ORIGINAL ARTICLE

The Safety and Effectiveness of 0.03% Tacrolimus in Pediatric Patients Presenting with Vernal Keratoconjunctivitis in Children Hospital, Multan

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ABSTRACT

Objective: This study evaluated the safety and effectiveness of tacrolimus (0.03%) ointment in treating pediatric patients with vernal keratoconjunctivitis.

Study Design: A prospective, interventional study.

Place and Duration of Study: The study was conducted at the Department of Pediatrics, The Children's Hospital and The Institute of Child Health Multan, Pakistan over one year from February 2021 to February 2022.

Methods: The research involved sixty pediatric patients who had bilateral vernal keratoconjunctivitis. Patients in the tacrolimus cohort were treated with 0.03 percent tacrolimus ointment two times daily for 60 days, followed by a single application daily for 60 days, and once on alternate days for the next two months. The control group got topical fluorometholone 0.1% drops in their eyes for two weeks, after which the amount given was gradually lowered for another two weeks. During the subsequent follow-up time frame, both groups received topical olopatadine 0.1% drops for the eyes twice daily. Modifications to symptoms and signs were documented among the groups to measure the success of therapy, and their severity was rated using a four-point scale.

Results: During the follow-up period, 60 children with bilateral VKC were observed, and the mean age of both groups was similar. Papillary hypertrophy and conjunctival hyperemia were the most common signs, while itching was the most frequently reported symptom. After treatment, Symptoms and signs decreased significantly in both of the groups. However, at three and six months, the group treated with 0.03 percent tacrolimus ointment showed a more notable improvement in symptom and sign scores. The tacrolimus group tolerated the treatment well, with only a few complaining of a stinging sensation. The control group experienced one incidence of elevated intraocular pressure.

Conclusion: 0.03% tacrolimus ointment is an effective and secure therapy for vernal keratoconjunctivitis in young individuals. This different treatment technique may help and lower the likelihood of steroid-related problems in patients with chronic VKC.

Keywords: *Eye, Pediatrics, Tacrolimus, Therapeutics, Vernal Keratoconjunctivitis*.

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Introduction

Vernal keratoconjunctivitis (VKC) is a known chronic inflammatory eye disorder that flares up during certain seasons and affects both eyes equally.[1,2] Although it can occasionally persist into maturity, it primarily affects children and is more frequent in men. Mixed, tarsal, and limbal manifestations are the three forms that VKC can take. Typical symptoms include burning, itching,

watering, redness, discharge, the sensation of something foreign in the eye, and photophobia.[3] Some clinical symptoms include an inflamed limbus, shiny spots, hyperemia, punctate keratitis, tarsal papillae, and Horner-Trantas dots.[4]

The cause of VKC includes inflammatory cells, mast cell proliferation, and cytokines that promote inflammation in tarsal papillae, inflammation of the limbal mucosa, conjunctival hyperemia, and congestion.[1,5] The responses are mediated by T-cells and immunoglobulin-E (IgE). Nowadays, VKC is treated with topical corticosteroids. Other drugs, mast cell stabilizers, antihistamines, and immunomodulatory drugs, are also used in VKC.[6] Antiallergic drugs decrease symptoms but don't benefit tarsal papillae. Tacrolimus ointment is one alternative to corticosteroids, which can lead to glaucoma and cataracts if used excessively and continuously.[7]

A macrolide immunomodulator called tacrolimus, which comes from Streptomyces tsukubaensis is beneficial in treating papillary conjunctivitis, atopic keratoconjunctivitis, and VKC.[8,9] Mode for the action of tacrolimus ointment (0.03%-0.1%) includes suppression of generation of T helper 1 (Th1) and Th2 cytokines, inhibition of calcineurin activity, and reduction of mast cell histamine release. Studies have shown that chronic VKC can be effectively cured with 0.03% tacrolimus ointment with a reduced risk of corticosteroid adverse effects.[10] The goal of this study is to see if 0.03% tacrolimus ointment is secure and efficient for long-term usage in VKC management in pediatric patients.

