Journal of Health and Rehabilitation Research 2791-156X JHRR

Original Article

Effect of Topical (0.03%) Tacrolimus Eye Ointment in the Management of Vernal Keratoconjunctivitis

Huzaifa Malik[1], Shagufta Parveen[1], Ijlal Taimoor[1], Umar Ijaz[1], Javeria Zahid[1], Shahzad Raza[1], Muhammad Farukh Habib[*2]

1. Resident Ophthalmology, Armed Forces Institute of Ophthalmology, Pak-Emirates Military Hospital, Rawalpindi., Pakistan
2. Department of Management Sciences, Shifa Tameer E Millat University Islamabad, Pakistan.

Corresponding author: : muhammadfarrukhhabib@gmail.com

Keywords: Topical Tacrolimus, Vernal Keratoconjunctivitis, Ocular Inflammation, Ophthalmic Treatment, Allergic Conjunctivitis

Abstract

Background: Vernal keratoconjunctivitis (VKC) is a chronic, severe ocular inflammatory disorder predominantly affecting children and young adults. Current treatments, including antihistamines and corticosteroids, can have significant side effects, particularly with long-term use. Tacrolimus, a macrolide immunosuppressant, has emerged as a promising alternative due to its ability to inhibit T-cell proliferation and cytokine release, key factors in VKC pathogenesis.

Objective: To determine the efficacy and safety of 0.03% tacrolimus eye ointment in the management of vernal keratoconjunctivitis compared to standard steroid-based treatment.

Methods: This quasi-experimental study was conducted at the Department of Ophthalmology, Pak-Emirates Military Hospital, Rawalpindi, from January 2022 to May 2024. A total of 40 patients (80 eyes) diagnosed with VKC were included. Patients aged 5 to 60 years with bilateral VKC and no prior treatment in the last month were enrolled. Exclusion criteria included concurrent eye infections, use of contact lenses, systemic comorbidities, and previous ocular surgeries. The intervention group received 0.03% tacrolimus ointment twice daily for two months, followed by once daily for two months, and then on alternate days for the final two months. The control group received a combination of 0.1% fluorometholone eye drops, 0.3% tobramycin/0.1% dexamethasone ointment, and 0.1% olopatadine, with steroid tapering after two weeks. Patients were followed up at two weeks, one month, three months, and six months. The primary outcome was the change in symptom and sign scores from baseline to six months. Data were analyzed using SPSS version 25, with statistical significance set at $p \leq 0.05$.

Results: The median age of the study population was 15.50 years (IQR: 10.00), with 57.4% female. The tacrolimus group showed significant improvement in eye discharge ($p=0.033$), itching ($p=0.004$), lacrimation ($p=0.008$), and foreign body sensation ($p=0.015$) compared to the control group. The average symptom score decreased more significantly in the tacrolimus group ($p<0.001$). Clinical signs such as punctate keratitis ($p=0.031$) and papillae ($p=0.018$) also showed greater resolution in the tacrolimus group, with a significant reduction in the average sign score ($p=0.009$).

Conclusion: Topical 0.03% tacrolimus eye ointment is an effective and safe treatment for VKC, providing superior symptom relief and clinical improvement compared to standard steroid-based therapy. It offers a promising alternative for long-term management of VKC, with fewer side effects than traditional corticosteroids.

1 Introduction

Vernal keratoconjunctivitis (VKC) is a chronic, severe, and often bilateral ocular inflammatory disorder that predominantly affects children and young adults. The prevalence of VKC varies significantly across different geographical regions, ranging from as low as 0.02% in the United States to as high as 11% in certain parts of Africa (1). VKC is characterized by intense itching, photophobia, tearing, and mucous discharge, which substantially impair the quality of life and, if left untreated, can lead to vision-threatening complications (2). Conventional management strategies for VKC typically involve the use of antihistamines, mast cell stabilizers, and corticosteroids. While these treatments are generally effective, they are associated with significant side effects, particularly with long-term use, which poses a challenge in the management of this chronic condition. The ongoing need to find safer, yet equally effective, treatment options has led to the exploration of alternative therapies (3).

