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Tacrolimus 0.03% Vs Steroids Topical Eye Drops in Vernal Keratoconjunctivitis

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ABSTRACT

Background: Vernal keratoconjunctivitis (VKC) is a persistent allergic eye condition that affects children and young adults. This research compares the effectiveness and safety of topical tacrolimus 0.03% to corticosteroids in its therapy. **Objective:** To compare treatment regimens of tacrolimus and topical steroids for VKC and suggest a treatment protocol according to our clinical experience. **Patients and Methods:** A prospective randomized comparative clinical study involved 32 eyes of patients diagnosed with active VKC (acute or chronic) needing treatment who attended to Ophthalmology Outpatient Clinic of Menoufia University and Berket Elsabaa Hospitals during March 2024 till March 2025. All studied patients randomly assigned to Group (A) included 16 patients who received Tacrolimus (0.03%) and lubricant topical eye drops (normal saline) and Group (B) included 16 patients who received topical steroids and lubricant eye drops along with cold compression for 6 weeks.

Results: grading of symptoms significantly lower frequent among patients who received Tacrolimus (0.03%) and lubricant topical eye drops compared to those patients who received topical steroids after 1, 2, and 4 weeks of treatment ($p<0.05$). However, it started to gradually become absent and matched after 6 and 8 weeks of treatment ($p=1.00$). Grading of conjunctival hyperemia was less common among patients who received Tacrolimus and lubricant topical eye drops compared to those patients who received topical steroids after 1, 2, and 4 weeks of treatment, but the differences between them did not reach significant level ($p>0.05$), it started to gradually absent and match after 6 and 8 weeks of treatment ($p=1.00$). **Conclusion:** Both treatment modalities significantly improved clinical signals and symptoms. However, Tacrolimus showed a more rapid and sustained reduction in symptom scores (TSSS and TOSS) during the early treatment phase (weeks 1–4), particularly in ocular irritation and conjunctival hyperemia, without significantly increasing adverse effects or intraocular pressure.

Keywords: Eye Drops, Vernal keratoconjunctivitis, Steroids, Topical, symptom scores, Tacrolimus 0.03%.

INTRODUCTION

Children and young people are most affected by VKC, a severe, chronic type of allergic conjunctivitis that is aggravated by the seasons. VKC is regarded as a type 1 hypersensitivity reaction linked to mast cell activation in conjunctival tissue mediated by IgE. Furthermore, VKC could be an eye surface disease, according to current research [(1)]. VKC is diagnosed by reviewing the patient's clinical history and symptoms. There is no consensus grading system; however numerous scales have been devised that focus on the severity of symptoms, ranging from minimal inflammatory changes to severe alterations [(2)].

The palpebral type is distinguished by enormous tarsal papillae, often referred to as cobblestone papillae, which range in size from 1 to 7–8 mm. Conjunctival hyperemia, a kind of limbal nodule that manifests as gray, jelly-like, raised lumps with vascular centers, is a part of the limbal form. The elevated lesion may have Horner-Trantas dots, which are distinctive, white cores packed with eosinophils and epithelioid cells. The clinical manifestations of the other two types are present in the mixed type. Sometimes called a fourth type of VKC, corneal involvement involves gelatinous limbal enlargement, plaque development, epithelium macroerosions, and superficial punctate keratitis. Up to 11% of cases that go untreated might develop into shield ulcers, which are oval-shaped corneal epithelial defects [(3)]. Antihistamines, mast cell stabilizers, dual-acting medicines, corticosteroids, and immunomodulators or immunosuppressants are among the medications now used to treat VKC. It can be extremely difficult to restore vision in eyes with severe and protracted allergic eye disorders like VKC or AKC. Topical corticosteroids are the mainstay of treatment since topical antihistamines and mast cell stabilizers are frequently ineffective [(4)]. Topical corticosteroids were the cornerstone of treatment for severe allergic ocular conditions until recently. For moderate-to-severe types of allergic ocular disorders, topical corticosteroids are an effective treatment that significantly reduces acute symptoms and indicators [(5)].