Methods

A prospective interventional design was conducted at the Department of Pediatrics, The Children's Hospital, and The Institute of Child Health Multan, Pakistan over one year from February 2021 to February 2022. A total of 60 children with Vernal Keratoconjunctivitis (VKC) were selected for the study. The WHO calculator calculated the sample size based on a 30% predicted prevalence, a precision of ±5%, and a confidence level of 95%. Patients of both genders, aged 3 to 14 years, with moderate to severe VKC, patients refractory to conventional therapy, with TSSS (Total Symptom Severity Score) and TOSS (Total Ocular Symptom Score) criteria scoring 3 or 4, ensuring consistency in symptom assessment (details in supplementary data) were included while patients with coexisting conjunctival disorders, ocular infections, uveitis, tumours, glaucoma, cataracts etc, with previous ocular surgery, having tacrolimus hypersensitivity, or lack of consent were excluded.

The ethical approval was obtained from the institute via letter no: PMD/2021-CHC 4737/13-1-21, held on January 13, 2021. We have ensured that written informed consent has been obtained from all participants or their legal guardians.

Participants were consecutively assigned to the intervention group, which received 0.03 percent tacrolimus ointment applied twice daily for 60 days, followed by once daily for two months, and then once every other day for the last two months. The control group was treated with topical fluorometholone eye drops three times daily and external olopatadine 0.1% twice daily for two weeks. If the symptoms were resolved after this time, the steroid dosage was gradually reduced, and external olopatadine 0.1 % was given as maintenance therapy.

Clinical symptoms were assessed at one-week, one-month, three-month, and six-month intervals after patients completed a symptom questionnaire. Ophthalmic examinations were performed, including intraocular pressure (IOP), visual acuity (VA), and fundoscopy.

The primary tool used to assess the treatment's effectiveness was a four-point scale analysis of changes in symptoms and signs. We used IBM SPSS Statistics 20.0 for Windows to analyze the data. After the continuous data was examined for normality, the results were presented as a range, mean, median, and standard deviation. We used either the Mann-Whitney U test or the student's *t*-test to assess the two groups, depending on how the data was distributed. ANOVA was employed to compare different

times. Pairwise comparisons were conducted using post hoc testing at a *P*-value of less than 0.05.

Results

The analysis comprised 60 children with bilateral vernal keratoconjunctivitis (VKC) who had completed the follow-up. In the Tacrolimus group, 80 % comprised males, and 20.0% comprised females. Among the Control group, 76.7% comprised males, and 23.3% comprised females. The mean age in the Tacrolimus group was 7.80 ± 3.10 years, compared to 8.48 ± 2.19 years in the Control group. Tarsal Form VKC was appreciated by 83.3% of the Tacrolimus group and 70.0% of the Control group. Mixed Form VKC was found in 16.7% and 30.0% of participants in the Tacrolimus and Control groups, respectively. The statistical analysis revealed an insignificant distinction (*P* = 0.238) between the two groups. (Table-1). Table-2 compares composite

Table-1: Baseline features of study patients

Variable	Intervention Group (n = 30)	Control Group (n = 30)	*Chi Square*	*P*-value
Gender			10.00	0.754
Male	24 (80%)	23 (76.7%)		
Female	6 (20%)	7 (23.3%)		
Age (years), Mean ± SD	7.80 ± 3.10	8.48 ± 2.19	-0.98	0.331
Tarsal Form VKC, n (%)	25 (83.3%)	21 (70.0%)	1.49	0.222
Mixed Form VKC, n (%)	5 (16.7%)	9 (30.0%)		

**chi-square test*

Table-2: Comparison of Composite Symptom Scores

Periods	Intervention Group (n=30)	Control Group (n=30)	Test Statistics	*P*-value
Baseline	17.60 ± 2.20	17.70 ± 1.35	-0.21	0.833
1 Month	8.80 ± 2.60	7.70 ± 1.30	2.07	0.043
3 Months	4.10 ± 2.00	4.90 ± 1.20	5.17	0.000
6 Months	2.00 ± 0.70	3.10 ± 0.80	-5.67	<0.001