Tacrolimus, a macrolide immunosuppressant initially utilized in organ transplantation, has emerged as a promising candidate for the treatment of various ocular surface diseases due to its ability to inhibit T-cell proliferation by binding to FK506 binding protein and subsequently inhibiting the calcineurin pathway (4, 5). The pathogenesis of VKC involves T-lymphocyte activation and cytokine release,

making tacrolimus an attractive therapeutic option given its mechanism of action that specifically targets these processes (6, 7). Traditionally, corticosteroids have been the mainstay for managing severe VKC, particularly in cases unresponsive to antihistamines and mast cell stabilizers. However, the long-term use of corticosteroids is fraught with potentially severe complications such as ocular hypertension and glaucoma, which can lead to permanent vision loss (8, 9). Recent studies have indicated that low-concentration topical formulations of tacrolimus could offer substantial relief from VKC symptoms with a reduced risk of adverse effects compared to corticosteroids, making it a potentially valuable alternative in clinical practice (10).

This study aims to evaluate the efficacy and safety of 0.03% tacrolimus eye ointment in the management of VKC, with a specific focus on balancing therapeutic benefits with minimal side effects. The choice of a 0.03% concentration is informed by the need to mitigate the risk of systemic absorption and local adverse reactions, which may increase with higher concentrations of the drug. By conducting this investigation, we seek to contribute to the growing body of evidence supporting the use of tacrolimus in ophthalmology, potentially establishing it as a new standard of care for VKC patients. This study is particularly significant as it addresses both the efficacy and safety profiles of tacrolimus 0.03% eye ointment, offering a balanced perspective that could influence future therapeutic protocols for VKC management. The findings of this research could have important implications for the treatment landscape of VKC, especially in cases where long-term management is necessary to prevent disease progression and maintain quality of life for affected individuals.

2 Material and Methods

This quasi-experimental study was conducted in the Department of Ophthalmology at Pak-Emirates Military Hospital, Rawalpindi, from January 2022 to May 2024, involving 40 patients (80 eyes) diagnosed with vernal keratoconjunctivitis (VKC). Ethical approval was obtained from the ethical committee of Pak-Emirates Military Hospital, Rawalpindi, and the study adhered strictly to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants before their inclusion in the study.

Participants were selected using consecutive, non-probability sampling. The inclusion criteria were patients aged between 5 and 60 years with a recent diagnosis of VKC affecting both eyes, as defined by the presence of seven symptoms: discharge, watering, photophobia, redness, itching, burning, and foreign-body sensation, along with five clinical signs: papillary hypertrophy, Horner–Trantas dots, hyperemia, limbal inflammation, and corneal involvement (11). Patients who had not received any treatment for VKC in the past month were eligible for the study. Exclusion criteria included concurrent eye infections, use of contact lenses, a history of systemic comorbidities, use of systemic immunosuppressive drugs, herpes keratitis, previous ocular surgery, known hypersensitivity to tacrolimus, the presence of cataracts, glaucoma, or congenital ocular anomalies.

Baseline assessments were performed for all patients, including comprehensive bilateral ocular examinations at each clinical visit. This included visual acuity assessment using a Snellen chart, slit-lamp examination with fluorescein staining, and intraocular pressure (IOP) measurement. Patients in the intervention group were treated with 0.03% tacrolimus topical ophthalmic ointment, applied twice daily for the first two months, then reduced to once daily for another two months, and finally on alternate days for the last two months, for a total of six months of treatment. Patients in the control group received topical 0.1% fluorometholone eye drops three times daily for two weeks, along with a 0.3% tobramycin/0.1% dexamethasone eye ointment and 0.1% olopatadine twice daily. A steroid taper was initiated after two weeks of treatment. Upon resolution of symptoms, patients were placed on maintenance therapy with olopatadine alone, maintaining the aforementioned dosage until the completion of six months. In cases of symptom exacerbation, 0.1% dexamethasone eye ointment was resumed for another two weeks before tapering. All patients were followed up at two weeks, and at one, three, and six months post-treatment initiation.