Because long-term use of topical corticosteroids can lead to serious side effects and complications, including the development of posterior subcapsular cataracts, glaucoma, and secondary infections, like bacterial or fungal infections after prolonged steroid exposure, their use should be strictly limited and closely monitored. Thus, topical contamination seems to be more suitable for short-term therapy regimens [(6)].

In terms of how it works, tacrolimus is similar to cyclosporine A, but it is 100 times more potent. Analysis of long-term research shows that topical tacrolimus has a high safety profile and was well tolerated. Topical tacrolimus in various forms and doses has been evaluated for the treatment of long-term allergic eye conditions. VKC and steroid-resistant refractory VKC can be safely and effectively treated with topical 0.03% tacrolimus eye drop; nevertheless, long-term care is required to manage the condition [(7)].

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Hypertension, hyperglycemia, and renal damage are among the adverse consequences of systemic tacrolimus [8]. Due to its extremely low serum concentrations, tacrolimus should not produce these systemic adverse effects when given topically. When topical tacrolimus is applied to the skin or the eye, the main adverse effect is a burning sensation. Tacrolimus ointment at doses of 0.03 or 0.1% was assessed in a number of investigations using vehicle control [9]. According to this study, about half of the patients undergoing a 12-week tacrolimus therapy have skin blistering. Aside from burning, the main side effect was skin itching, which went away over the first week of treatment [10]. So, the aim of the study was to compare treatment regimens of tacrolimus and topical steroids for VKC and suggest a treatment protocol according to our clinical experience.

PATIENTS AND METHODS

A prospective randomized comparative clinical study involved 32 eyes of patients diagnosed with active VKC (acute or chronic) needing treatment who attended to ophthalmology outpatient clinic of Menoufia University and Berket Elsabaa Hospitals during the period study from March 2024 till March 2025.

Inclusion criteria selection:

In this study, we included four years of age, active VKC (acute or chronic) that required treatment, one or more characteristic symptoms (ocular irritation, itching, tearing pain, and photophobia), characteristic ocular examination findings (two or more of the following: hyperemia, tarsal papillae, Horner-trantas dots, and corneal epithelial defects), concurrent history with VKC (recurrent events, history of atopy, seasonal exacerbations, and family history), and informed consent.

Exclusion criteria: We excluded the presence of coexisting ocular diseases such as glaucoma, active uveitis, keratopathy, concomitant corneal ulcer of infectious origin, a history of drug or alcohol addiction, severe systemic allergies that require systemic treatment at trial enrollment, abnormalities of the nasolacrimal drainage apparatus, active herpes, or a history of cancer or a recurrence within the past five years, female of childbearing potential and patients who were not willing to go under treatment at the study center.

The procedure of the study:

Clinical diagnosis of VKC was made based on the presence of traditional symptoms and indicators. After obtaining appropriate written informed permission, the guardians of verbal children or adolescents with active diseases—that is, total subjective symptom score (TSSS>6) and total objective sign score (TOS>4)—who appear in the outpatient department (OOD) consented to the regular follow-up. Co-occurring ocular conditions such glaucoma, uveitis, corneal disease, ocular infection, systemic illnesses like renal or hepatic dysfunction, and any documented tacrolimus hypersensitivity were grounds for exclusion from the experiment. Comprehensive physical, ophthalmologic, and general exams were performed.

Following a 2-week period of discontinuation of all topical and oral allergy medications, if any, the patients were examined, had their baseline symptoms (TSSS) and signs (TOSS) recorded, and were then randomly assigned to one of the two study groups using a computer-generated system. Members of Group (A) received 0.03% tacrolimus and lubricant topical eye drops (normal saline), while members of Group (B) received topical steroids and lubricant eye drops in addition to cold compression for six weeks. The follow-up period lasted 8 weeks (6 weeks during treatment and 2 weeks after treatment). The primary results were assessed before and after treatment at each visit using Total subjective symptom scores (TSSS) and Total objective ocular sign score (TOSS). Secondary outcomes were medication-related temporary adverse effects and the recurrence of symptoms and signs two weeks following treatment.

