | 1.95 | 00.72 | 0.022* |
| 2 weeks | 1.63 | 00.71 | |
| Baseline | 1.95 | 00.72 | 0.001* |
| 8 weeks | 1.08 | 00.53 | |
| Baseline | 1.95 | 00.72 | 0.001* |
| 12 weeks | 0.63 | 00.59 | |

- In Left eye

| Time | Mean | SD | p value |
|---|---|---|---|
| Baseline | 1.88 | 00.86 | 0.024* |
| 2 weeks | 1.5 | 00.82 | |
| Baseline | 1.88 | 00.86 | 0.002* |
| 8 weeks | 1.03 | 00.54 | |
| Baseline | 1.88 | 00.86 | 0.001* |
| 12 weeks | 0.58 | 00.51 | |

In first visit after 2 weeks, the p value of right eye is 0.022, after 8 weeks is 0.001 and after 12weeks p value is 0.001. Similarly, for left eye, the p value after 2 weeks, 8 weeks and 12 weeks is 0.024, 0.002 and 0.001 respectively.

**Table 4: Showing assessment of Itching with Cyclosporine:**

- In Right eye

| Time | Mean | SD | p value |
|---|---|---|---|
| Baseline | 1.98 | 00.74 | 0.011* |
| 2 weeks | 1.61 | 00.73 | |
| Baseline | 1.98 | 00.74 | 0.001* |
| 8 weeks | 1.1 | 0.61 | |
| Baseline | 1.98 | 0.74 | 0.002* |
| 12 weeks | 0.66 | 0.62 | |

- In Left eye

| Time | Mean | SD | P value |
|---|---|---|---|
| Baseline | 1.91 | 00.87 | 0.012* |
| 2 weeks | 1.49 | 00.83 | |
| Baseline | 1.91 | 00.87 | 0.001* |
| 8 weeks | 1.03 | 00.6 | |
| Baseline | 1.91 | 00.87 | 0.005* |
| 12 weeks | 0.56 | 00.51 | |

The effect of Cyclosporine on itching in each subsequent visits in decreasing order.The p value of right eye is significant on each visit after 2 weeks, 8 weeks and 12 weeks which is 0.011, 0.001 and 0.002 respectively. Similarly for left eye, the p value is 0.012,0.001 and 0.005 respectively.

**Table 5: Showing assessment of papillae with Tacrolimus**

- In Right eye

| Time | Mean | SD | p-value |
|---|---|---|---|
| Baseline | 0.13 | 00.41 | 0.153 |
| 2 weeks | 0.05 | 00.23 | |
| Baseline | 0.13 | 00.41 | 0.153 |
| 8 weeks | 0.05 | 00.23 | |
| Baseline | 0.13 | 00.41 | 0.027* |
| 12 weeks | 0 | 0 | |

- In Left eye

| Time | Mean | SD | p-value |
|---|---|---|---|
| Baseline | 0.13 | 00.41 | 0.257 |
| 2 weeks | 0.08 | 00.27 | |
| Baseline | 0.13 | 00.41 | 0.153 |
| 8 weeks | 0.05 | 00.23 | |
| Baseline | 0.13 | 00.41 | 0.027* |
| 12 weeks | 0 | 0 | |

The effect of Tacrolimus on papillae in each subsequent visits In first visit after 2 weeks, the p value of right eye is 0.153, after 8 weeks is 0.153 and after 12 weeks p value is 0.027. Similarly, for left eye, the p value after 2 weeks, 8 weeks and 12 weeks is 0.257, 0.153 and 0.027 respectively.