The primary outcome measure was the change in individual symptom and sign scores from baseline to the end of the treatment period. Symptoms were graded according to a standardized scoring system (Table-I), and signs were graded similarly (Table-II). Patient compliance with the treatment regimen was assessed at each visit through patient diaries and by counting the remaining ointment. Patients were also monitored for the development of any side effects, such as burning, stinging, or discomfort during application.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA). Quantitative variables, including patient age and individual symptoms and sign scores, were reported as mean ± standard deviation or median with interquartile range, as appropriate. Qualitative variables, such as gender and type of VKC, were documented as frequencies and percentages. Comparisons of qualitative data between the two groups were performed using the Chi-square test or Fisher's exact test, while quantitative data were compared using the independent samples t-test or Mann-Whitney U test, depending on the distribution of the data. Normality was assessed using the Shapiro-Wilk test. A p-value of ≤0.05 was considered statistically significant.

All data collection and analysis procedures were conducted in accordance with ethical standards, ensuring the integrity and reliability of the study's findings. The rigorous methodology employed in this study aimed to provide robust and generalizable results to inform future clinical practice in the management of VKC.

3 Results

This study included 40 patients, encompassing 80 eyes, who were diagnosed with vernal keratoconjunctivitis (VKC). The median age of the participants was 15.50 years (IQR: 10.00), with 23 (57.4%) being female. The distribution of VKC subtypes revealed that 31 patients (77.5%) had the tarsal form, while 9 patients (22.5%) exhibited the mixed subtype. No significant differences were observed in baseline characteristics, including age, gender, and VKC subtype, between the tacrolimus and control groups, ensuring comparability (Table 1).

Table 1: Baseline Characteristics and Pre-treatment Symptom and Sign Scores by Group (n=40 patients, n=80 eyes)

Variable	Tacrolimus Group (n=40)	Control Group (n=40)	p-value
Age (years) (Median, IQR)	14.00 (9.00)	16.50 (9.00)	0.495
Gender			0.749
- Male	9 (45.0%)	8 (40.0%)	
- Female	11 (55.0%)	12 (60.0%)	
Type of VKC			0.451
- Tarsal	14 (70.0%)	17 (85.0%)	
- Mixed	6 (30.0%)	3 (15.0%)	
Pre-treatment Symptom Scores (Median, IQR)			
- Burning	2.00 (0.00)	2.00 (2.00)	0.628
- Discharge	2.00 (1.00)	2.00 (1.00)	0.346
- Itching	2.00 (1.00)	2.00 (1.00)	0.857
- Photophobia	2.00 (2.00)	2.00 (1.00)	0.885
- Redness	2.00 (1.00)	2.00 (0.00)	0.891
- Lacrimation	2.00 (0.00)	2.00 (1.00)	0.633
- Foreign body sensation	2.00 (0.00)	2.00 (1.00)	0.291
- Average symptom score	2.00 (0.43)	2.00 (0.28)	0.884
Pre-treatment Sign Scores (Median, IQR)			
- Hyperemia	2.00 (1.00)	2.00 (2.00)	0.996
- Horner–Trantas dots	2.00 (1.00)	2.00 (1.00)	0.764
- Limbal inflammation	2.00 (1.00)	2.00 (2.00)	0.889
- Punctate keratitis	2.00 (2.00)	2.00 (0.00)	0.978
- Papillae	2.00 (0.00)	2.00 (1.00)	0.601
- Average sign score	1.87 (0.42)	2.04 (0.42)	0.686

After the six-month treatment period, the tacrolimus group exhibited significant improvements in both symptoms and clinical signs compared to the control group. The tacrolimus group demonstrated superior resolution of symptoms such as eye discharge (p=0.033), itching (p=0.004), lacrimation (p=0.008), and foreign body sensation (p=0.015). Additionally, the reduction in the average symptom score was significantly greater in the tacrolimus group (p<0.001) (Table 2).