Ethical consideration:

Participation in the study is voluntary; each patient has the right to withdraw from the study when he wants. Confidentiality and anonymity of the participants are assured through coding. All study protocols were approved by the local committee of the Faculty of Medicine, Menoufia University (IRB: 4/2023 OPHT). All participants were informed about the study's advantages, possible risks, and every procedure step. They all completed a formal informed consent form before participating in the study. The study followed the Helsinki Declaration throughout its implementation.

Sample size estimation:

Based on reviews of past literature [11], who found that the efficacy of treatment of VKC by cyclosporine (50% symptom reduction) and tacrolimus (80% symptom reduction) during 2 weeks of treatment. 76 eyes split into two equal groups is the smallest sample size that can be determined using statistics and sample size pro software version 6. The study has an 80% power and a 95% confidence level. Sample size: 76 eyes.

Statistical analysis

Using SPSS v. 25.0 on a personal computer, the results were tabulated and statistically evaluated. The descriptive statistics included mean., median, and SD. The distribution of the variables was shown to be normal using the Kolmogorov-Smirnov test. The analytical statistics comprised the X^2-test, Fisher exact-test (FE), independent t-test(t), Mann-Whitney U-test(U), and Kaplan–Meier survival curves, estimated median resection time for Clavien-Dindo classification complications. P-values were considered statistically significant if they were less than 0.05.

RESULTS

A flowchart of the population under study of 36 patients diagnosed with VKC at the Ophthalmology outpatient clinic of Menoufia University and Berket Elsabaa Hospitals during the period of the study. Four patients were excluded from the study (2 patients declined consent, and 2 did not meet the inclusion criteria), so 32 patients participated in the study, 16 patients received Tacrolimus (0.03%) and lubricant topical eye drops (normal saline) and other 16 patients received topical steroids, and lubricant eye drops along with cold compression for 6 weeks, **(Figure 1).**