**Table 6: Showing assessment of papillae with Cyclosporine**

- In Right eye

| Time | Mean | SD | p-value |
|---|---|---|---|
| Baseline | 0.28 | 00.83 | 0.279 |
| 2 weeks | 0.19 | 0.63 | |
| Baseline | 0.28 | 00.83 | 0.219 |
| 8 weeks | 0.17 | 00.54 | |
| Baseline | 0.28 | 00.83 | 0.090 |
| 12 weeks | 0.1 | 00.37 | |

- Left eye

| Time | Mean | SD | p-value |
|---|---|---|---|
| Baseline | 0.28 | 00.83 | 0.331 |
| 2 weeks | 0.21 | 0.64 | |
| Baseline | 0.28 | 00.83 | 0.123 |
| 8 weeks | 0.12 | 00.4 | |
| Baseline | 0.28 | 00.83 | 0.058 |
| 12 weeks | 0.07 | 00.26 | |

The effect of Cyclosporine on papillae in each subsequent visits In first visit after 2 weeks, the p value of right eye is 0.279, after 8 weeks is 0.219 and after 12weeks p value is 0.090. Similarly, for left eye, the p value after 2 weeks, 8 weeks and 12 weeks is 0.331, 0.123 and 0.058 respectively

The effect of Cyclosporine on Horner Trantas spots in each subsequent visits In first visit after 2 weeks, the p value of right eye is 0.258, after 8 weeks is 0.074 and after 12weeks p value is 0.074. Similarly, for left eye, the p value after 2 weeks, 8 weeks and 12 weeks is 0.274, 0.043 and 0.043 respectively.

The data was tabulated in Microsoft Excel software and analyzed with SPSS V.24 software. Paired t test was used for the comparisons between the groups. The p value≤0.05 was considered as statistically significant.

## Discussion

Vernal keratoconjunctivitis (VKC) is an atopic, chronic condition of external ocular surface. VKC starts before the age of 10 years and is more common in males. In the present study, the majority of the patients attending the Eye OPD for VKC were in the age group of 5 – 8 yrs with significant p-value of 0.03. The gender distribution of the patientsin the study was predominantly male with p value = 0.001 Treatment of VKC requires multiple approaches that include conservative measures and pharmacological treatment. Patients and parents should be made aware of the chronic evolution, long duration of the disease and its possible complications. Immunomodulators like cyclosporine and tacrolimus are used in the treatment of VKC. Topical cyclosporine in concentrations of 0.05% to 2% has been shown to decrease inflammatory cytokines and the signs and symptoms of treated VKC patients. Tacrolimus 0.1% topically has also shown to improved signs and symptoms of disease. [8-9] In a similar study conducted by H Nagpal in 2017 in the settings of tertiary care hospital, Patiala has shown that out of 150 patients, 110 (73.33%) were male and 40 (26.67%) were female. The highest incidence of VKC occurred in the age group of 11–15 years. Maximum cases (62%) had palpebral form followed by mixed form (23.33%) and bulbar form (14.67%). Corneal complications occurred in 22 (14.67%) patients. In a similar study conducted by Priya Choudhary which was published in International Journal of Basic & Clinical Pharmacology in June 2019, it was found