Table 2: Post-treatment Symptom and Sign Scores by Group (n=40 patients, n=80 eyes)

Variable	Tacrolimus Group (n=40)	Control Group (n=40)	p-value
Post-treatment Symptom Scores (Median, IQR)			
- Burning	0.00 (1.00)	0.00 (1.00)	0.364
- Discharge	0.00 (1.00)	1.00 (1.00)	0.033
- Itching	0.00 (1.00)	1.00 (1.00)	0.004
- Photophobia	0.00 (1.00)	0.00 (1.00)	0.167
- Redness	0.00 (0.00)	0.00 (1.00)	0.146
- Lacrimation	0.00 (1.00)	1.00 (1.00)	0.008
- Foreign body sensation	0.00 (0.00)	0.00 (1.00)	0.015
- Average symptom score	0.29 (0.29)	0.57 (0.28)	<0.001
Post-treatment Sign Scores (Median, IQR)			
- Hyperemia	0.00 (1.00)	0.00 (1.00)	0.457
- Horner–Trantas dots	0.00 (1.00)	0.00 (1.00)	0.902
- Limbal inflammation	0.00 (1.00)	0.00 (1.00)	0.602
- Punctate keratitis	0.00 (1.00)	0.50 (1.00)	0.031

- Papillae	0.00 (1.00)	0.50 (1.00)	0.018
- Average sign score	0.40 (0.35)	0.60 (0.20)	0.009

In terms of clinical signs, the tacrolimus group showed significantly greater improvements in the resolution of punctate keratitis (p=0.031) and papillae (p=0.018) compared to the control group. Furthermore, the reduction in the average sign score was significantly more pronounced in the tacrolimus group (p=0.009). These findings indicated that tacrolimus was more effective than the standard steroid-based treatment in both reducing the subjective symptoms and improving the clinical signs associated with VKC.

The results clearly supported the hypothesis that 0.03% tacrolimus eye ointment provides superior clinical benefits in the management of VKC, with significant improvements observed in both symptom relief and the resolution of clinical signs compared to the control group. No significant adverse effects were reported in either group, underscoring the safety and tolerability of tacrolimus in this patient population.

4 Discussion

The findings of this study demonstrated that 0.03% tacrolimus eye ointment significantly outperformed standard steroid-based treatment in managing vernal keratoconjunctivitis (VKC), both in terms of symptom relief and the resolution of clinical signs. The results aligned with previous studies that highlighted the potential of tacrolimus as a safer and more effective alternative to corticosteroids, particularly in chronic conditions like VKC where long-term treatment is often required. The study showed significant improvement in key symptoms such as eye discharge, itching, lacrimation, and foreign body sensation, alongside a notable reduction in clinical signs like punctate keratitis and papillae. These outcomes suggested that tacrolimus not only addressed the subjective discomfort associated with VKC but also effectively reduced the underlying inflammatory response, thus providing a comprehensive management strategy for this condition.

Previous studies have supported the efficacy of tacrolimus in VKC management, with several reporting outcomes similar to those observed in the current research. For instance, Arnon et al. found that tacrolimus provided at least equivalent efficacy to corticosteroid therapy, particularly in patients with severe VKC who had not responded well to other treatments (13). Similarly, Samyukta et al. reported a significant reduction in both signs and symptoms of VKC with tacrolimus, with a large majority of patients showing substantial improvement without the need for corticosteroid rescue therapy (14). Eltagoury et al. also noted that tacrolimus resulted in greater improvements in symptom and sign scores compared to standard anti-allergic and corticosteroid therapy, which echoed the findings of the current study (11). These consistent results across different studies underscored the reliability of tacrolimus as an effective treatment for VKC, especially for patients requiring long-term therapy.

However, despite its promising results, the study had several limitations that warrant consideration. The relatively small sample size may have limited the generalizability of the findings, and the quasi-experimental design, although useful in clinical settings, lacked the rigor of randomized controlled trials (RCTs). This design could have introduced selection bias, which may have influenced the results. Additionally, the study's follow-up period was relatively short, making it challenging to assess the long-term efficacy and safety of tacrolimus. VKC is a chronic condition that often requires extended treatment and monitoring, so longer follow-up periods would be necessary to evaluate the sustainability of the benefits observed and to monitor for any delayed adverse effects. Moreover, adherence to the treatment regimen was self-reported, which could have introduced reporting bias and variability in compliance, potentially affecting the outcome measures.

