



**ASJO**

ISSN 3006-2543 (Online)

ISSN 1990-3863 (Print)

# **AL-SHIFA JOURNAL OF OPHTHALMOLOGY**

An Open Access, Peer Reviewed, Quarterly Journal of  
AL-SHIFA TRUST EYE HOSPITAL

**Vol. 19, No. 3, July – September 2023**

Indexed in

WHO Index Medicus (IMEMR)

Asian Digital Library (ADL)

Pak Medinet

Pakistan Medical and Dental Council IP/033

ISSN 3006-2543 (Online)  
ISSN 1990-3863 (Print)

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# Al-Shifa Journal of Ophthalmology

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Vol. 19, No. 3, July – September 2023

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- **Editorial: Challenges in Communicating Glaucoma Prognosis**
- **Aqueous vs. Vitreous Tap in Endophthalmitis Diagnosis**
- **Retinal Nerve Fibre Layer Thickness in Pediatric Population**
- **Gas versus Air Tamponade in Pars Plana Vitrectomy**
- **Tacrolimus in Refractory Vernal Keratoconjunctivitis**
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## Al-Shifa Journal of Ophthalmology

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# Efficacy of 0.03% Tacrolimus in Refractory Vernal Keratoconjunctivitis

Afia Matloob Rana<sup>1</sup>, Sidra Jabeen<sup>2</sup>, Sidra Fatima<sup>2</sup>

## Abstract:

**Objective:** To determine the efficacy of 0.03% tacrolimus in the management of refractory vernal keratoconjunctivitis.

**Methodology:** In this quasi-experimental study, the data of 152 patients who presented with “refractory vernal keratoconjunctivitis (VKC)” was collected through “non-probability consecutive sampling” technique. Baseline characteristics including age, gender, duration of disease and baseline OSS score were documented. Patients were treated with 0.03% tacrolimus and post-therapy OSS scores were assessed at week 4 and week 12. To determine the efficacy of 0.03% tacrolimus, the frequency of “treatment success” was measured. Data was analyzed using SPSS version 22.

**Results:** Mean age of the study participants was  $13.48 \pm 5.22$  years. 98 (64.47%) of the patients were males and remaining 54 (35.53%) patients were female. Mean baseline OSS score was  $20.93 \pm 2.34$ . Mean OSS score after 4 weeks of therapy was  $14.87 \pm 2.32$  and after 12 weeks of therapy was  $7.59 \pm 3.49$ . Frequency of “treatment success” was 124 (81.58%). Conclusion: 0.03% tacrolimus is an efficacious therapeutic option to treat patients with “refractory vernal keratoconjunctivitis (VKC)”.

**Conclusion:** In conclusion, 0.03% topical tacrolimus provides successful treatment of refractory “vernal keratoconjunctivitis (VKC)” in 81.58% which shows that it is a highly useful and efficacious mode of intervention to manage this vision threatening ocular condition. *Al-Shifa Journal of Ophthalmology 2023; 19(3): 115-120. © Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan.*

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Originally Received: 05 April 2023

Revised: 27 May 2023

Accepted: 30 May 2023

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## Introduction:

One of the commonly encountered ocular conditions involving the external surface of the eye is “vernal keratoconjunctivitis (VKC)” which usually presents asymmetrically with bilateral eye involvement and can be of varying grades of severity affecting both the younger and the adult population.<sup>1</sup> In pediatric population, the prevalence of “vernal keratoconjunctivitis (VKC)” have been reported to range from 11.10% to 32.9%.<sup>1</sup> Among the adult population, a study reported the prevalence of this common ocular disease at 10.4%.<sup>3</sup> When it comes to pathogenesis of “vernal keratoconjunctivitis (VKC)” it is not well understood and is controversial at best. Literature states that allergy mediated by IgE, atopy, Th2 helper cell mediated inflammation, eosinophilic infiltration of the diseased ocular surface and systemic inflammatory response mediated by “high



mobility group 1 (HMGB1)” and its “receptor for the advanced glycation end product (sRAGE)” are few pathophysiological processes that possibly mediate this disease process.<sup>4</sup>

Clinically patients who have “vernal keratoconjunctivitis (VKC)” present with a myriad of symptoms and signs including photophobia, itching in the eye, excessive tearing, sensation of burning/foreign body in the eye, presence of “Tranta dots”, shield ulcers, “punctate keratitis” and macroerosions.<sup>5</sup> Diagnosis of “vernal keratoconjunctivitis (VKC)” is through a careful clinical assessment of the eye through a detailed history and careful slit lamp examination.<sup>6</sup> Management of “vernal keratoconjunctivitis (VKC)” is largely symptomatic which primarily involves avoidance of any possible offending agent acting as an “allergen”, using commercially available ocular lubricants (like artificial tears) and certain agents like immune modulators (e.g.; cyclosporine A), prostaglandin inhibitors, alpha-agonists, anti-histamines, steroids, mast cell stabilizers and NSAIDs.<sup>6, 7</sup> However, in certain cases, where disease is severe, sight-threatening and refractory, steroids become best choice of drug but their long-term use is associated with certain adverse effects including formation of cataracts, increased propensity to develop infection and glaucoma.<sup>8</sup> Therefore, an alternative therapeutic agent needs to be evaluated that can be used to treat refractory “vernal keratoconjunctivitis (VKC)”.