that tacrolimus is clinically better drug for treatment of vernal keratoconjunctivitis than cyclosporine and is alsocost effective. Another study conducted by Ozlem Eski Yücel which was published in Singapore Medical Journal in 2016 concluded that the use of topical Cyclosporine A(0.05%) four times a day is an effective and safe alternative therapy for VKC.In the present study, use of Tacrolimus showed a decreasing effect on itching in each subsequent visits. In first visit after 2 weeks, the p value of right eye was 0.022, after 8 weeks, 0.001 and after 12 weeks p value was 0.001. Similarly, for left eye, the p value after 2 weeks, 8 weeks and 12 weeks 0.024, 0.002 and 0.001 respectively. The effect of Cyclosporine on itching in each subsequent visits in decreasing order with significant p value of right eye on each visit after 2 weeks, 8 weeks and 12 weeks were 0.011, 0.001 and 0.002 respectively. Similarly for left eye, the p value is 0.012, 0.001 and 0.005 respectively. The effect of Tacrolimus on tearing in subsequent visits after 2 weeks, 8 weeks and 12 weeks showed decline with p value for right eye 0.021,0.001 and 0.005 respectively. Similarly, for left eye, the p value after 2 weeks, 8 weeks and 12 weeks were 0.024, 0.004 and 0.001 respectively. Effect of Cyclosporine on tearing on right eye after 2, 8 and 12 weeks were 0.008, 0.001 and 0.006. Similarly, for left eye, the p value after 2, 8 and 12 weeks were 0.007, 0.001 and 0.004 respectively. In another similar study conducted in 2019 by Labcharoenwongs P et al., Labcharoenwongs compared the efficacy of 0.1% tacrolimus (FK-506) ophthalmic ointment with 2% cyclosporine eye drops in the treatment of VKC in a prospective, double-masked randomized comparative trial involving 24 patients. Both the groups showed a similar reduction in signs and symptoms at four and eight weeks of therapy. Besides, there was no difference in side effects between the groups. In the present study, foreign body sensation after use of tacrolimus decreased in each subsequent visits after 2, 8 and 12 weeks. The p value for right eye were 0.001, 0.001 and 0.006 respectively. Similarly for left eye, it was 0.03, 0.001 and 0.001 respectively. Foreign body sensation after usage of cyclosporine, the p value after 2 weeks was 0.001, 8 weeks 0.001 and after 12 weeks was 0.002. Similarly, for left eye, it was 0.001, 0.001 and 0.001 respectively. The p value for photophobia for right eye after using tacrolimus was significant. It was 0.033, 0.008 and 0.001 after 2, 8 and 12 weeks respectively. For left eye, the p value were 0.020,0.004 and 0.001 respectively. The group using cyclosporine showed similar decrease ie for right eye, 0.262, 0.104 and 0.026 and for left eye, it was 0.310, 0.129 and 0.053 respectively. On subsequent visits after 2 weeks, 8 weeks and 12 weeks, the p value fordischarge after using tacrolimus were 0.281, 0.078 and 0.078 for right eye and 0.281, 0.078 and 0.078 for left eye respectively. On subsequent visits after 2, 8 and 12 weeks, the p value for discharge after using cyclosporine were 0.218, 0.141 and 0.082 for right eye and 0.317, 0.141 and 0.141 for left eye respectively. The p value for hyperemia using tacrolimus on subsequent visits were 0.021, 0.001 and 0.004 for right eye and 0.015,0.001 and 0.003 for left eye. Using cyclosporine, it was 0.021, 0.001 and 0.004 for right eye and 0.008, 0.001 and 0.001 for left eye. The p value for oedema tacrolimus on subsequent visits were 0.281, 0.078, 0.078 for right eye and 0.078, 0.078 for left eye. Using cyclosporine, it was 0.236, 0.049, 0.049 for both eyes. In the present study, the p value for corneal involvement using tacrolimus on subsequent visits were 0.236, 0.125, 0.049 for right eye and 0.236, 0.125 and 0.049 for left eye. Using cyclosporine, it was 0.258, 0.074, 0.074 for right eye and 0.236, 0.125 and 0.049 respectively for left eye. The p value was significant for Horner trantas spot using tacrolimus on subsequent visits were 0.236, 0.049 and 0.049 for both eyes.

Using cyclosporine, it was 0.382, 0.261 ,0.11 for right eye and 0.274, 0.043 and 0.043 respectively for left eye

## Conclusion

Both tacrolimus and cyclosporine shows promising results to control the disease for a significant period of time. From this study, it is concluded that both 0.03 % tacrolimus eye ointment and 0.05 % cyclosporine eyedrop can be used in the treatment of vernal keratoconjunctivitis with both showing comparable results and efficacy. This study has shown that in treating vernal keratoconjunctivitis, the most important factor inthe management is patient's compliance and motivation to continue the medications for longer period of time and thus improving the quality of life in these patients of vernal keratoconjunctivitis.

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