Despite these limitations, the study had several strengths, including its comprehensive assessment of both symptoms and clinical signs, which provided a thorough evaluation of tacrolimus's efficacy in VKC management. The study also maintained strict adherence to ethical guidelines and utilized well-established scoring systems for symptom and sign assessment, ensuring the reliability and validity of the findings. Furthermore, the study contributed valuable data to the growing body of evidence supporting the use of tacrolimus in ophthalmology, particularly in the management of chronic inflammatory ocular conditions like VKC.

In light of these findings, tacrolimus appeared to offer a promising alternative to traditional corticosteroid therapy in the management of VKC, especially for patients at risk of steroid-related side effects or those requiring long-term treatment. Future research should focus on larger, randomized controlled trials with longer follow-up periods to confirm these findings and to establish a more comprehensive understanding of tacrolimus's long-term safety and efficacy profiles. Additionally, studies could explore different concentrations of tacrolimus to determine the optimal dose that balances therapeutic efficacy with minimal side effects, particularly in patients with severe or steroid-resistant VKC. By addressing these aspects, future research could further solidify the role of tacrolimus as a key component in the therapeutic arsenal against VKC, ultimately improving patient outcomes and quality of life.

5 Conclusion

In The study concluded that 0.03% tacrolimus eye ointment is an effective and safe treatment for vernal keratoconjunctivitis, providing superior relief of symptoms such as eye discharge, itching, and lacrimation, as well as significant improvement in clinical signs like

punctate keratitis and papillae resolution, compared to standard steroid-based therapy. These findings suggest that tacrolimus could serve as a valuable alternative for long-term management of VKC, aligning with the study's objective to assess its efficacy and safety.

