

Efficacy of single dose dermatological 0.1% Tacrolimus Ointment in the treatment of vernal keratoconjunctivitis

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Abstract

Objective: To assess the safety of dermatological 0.1% tacrolimus ointment when used topically and its efficacy in the treatment of vernal keratoconjunctivitis.

Method: The quasi-experimental, multi-centre study was conducted at the Gujranwala Medical College/District Headquarters Teaching Hospital, Gujranwala, and the Gomal Medical College/Mufti Mehmood Teaching Hospital, Dera Ismail Khan, Pakistan, from July 2019 to March 2020, and comprised patients of severe vernal keratoconjunctivitis. Symptoms and clinical signs were graded on a pre-devised scale. Patients were given small amount of tacrolimus 0.1% ointment applied to the inferior conjunctival fornix before going to bed. The duration of treatment was 3 months and the patients were followed up for up to 6 months. Data was analysed using SPSS 20.

Results: Of the 50 patients, 30(60%) were males and 20(40%) were females. The overall mean age was 10.64±3.199 years. Mean symptom score and clinical signs score gradually reduced on each follow-up ($p < 0.05$). Mild recurrence was noted in 12(24%) patients who were managed with lubricants and anti-histamine topical drops. No complication was noted.

Conclusion: Tacrolimus 0.1% was found to be effective and safe in the treatment of severe refractory vernal keratoconjunctivitis even when given once a day.

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Introduction

Tacrolimus is a macrolide obtained from bacteria streptomyces tsukubaensis. It was reported by the Japanese back in 1984, and has since carried the code number FK-506¹ as it binds to FK-506-binding proteins in T-lymphocytes and inhibits calcineurin activity. It was among the initial immunosuppressants introduced. After its discovery, trials were initiated related to transplant rejection.² Various studies were also conducted to evaluate its safety and effectiveness in ophthalmology.³ In 1989, it was first reported that tacrolimus suppressed corneal graft rejection in rabbits.⁴ Dermatological preparations are approved by the United States Food and Drug Administration (FDA) for the treatment of atopic dermatitis. They are available in two strengths 0.03% and 0.1%.⁵ These dermatological preparations are used off-label in ophthalmology, but have been reported to be safe and effective.^{3,5}

Allergic conjunctivitis is a broad term that includes

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seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis. VKC is a unique disorder in this category. It is a chronic bilateral, inflammatory condition which more commonly affects young male patients.⁶

Activated cluster of differentiation-4 (CD4) + T-lymphocytes are seen in increased number in VKC patients. These predominantly involve T helper type 2 (Th2) cells. There is also increased levels of inflammatory cytokines, including interleukin-3 (IL-3), IL-4 and IL-5.⁷

There is no definitive gold standard treatment for VKC. Patients should be monitored closely during the disease course and treatment plan should be designed for individual patients. Different options available include antihistamines, mast cell stabilisers, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, cyclosporine and tacrolimus.^{6,7}

Steroid-sparing topical immunomodulatory drugs have a pivotal role in VKC management.⁷ Cyclosporine A (CsA) and tacrolimus are both used as immunomodulatory drugs.⁸ With CsA, relapse after stopping the treatment has been reported.⁹ CsA has been shown to be less effective in cases with giant papillae.⁹ Topical tacrolimus has shown good results in cases refractory to CsA.¹⁰

Studies have reported that topical use of tacrolimus is safe

and effective in VKC patients.¹¹ Most of the studies which reported the safety and efficacy of tacrolimus used it in bis in die (BID; twice daily) dose.^{12,13} Using ointment during day-time often becomes problematic for patients, especially when the diseased population is paediatric. The current study was planned to assess the safety of dermatological 0.1% tacrolimus ointment when used topically and its efficacy in VKC treatment.

Patients and Methods

The quasi-experimental, multi-centre study was conducted from July 2019 to March 2020 at the Gujranwala Medical College/ District Headquarters (DHQ) Teaching Hospital, Gujranwala, and the Gomal Medial College/Mufti Mehmood Teaching Hospital, Dera Ismail Khan, Pakistan. The study was approved by the Institutional Review Board Gujranwala Medical College (Admin 182/GMC dated 8/07/2019). The interventional study was registered with the Chinese clinical trial registry (ChiCTR) id ChiCTR2000031929 link: www.chictr.org.cn/hvshowproject.aspx?id=28053. Sample size was calculated using WHO calculator,¹⁴ assuming symptom reduction rate of 15% for tacrolimus ointment in the treatment of vernal keratoconjunctivitis.¹⁵ A sample of 50 patients was required with 90% power of study and 5 % level of significance.

Those included were patients of severe VKC, or those having a recurrence after discontinuation of steroids or having steroid-induced complications. Patients with any coexisting ocular disorder, such as conjunctival or corneal diseases, ocular infections, uveitis, Stevens-Johnson syndrome, contact lens usage, and history of ocular surgery were excluded. Data was collected after taking informed consent from all the subjects.