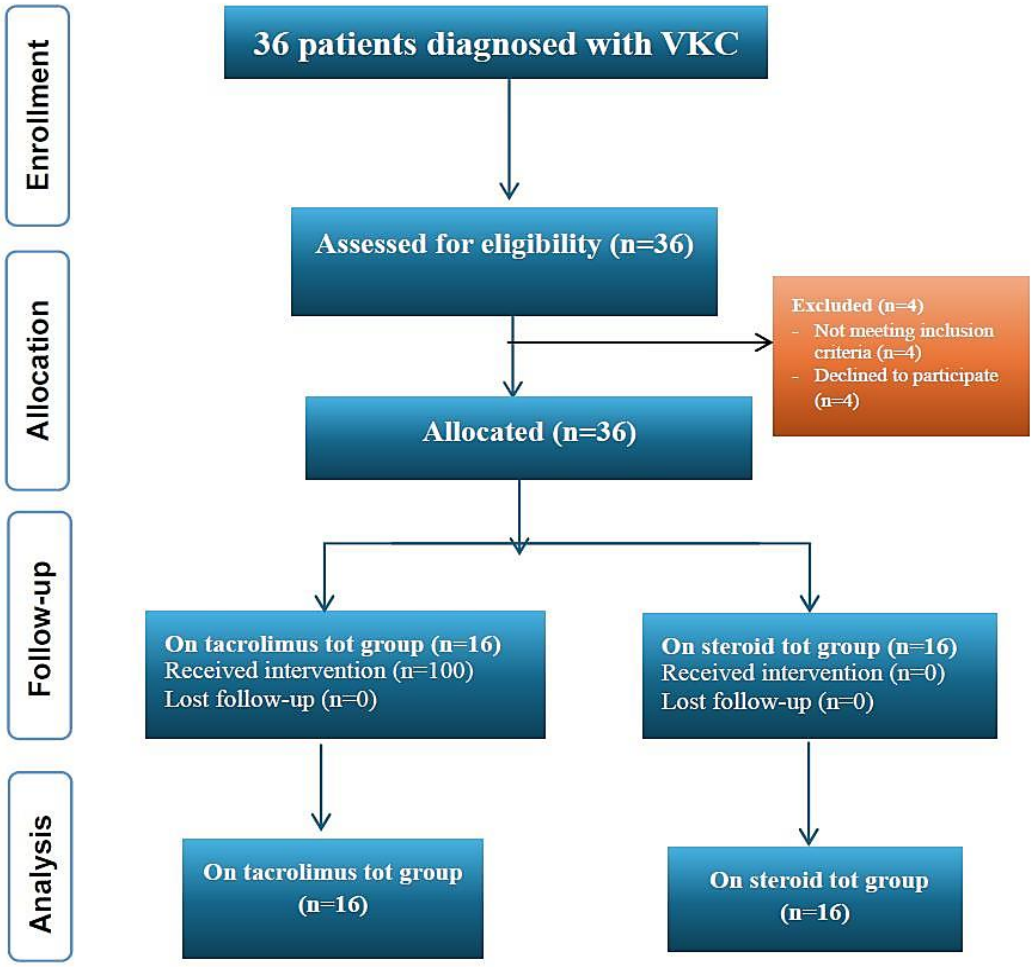

Figure (1): The patients studied diagnosed with VKC.

In the current study, the age of patients was significantly lower among patients who received Tacrolimus (0.03%) and lubricant topical eye drops (8.4375±2.70 years) compared to those patients who received topical steroids (15.93±7.93 years), (p=.001), while sex was matched among the studied groups (p>0.05). The best corrected visual acuity and intraocular pressure were matched among the studied groups (p>0.05), **(Table 1).**

Table (1): Demographic data and ophthalmological examination of the patients studied.

	On tacrolimus tot (N=16)	On steroid tot (N=16)	Sig. test	P-value
Age/year Mean ±SD Median (Range)	8.4375±2.70 9(4-13)	15.93±7.93 15.5(5-32)	t=3.577	0.001*
Gender				
Female	2 (12.5%)	7 (43.75%)	FE=3.74	0.053
Male	14 (87.5%)	9 (56.25%)		
BCVA			X^2=1.29	0.522
6/9	8 (50%)	10 (62.5%)		
6/6	7 (68.75%)	6 (37.5%)		
6/12	1 (6.25%)	0 (0%)		
IOP pretreatment Mean ±SD Median (Range)	15.53±1.83 15.25(13.50-17)	14.84±.85 14.75(14-16.50)	t=1.992	0.056
IOP after treatment Mean ±SD Median (Range)	15.53±1.08 (13.50-17)	15.90±1.38 (14-19)	t=.853	0.400

Independent t test (t), Fisher exact test (FE).

Moreover, there were statistically significant differences among the studied groups regarding grading of symptoms after 1, 2, and 4 weeks of treatment ($p<0.05$), it was significantly lower frequent among patients who received Tacrolimus (0.03%) and lubricant topical eye drops compared to those patients who received topical steroids after 1, 2, and 4 weeks of treatment. However, it started to gradually become absent and matched after 6 and 8 weeks of treatment ($p=1.00$). Grading of conjunctival hyperemia was less common among patients who received Tacrolimus and lubricant topical eye drops compared to those patients who received topical steroids after 1, 2, and 4 weeks of treatment, but the differences between them did not reach significant level ($p>0.05$), it started to gradually absent and match after 6 and 8 weeks of treatment ($p=1.00$), **(Table 2).**

Table (2): Grading of symptoms and conjunctival hyperemia among the studied patients.