**Mann-Whitney U test*

Table-3: Comparing the composite symptom scores at different study periods

Groups (Mean ± SD)	Composite Symptom Scores				*P-value*
	Baseline	1-Month	3-Month	6-Month	
Intervention Group	17.60 ± 2.20	8.80 ± 2.60	4.10 ± 2.00	2.00 ± 0.70	< 0.001
P0	-	-	< 0.001	< 0.001	
P1	0.003				-
P2	<0.001				-
P3	0.028				-
Control Group	17.70 ± 1.35	7.70 ± 1.30	4.90 ± 1.20	3.10 ± 0.80	< 0.001
P0	-	0.005	< 0.001	< 0.001	-
P1	0.004				-
P2	<0.001				-
P3	0.010				-

Abbreviations: SD = standard deviation; n = number. P-values less than 0.05 are bolded. P0 is the P-value for comparing each visit's results to the baseline. P1, P-value for visits lasting one to three months. P2, P-value for visits lasting one to six months

Table-4: Comparing the composite Sign Scores between the two groups

Periods	Intervention Group	Control Group	Tests Statistics	*P*-value
Baseline	8.80 ± 1.50	8.65 ± 1.45	0.39	0.695
1 Month	4.80 ± 1.00	4.30 ± 1.10	1.84	0.071
3 Month	2.50 ± 0.50	3.30 ± 0.70	-5.09	< 0.001
6 Month	1.30 ± 0.60	1.85 ± 0.70	-3.27	0.002

**Mann-Whitney U test*

symptom ratings among the tacrolimus & control groups across different periods. The time frames include baseline, one month, three months, and six months. In the baseline period, the tacrolimus group had a mean composite symptom score of 17.60 ±2.20, while the control group had a score of 17.70 ± 1.35, indicating no significant difference (*P* = 0.836). After one month, the tacrolimus group showed a mean score of 8.80 ± 2.60, compared to 7.70 ± 1.30 in the control group (*P*= 0.079). At 3 Months, the tacrolimus group exhibited a mean score of 4.10 ± 2.00, whereas the control group had a slightly higher mean score of 4.90 ± 1.20, showing a significant difference (*P* = 0.017). By 6 Months, the tacrolimus group demonstrated a substantial reduction in mean score to 2.00 ± 0.70, while the control group maintained a higher mean score of 3.10 ± 0.80, with a highly significant difference (*P* < 0.001). Table-3 compares the composite symptom scores at different study periods between the tacrolimus and control groups. For the tacrolimus group, the mean scores significantly decreased from Baseline (17.60 ± 2.20) to 1-month (8.80 ± 2.60), 3-month (4.10 ± 2.00), and 6-month (2.00 ± 0.70) periods (all *P*-values < 0.001). Similar significant reductions were observed in the control group, from baseline (17.70 ± 1.35) to 1-month (7.70 ± 1.30), 3-month (4.90 ± 1.20), and 6-month (3.10 ± 0.80) periods (all *P*-values < 0.001). Comparisons between periods within each group showed significant differences (P1 = 0.003, P2 < 0.001, P3 = 0.028 for tacrolimus; P1 = 0.004, P2 < 0.001, P3 = 0.010 for Control). Table-4 compares the composite sign scores between the two groups at different study periods. In the Tacrolimus group, the mean scores were 8.80 ± 1.50 at Baseline, 4.80 ± 1.00 at 1 Month, 2.50 ± 0.50 at 3 months, and 1.30 ± 0.60 at 6 months. For the control group, the mean scores were 8.65 ± 1.45 at baseline, 4.30 ± 1.10 at 1 Month, 3.30 ± 0.70 at 3 months, and 1.85 ± 0.70 at 6 months. The *P*-values for comparisons between the groups at each period are provided, indicating the significance of the differences observed.