After VKC diagnoses, the patients underwent complete ophthalmic examination by a consultant ophthalmologist consisting of slit lamp examination, fundoscopy, fluorescein staining and intraocular pressure (IOP). VKC was clinically evaluated by 4 symptoms of itching, redness, photophobia, mucoid discharge, and 4 clinical signs of conjunctival hyperaemia, papillary hypertrophy, Horner-Trantas dots and corneal involvement.

The evaluation of VKC symptoms was done on clinical basis, while severity was classified as 0=none, 1=mild, 2=moderate and 3=severe.

Clinical signs were categorised according to a score chart (Table 1).

The participants terminated all topical medications 1 week before starting the treatment. All the patients applied small amount of dermatological tacrolimus 0.1% ointment to the

Table-1: VKC clinical signs score system.

Clinical Signs	Score	Definition
Conjunctival hyperaemia	3	Diffuse dilated blood vessels over the entire bulbar conjunctiva
	2	Dilatation of many vessels
	1	Dilatation of few vessels
	0	None
Papillae	3	Papillae size: >0.3mm
	2	Papillae size: 0.2-0.3mm
	1	Papillae size: <0.2mm
	0	None
Tranta dots	3	>6 dots
	2	4-6 dots
	1	1-3 dots
	0	None
SPK	3	Total corneal surface
	2	More than half corneal surface
	1	Less than half corneal surface
	0	None

VKC: Vernal keratoconjunctivitis SPK: Superficial punctate keratopathy.

inferior conjunctival fornix before going to bed. Occasionally, tacrolimus ointment causes mild irritation, so topical lubricants were also prescribed four times a day, till last follow-up at 6 months. Patients were re-evaluated after 1 week and then followed up at 1, 3 and 6 months. On each follow-up visit, change in clinical signs and symptoms score was studied, and noted. To check the safety and adverse effects of the treatment, IOP, lens opacifications, secondary infections and other possible complications were also evaluated. After one month of initial therapy, the frequency of topical application of tacrolimus was subsequently tapered over the following two months. In the second month, the patients used tacrolimus before going to bed on alternate days. In the third month, they applied tacrolimus twice per week. The treatment was stopped after three months in all patients, and they were advised to use topical lubricants and anti-histamine drops, if required. Treatment failure was defined by the need to use topical steroids for disease recurrence on successive follow-up after stopping tacrolimus.

Data was initially stored in Excel, and was analysed using SPSS 20. Descriptive statistics were calculated. Repeated-measure analysis of variance (ANOVA) was used to statistically analyse the changes in mean clinical score before treatment, at 1 week, 1 month, 3 months and 6 months post-treatment. $P < 0.01$ was taken as statistically significant.

Results

Of the 50 patients, 30(60%) were males and 20(40%) were females. The overall mean age was 10.64 ± 3.199 years. Of the total, 45(90%) patients presented with severe symptoms.

Table-2: Mean symptom and sign scores.

Variables	Before Treatment	1week After Treatment	1 month after treatment	3 Months after Treatment	Final Follow-up at 6 Months	p-value a
Symptoms	2.90±0.303	2.64±0.485	0.96±0.669	0.16±0.370	0.04±0.198	<0.01
Conjunctival Hyperaemia	2.34±0.479	2.56±0.501	1.30±0.678	0.58±0.673	0.08±0.274	
Papilla	2.44±0.501	2.30±0.505	0.98±0.795	0.14±0.351	-	
Tranta Dots	2.86±0.351	2.71±0.454	0.80±0.639	0.34±0.479	0.2±0.141	
Superficial Punctate keratopathy	0.42±0.702	0.42±0.702	0.22±0.418	0.06±.240	-	

12(24%) patients who were managed with lubricants and anti-histamine topical drops.

No complication was noted and topical steroids were not required at 6-month follow-up.

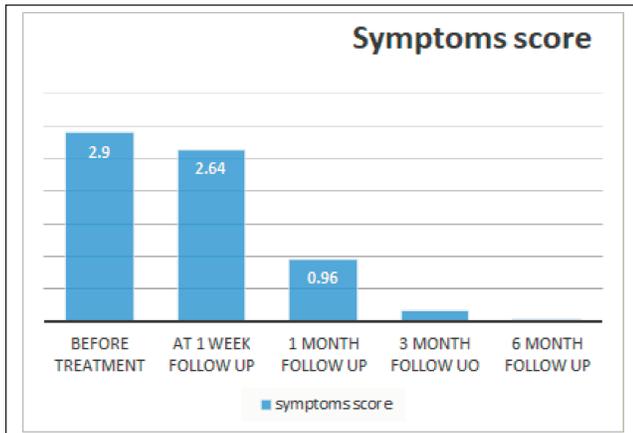


Figure-1: (A) Symptoms score before treatment and on each follow-up.