One such therapeutic option that has been considered and is undergoing research as a suitable option to manage refractory “vernal keratoconjunctivitis (VKC)” is topical formulation of “tacrolimus” which is a “calcineurin inhibitor” that primarily acts by blocking the activation of T-lymphocytes.<sup>9</sup>

This study, therefore, focused on determining the efficacy of 0.03% tacrolimus in management of refractory “vernal keratoconjunctivitis (VKC)”. This may contribute to the addition of information regarding an effective alternate drug to manage refractory “vernal keratoconjunctivitis (VKC)”.

### **Materials and Methods:**

The quasi-experimental study was conducted at HBS Medical and Dental College, Islamabad from 6<sup>th</sup> March 2022 to 5<sup>th</sup> January 2024 after obtaining approval from the ethical review board of institution. For the calculation of appropriate sample size for the study, WHO sample size calculator was used by assuming “confidence interval of 95%”, “absolute precision of 5%” and “anticipated frequency of success rate of tacrolimus of 88.88%”<sup>10</sup> using following formula<sup>11</sup>. Calculation gave the sample size of 152 patients selected for the study through “non-probability consecutive sampling” technique. Patients of age  $\geq 5$  years, both males and females, who had refractory “vernal keratoconjunctivitis (VKC)” were included in the study. Patients who had a previous history of treatment of VKC by tacrolimus, presence of red flags of VKC, those who had hypersensitivity to tacrolimus, those who had any recent ocular surgery, were immunocompromised, ongoing ocular infection and pregnant females were excluded from the study. After inclusion in the study, baseline characteristics of the patients including age (in years), gender, duration of disease and “Ocular Symptom and Signs (OSS) score” was documented. OSS score utilized in present study was obtained from a study conducted by Al-Amri et al.<sup>12</sup> given below in figure 1:

Scores	0	1	2	3
<b>Symptoms</b>				
Itching	No need to rub the eyes	Occasional need to rub the eyes	Frequent need to rub the eyes	Constant need to rub the eyes
Redness	Absent	Detected only on close observation	Detected from near	Detected from far
Watering	Normal tear production	Watery sensation but no spilling of tears	Intermittent, infrequent spilling of tears	Constant/nearly constant spilling of tears
Discharge	No discharge	Small amount of mucoid discharge in lower cul-de-sac	Moderate amount of mucoid discharge in the lower cul-de-sac	Eyelids tightly matted, requiring frequent cleaning
Burning	Absent	Mild	Moderate	Severe
Photophobia	Absent	Intolerance to sunlight but can open the eyes	Intolerance to sunlight such that cannot keep the eyes open for long time	Intolerance to sunlight resulting in avoidance and inability to open the eyes at all
<b>Signs</b>				
Congestion	None to few dilated blood vessels	Dilatation of some blood vessels	Dilatation of many blood vessels	Diffuse dilatation
Tarsal conjunctival papillary hypertrophy	No evidence of papillae formation	Mild papillary hyperemia	Moderate papillary hypertrophy with edema of the palpebral conjunctiva	Severe papillary hypertrophy obscuring the visualization of the deep tarsal vessels
Cobblestone papillae	No evidence of cobblestone formation	Few cobblestones	Many cobblestones	Numerous cobblestones
Limbal inflammation or hypertrophy	Absent thickening/no Tranta dots	Thickening with <1/2 limbus with/without few Tranta dots	Thickening >1/2 limbus but not whole with/without many Tranta dots	Thickening of entire limbus with/without many Tranta dots
Corneal staining (with fluorescein)	Absent	Few scattered or 1 quadrant	More than 1 quadrant but fine	Diffuse or coarse superficial punctate keratitis

Figure 1: “Ocular Symptom and Signs (OSS) score”<sup>12</sup>

Treatment was offered to all 152 patients in the form of “0.03% tacrolimus” eye ointment. All the patients were guided to put a “rice grain-sized” amount in both eyes on the “lower conjunctival cul-de-sac” every eight hours followed by five minutes of eye closure. This practice was to be performed for 12 weeks. Since, in most cases “vernal keratoconjunctivitis (VKC)” is asymmetrical, left eye was chosen for study. Patients were instructed to follow up at week 4 and 12 of therapy and on each visit OSS score was documented. Efficacy was measured based on frequency of “treatment success” which was defined as “≥ 50% reduction in OSS score from baseline”. In case of “treatment failure”, appropriate alternative care depending upon consensus of patient and consultant ophthalmologist was provided.

“Data was analyzed by using Statistical Package for Social Sciences (SPSS) 22.00. Quantitative data (age, duration of disease and OSS score) was represented using mean ± standard deviation. Qualitative data (gender and treatment success) was represented by using percentage and frequency. To compare baseline, week 4- and 12-weeks post-therapy OSS scores, Student t-test was used. A p-value of ≤ 0.05 was considered as statistically significant”.