6 References

1. Ali A, Bielory L, Dotchin S, Hamel P, Strube YN, Koo EB. Management of Vernal Keratoconjunctivitis: Navigating a Changing Treatment Landscape. Surv Ophthalmol. 2024;69(2):265-78.
2. Bruschi G, Ghiglioni DG, Cozzi L, Osnaghi S, Viola F, Marchisio P. Vernal Keratoconjunctivitis: A Systematic Review. Clin Rev Allergy Immunol. 2023;65(2):277-329.
3. Mehta JS, Chen WL, Cheng AC, Cung LX, Dualan IJ, Kekunnaya R, et al. Diagnosis, Management, and Treatment of Vernal Keratoconjunctivitis in Asia: Recommendations From the Management of Vernal Keratoconjunctivitis in Asia Expert Working Group. Front Med (Lausanne). 2022;9:882240.
4. Araya AA, Tasnif Y. Tacrolimus. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544318/
5. Erdinest N, Ben-Eli H, Solomon A. Topical Tacrolimus for Allergic Eye Diseases. Curr Opin Allergy Clin Immunol. 2019;19(5):535-43.
6. Brindisi G, Cinicola B, Anania C, De Castro G, Nebbioso M, Miraglia Del Giudice M, et al. Vernal Keratoconjunctivitis: State of Art and Update on Treatment. Acta Biomed. 2021;92(S7)
7. Sacchetti M, Plateroti R, Bruscolini A, Giustolisi R, Marenco M. Understanding Vernal Keratoconjunctivitis: Beyond Allergic Mechanisms. Life (Basel). 2021;11(10):1012.
8. Senthil S, Thakur M, Rao HL, Mohamed A, Jonnadula GB, Sangwan V, et al. Steroid-Induced Glaucoma and Blindness in Vernal Keratoconjunctivitis. Br J Ophthalmol. 2020;104(2):265-9.
9. Sen P, Jain S, Mohan A, Shah C, Sen A, Jain E. Pattern of Steroid Misuse in Vernal Keratoconjunctivitis Resulting in Steroid-Induced Glaucoma and Visual Disability in Indian Rural Population: An Important Public Health Problem in Pediatric Age Group. Indian J Ophthalmol. 2019;67(10):1650-5.
10. Yoon CH, Park JW, Ryu JS, Kim MK, Oh JY. Corneal Toxicity of Topical Tacrolimus Ointment in Mice With Corneal Epithelial Injury. J Ocul Pharmacol Ther. 2018;34(10):685-91.
11. Eltagoury M, Abou Samra W, Ghoneim E. Safety and Efficacy of Topical Tacrolimus 0.03% in the Management of Vernal Keratoconjunctivitis: A Non-Randomized Controlled Clinical Trial. Med Hypothesis Discov Innov Ophthalmol. 2022;11(2):52-63.
12. Zicari AM, Capata G, Nebbioso M, De Castro G, Midulla F, Leonardi L, et al. Vernal Keratoconjunctivitis: An Update Focused on Clinical Grading System. Ital J Pediatr. 2019;45(1):64.
13. Arnon R, Rozen-Knisbacher I, Yahalomi T, Stanescu N, Niazov Y, Goldberg D, et al. When to Start Tacrolimus Ointment for Vernal Keratoconjunctivitis? A Proposed Treatment Protocol. Int Ophthalmol. 2022;42(6):1771-80.
14. Samyukta SK, Pawar N, Ravindran M, Allapitchai F, Rengappa R. Monotherapy of Topical Tacrolimus 0.03% in the Treatment of Vernal Keratoconjunctivitis in the Pediatric Population. J AAPOS. 2019;23(1):36.e1-36.e5.
15. Sharjeel M, Iqbal U, Jabran A, Mehmood A, Mohiuddin M. Efficacy of Single Dose Dermatological 0.1% Tacrolimus Ointment in the Treatment of Vernal Keratoconjunctivitis. J Pak Med Assoc. 2022;72(9):1694-8.
16. Fiorentini SF, Khurram D. Therapeutic Effects of Topical 0.03% Tacrolimus Ointment in Children With Refractory Vernal Keratoconjunctivitis in Middle East. Saudi J Ophthalmol. 2019;33(2):117-20.
17. Wan Q, Tang J, Han Y, Wang D, Ye H. Therapeutic Effect of 0.1% Tacrolimus Eye Drops in the Tarsal Form of Vernal Keratoconjunctivitis. Ophthalmic Res. 2018;59(3):126-34.
18. Liu FY, Liu HY, Chu HS, Chen WL, Hu FR, Wang IJ. Dermatologic Tacrolimus Ointment on the Eyelids for Steroid-Refractory Vernal Keratoconjunctivitis. Graefes Arch Clin Exp Ophthalmol. 2019;257(5):967-74.
19. Saha BC, Kumari R, Ambasta A. Comparison of Efficacy and Safety of 0.03% and 0.1% Tacrolimus Ointment in Children With Vernal Keratoconjunctivitis. Ther Adv Ophthalmol. 2023;15:25158414231173532.
20. Müller GG, José NK, de Castro RS, de Holanda EC. Long-Term Use of Topical Tacrolimus Ointment: A Safe and Effective Option for the Treatment of Vernal Keratoconjunctivitis. Arq Bras Oftalmol. 2019;82(2):119-23.

Disclaimers	
Author Contributions	All authors contributed significantly to this work. Dr. Huzaifa Malik designed the study and conducted the experiments, while Dr. Shagufta Parveen analyzed the data and wrote the manuscript. Dr. Ijlal Taimoor, Dr. Umar Ijaz, Dr. Javeria Zahid, and Dr. Shahzad Raza assisted in data collection and interpretation. Muhammad Farrukh Habib provided critical revisions and oversight of the manuscript preparation.
Conflict of Interest	The authors declare that there are no conflicts of interest.
Data Availability	Data and supplements available on request to the corresponding author.
Funding	NA
Ethical Approval	Institutional Review Board (IRB) Pak-Emirates Military Hospital.
Trial Registration	NA
Acknowledgments	NA

~ JHRR, ISSN: 2791-156X ~