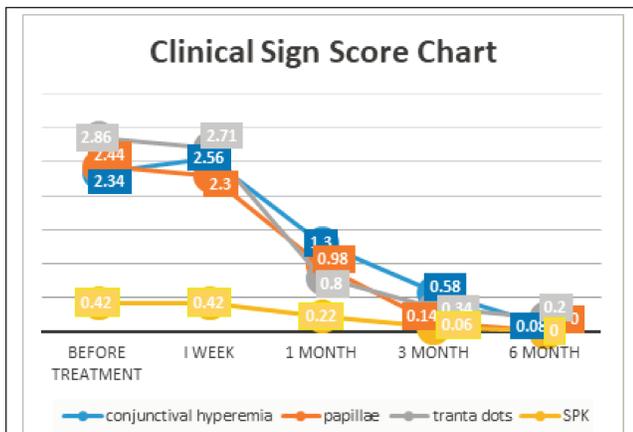


Figure-1: (B) Clinical signs score before treatment and on each follow-up.

Mean symptom score and clinical signs score gradually reduced on each follow-up (Table 2; Figure-1A & Figure-1B).

Diffused dilation of conjunctival vessels was observed in 17(34%) patients, whereas giant papillae of size >0.3mm and >6 Horner-Trantas dots were found in 22(44%) and 43(86%) patients, respectively, while 16(32%) patients had superficial punctate keratopathy at presentation.

A few patients 6(12%) complained of irritation during the first week of treatment, which settled with topical lubricants after 1 week. Mild recurrence was noted in

Discussion

VKC is a chronic disease mediated by Th2 lymphocytes. It commonly affects young population.^{6,7} The mean age of patients in the current study was 10.64±3.199 years with male dominance. Similar trends were observed in local,^{12,13} regional,¹⁶ American¹⁷ and European studies.¹⁸

Immunomodulatory drugs are often required to treat severe cases of VKC. Topical steroids have been used to control symptoms in severe cases, but their prolonged use can lead to blinding complications like glaucoma and cataract.¹²

All the studies which assessed the efficacy of tacrolimus in severe VKC used it in BID dose.^{3,5,12,13,15-18} Application of ointment preparation in fornices during day-time is associated with blurring of vision. It can affect daily activities of patients, leading to decreased compliance with treatment regime. Application of ointment preparation hora somni (HS), or before going to bed, appeared to address these issues. To our knowledge, the current study is the first to report efficacy of 0.1% tacrolimus in HS dose. Improvement was seen as early as 1 month after starting treatment. The symptoms and signs improved further on subsequent follow-ups and by three months almost all the patients recovered. Results are comparable with other studies which used tacrolimus in BID dose.^{3,4,12,13,15-20}

Duration of topical application varies in different studies from 3 to 8 months. Most of the studies have reported success rate >95% with no severe recurrence after stopping the treatment.^{3,5,12,13,15,16} One study showed recurrence in 11% patients after 2 months of monotherapy with tacrolimus.¹⁶ These patient required topical steroids for recurrent disease. In the current study there was no severe recurrence of clinical signs after stopping the treatment at 3 months and no patient required topical steroids after completing 3 months of treatment. Mild-moderate recurrence of disease symptoms in 24% patients was managed successfully by topical lubricants and anti-histamines.

No major adverse event or complication was reported in

any patient. Six (12%) patients complained of burning and redness during the first week of treatment. This was managed by topical lubricant. Barot et al. reported burning sensation in 36.11% patients treated with 0.1% Tacrolimus ointment.¹⁹ Topically, tacrolimus is usually well-tolerated. The most common side effect is usually mild irritation²¹ as in the current study. Blood level of tacrolimus studied in patients who were using it for ophthalmic disease showed that maximum blood concentration was <2ng/mL, and also the risk of systemic adverse effects due to exposure to topical tacrolimus is very minimal.²¹

Drop formulation of tacrolimus 0.1% are also under investigation and are reported to be safe and effective.²⁰ The current study used the ointment form. Beside VKC, tacrolimus is also being used in ophthalmology to treat various conditions,^{22,23} while the current study only focussed on VKC.

The limitations of the current study include limited sample size and involvement of only two health centres. The 6-month follow-up time was short. Also, the registration of the interventional study was done retrospectively. There is lack of World Health Organization (WHO) recognised publicly accessible public trial registration facilities in the country that may meet the requirements of the International Committee of Medical Journal Editors (ICMJE).^{24,25}

Large multi-centre trials with long follow-up are recommended. Further studies are also required in other global regions to establish the efficacy of 0.1 % tacrolimus in HS dose.

Conclusion

Tacrolimus 0.1% dermatological ointment was found to be effective and safe in the treatment of severe refractory VKC when given once daily at bed time.

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Conflict of Interest: None.

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