**Results:**

A total of 152 patients were included in the study. Mean age of the study participants was 13.48 ± 5.22 years. 98 (64.47%) of the patients were males and remaining 54 (35.53%) patients were female. Mean duration of VKC was 11.61 ± 3.18 weeks. Mean baseline OSS score was 20.93 ± 2.34. Baseline characteristics of study population are tabulated below in table I:

Table 1: Baseline characteristics (n = 152)

Parameter	n (%)
Mean age	13.48 ± 5.22 years
Gender	
Male	98 (64.47%)
Female	54 (35.53%)
Mean duration of VKC	11.61 ± 3.18 weeks
Baseline OSS score	20.93 ± 2.34

Mean OSS score after 4 weeks of therapy was  $14.87 \pm 2.32$  and after 12 weeks of therapy was  $7.59 \pm 3.49$ . Frequency of

“treatment success” was 124 (81.58%); [figure 2].

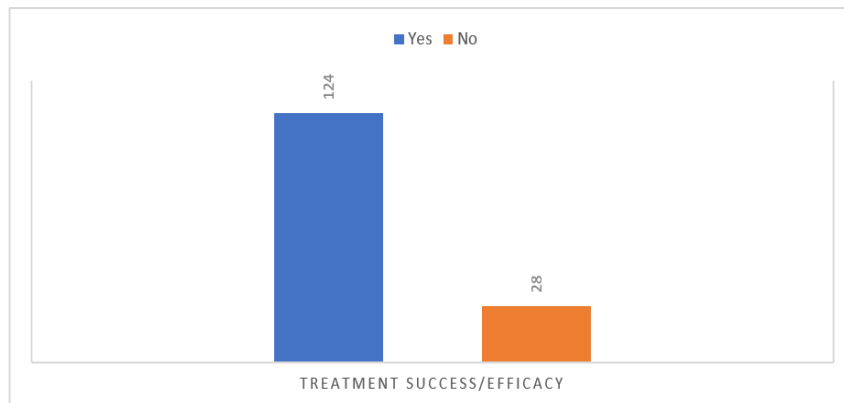


Figure 2: Frequency of treatment success (n = 152)

### Discussion:

Poorly treated, first line therapy refractory and long standing “vernal keratoconjunctivitis (VKC)” cases are highly vulnerable to poor visual outcomes since there is a high chance of irreversible loss of vision.<sup>13, 14</sup> Mechanism by which vision is threatened in “vernal keratoconjunctivitis (VKC)” is development of high-grade ulcers on the surface of cornea that may result in permanent damage to corneal surface.<sup>15</sup> For this purpose, it is essential to provide appropriate and timely treatment for this vision threatening ocular pathology. This study focused on efficacy of one such intervention i.e., topical tacrolimus 0.03% in management of refractory “vernal keratoconjunctivitis (VKC)”.

In this study, average age of the patients was approximately  $13.48 \pm 5.22$  years which was similar to what has been reported in a study conducted by Lambiase et al.<sup>16</sup> who reported mean age of patients having VKC to be  $13.8 \pm 8.8$  years. Majority of the patients who had “vernal keratoconjunctivitis (VKC)” were males with a male-to-female ratio of 1.9:1. This was congruent with the findings of a study conducted by Ghigliani et al.<sup>17</sup> and Brindisi et al.<sup>18</sup> both of which reported that male-to-

female ratio regarding VKC prevalence ranges from 2:1 to 4:1. One of the major finding of present study was that use of topical tacrolimus resulted in significant reduction of mean OSS score from the baseline at week 4 ( $p < 0.001$ ) and week 12 ( $p < 0.001$ ) after therapy. This was congruent with the findings of studies conducted by Saha et al.<sup>10</sup>, Fiorentini et al.<sup>19</sup>, Imtiaz et al.<sup>20</sup> and Chatterjee et al.<sup>21</sup> all of which had similar results. In terms of “treatment success” present study found it to be achieved in 81.58%. This was similar to what has been reported in studies conducted by multiple studies.<sup>10, 21</sup>

Present study shows that 0.03% tacrolimus is a highly useful intervention to manage patients who have refractory “vernal keratoconjunctivitis (VKC)”. Based on this, it can be safely recommended to be used to effectively treat refractory VKC cases in future. However, this study reported findings only for the short term for which we suggest that it is essential to determine long term effects and outcomes of topical tacrolimus use in refractory cases of “vernal keratoconjunctivitis (VKC)”. For this purpose, it is recommended to conduct further studies that primarily focus on the long-term outcomes of use of 0.03% topical tacrolimus.

**Conclusion:**

In conclusion, 0.03% topical tacrolimus provides successful treatment of refractory “vernal keratoconjunctivitis (VKC)” in 81.58% which shows that it is a highly useful and efficacious mode of intervention to manage this vision-threatening ocular condition.

**Limitations**

Single center study, limited sample size, short follow up period and absence of control arm were few limitations of this study.

**Conflict of interest**

None.

**Source of funding**

None.

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 Critical Revision: Afia Matloob Rana