The composite sign scores at different study periods within each group were also compared. Overall, the tacrolimus group's *P*-values for shifts from baseline to one month, three months, and six months were 0.008, < 0.001, and < 0.001, respectively. In the control group, the *P*-values for these changes are 0.007, < 0.001, and 0.046, respectively. These values denote the significance levels of the observed changes over time within each group.

The study also discovered that the tacrolimus and the control groups experienced significant improvements in ocular itching and redness, common symptoms of VKC, within two weeks of treatment initiation. However, itching persisted in all patients throughout the duration of the study. At the one-month assessment, the control group had a more substantial decrease in itching than the tacrolimus group. Nonetheless, by the six-month follow-up, the tacrolimus group saw a significant reduction in itching, suggesting tacrolimus's long-term efficacy in controlling juvenile VKC symptoms.

Discussion

The study's findings indicate a positive response to therapy in both groups, significantly reducing symptoms and VKC indicators.[11] Interestingly, the sole recorded negative outcome in the tacrolimus cohort was a temporary stinging sensation, well-tolerated and diminishing within a few days, contrasting with a single case of

elevated IOP in the control group, which was successfully managed.[12] Similar observations were reported by Brown et al., who noted a transient stinging sensation in their study participants.[13]

Consistent with previous research by Basu B et al., our data demonstrate considerable improvements in symptoms and indicators with tacrolimus treatment, particularly notable at three and six months compared to controls.[14] Samyukta et al. also had successful results in 89% of the study population after treatment with 0.03% tacrolimus, and none of the participants had adverse effects.[15] In Saha et al. there was a success rate of 88.88% in children treated with the 0.03% tacrolimus.[16] A 41 months follow-up in Muller et al. also showed a reduction and resolution of symptoms in 89% patients.[17]

These findings align with Eltagoury et al., who reported significant reductions in symptom scores with tacrolimus compared to alternative therapies.[10] Regarding signs, both study groups exhibited significant improvement at the 6-month follow-up compared to baselines. However, the tacrolimus group demonstrated more substantial improvements in sign scores at 3 and 6 months compared to the control group, consistent with findings reported by Eltagoury et al. and Hayakawa et al. Notably, both groups experienced a marked decrease in symptoms during the first month of treatment, with itching being particularly sensitive, consistent with prior studies.[10,18-20] Furthermore, significant improvements in symptoms, notably conjunctival hyperaemia and tarsal papillae, were observed within the first month of treatment, aligning with previous research.

The tacrolimus group demonstrated significant improvements in tarsal papillae after three months, with further enhancements in limbal swelling and tarsal papilla at six months of treatment, indicating tacrolimus's effectiveness in curing VKC symptoms.

While other studies found delayed or partial decreases in conjunctival papillae, our study found near-complete resolution in the tacrolimus group at the last month of follow-up. Overall, the study shows the efficacy and safety of topical tacrolimus (0.03%) ointment in controlling VKC, with minimal adverse reactions and significant benefits in symptoms and signs.[21] However, the study had a few limitations, including a small sample size, the absence of severity of illness assessment, and the absence of randomization. Future research should include double-blind studies with larger sample sizes and extended follow-up periods to validate these findings and assess the long-term efficacy of tacrolimus in treating VKC.

Conclusion

Our study underscores the effectiveness and safety of topical 0.03% tacrolimus ointment for treating vernal keratoconjunctivitis in the pediatric population. Tacrolimus demonstrated rapid symptom relief, particularly in alleviating itching, and significantly reduced symptoms and signs compared to the control group over six months. These findings highlight tacrolimus as a promising therapeutic option for vernal keratoconjunctivitis, offering sustained benefits with minimal side effects.

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Authors Contribution

MAC: Study designing, manuscript writing and proofreading

MSU: Data collection, data analysis, results and interpretation

MYT: Idea conception, data collection

RK: Study designing, data analysis, results and interpretation

SMH: Idea conception, data collection, data analysis, results and interpretation