Symptoms	**On tacrolimus tot N=16**	**On steroid tot N=16**	**X^2 test**	**P-value**
Start				
Grade1	1 (6.25%)	2 (12.5%)	1.043	0.593
Grade2	11 (68.75%)	12 (75%)		
Grade 3	4 (25%)	2 (12.5%)		
After 1 week				
Grade 0	3 (18.75%)	0 (0%)	13.45	0.004*
Grade 1	9 (56.25%)	2 (12.5%)		
Grade 2	4 (25%)	12 (75%)		
Grade 3	0 (0%)	2 (12.5%)		
After 2 weeks				
Grade 0	12 (75%)	2 (12.5%)	13.143	0.001*
Grade 1	4 (25%)	12 (75%)		
Grade 2	0 (0%)	2 (12.5%)		
After 4 weeks				
Grade 0	16 (100%)	10 (62.5%)	FE= 7.15	0.007*
Grade 1	0 (0%)	6 (37.5%)		
After 6 weeks				
Grade 0	16 (100%)	16 (100%)	.000	1.00
After 8 weeks				
Grade 0	16 (100%)	16 (100%)	.000	1.00
Conjunctival hyperemia				
Start				
Grade1	6 (37.5%)	6 (37.5%)	.000	1.00
Grade2	8 (50%)	8 (50%)		
Grade3	2 (12.5%)	2 (12.5%)		
After 1 week				
Grade 0	6 (37.5%)	2 (12.5%)	3.39	0.335
Grade 1	7 (43.75%)	9 (56.25%)		
Grade 2	3 (18.75%)	4 (25%)		
Grade 3	0	1 (6.25%)		
After 2 weeks				
Grade 0	14 (87.5%)	10 (62.5%)	2.95	0.229
Grade 1	2 (12.5%)	5 (31.25%)		
Grade 2	0 (0%)	1 (6.25%)		
After 4 weeks				
Grade 0	16 (100%)	15 (93.75%)	FE=1.00	0.317
Grade 1	0 (0%)	1 (6.25%)		
After 6weeks				
Grade 0	16 (100%)	16 (100%)	.000	1.00
After 8 weeks				
Grade 0	16 (100%)	16 (100%)	.000	1.00

Chi-square test (X^2), Fisher exact test (FE), *Significant.

Also, grading of Palpebral conjunctival papillae did not significant different among the studied patients at start, 1 and 2 weeks of treatment (p>0.05), grade 1 of palpebral conjunctival papillae was significantly increased among patients who received Tacrolimus and lubricant topical eye drops (n=14) compared to those patients who received topical steroids after 4 weeks of treatment (n=7), it was started to non-significant different among the studied groups after 6 and 8 weeks of treatment (p>0.05). punctate keratitis was less common among patients who received Tacrolimus and lubricant topical eye drops compared to those patients who received topical steroids after 1 week of treatment, but the differences between them did not reach significant level (p>0.05), it started gradually absent and match after 2, 4, 6 and 8 weeks of treatment (p=1.00)**, (Table 3).**

Table (3): Grading of palpebral conjunctival papillae and punctate keratitis among the studied patients.

Palpebral Conj Papillae	**On tacrolimus tot N=16**	**On steroid tot N=16**	**X^2 test**	**P-value**
Start				
Grade 1	2(12.5%)	6(37.5%)	4.84	0.089
Grade 2	7(43.75%)	8(50%)		
Grade 3	7(43.75%)	2(12.5%)		
After 1 week				
Grade 1	2(12.5%)	6(37.5%)	4.00	0.135
Grade 2	8(50%)	8(50%)		
Grade 3	6(37.5%)	2(12.5%)		
After 2 weeks				
Grade 1	5(31.25%)	6(37.5%)	2.56	0.277
Grade 2	11(68.75%)	8(50%)		
Grade 3	0(0%)	2(12.5%)		
After 4 weeks				
Grade 0	2(2.5%)	3(18.75%)	7.50	0.023*
Grade 1	14(87.5%)	7(43.75%)		
Grade 2	0(0%)	6(37.5%)		
After 6weeks				
Grade 0	3(18.75%)	6(73.5%)	4.19	0.123
Grade 1	13(81.25%)	8(50%)		
Grade 2	0(0%)	2(12.5%)		
After 8 weeks				
Grade 0	3(18.75%)	6(37.5%)	FE= 1.34	0.246
Grade 1	13(81.25%)	10(62.5%)		
Punctate keratitis	**On tacrolimus tot N=16**	**On steroid tot N=16**	**X^2 test**	**P-value**
Start				
Grade 0	13(81.25%)	12(75%)	FE=.177	0.674
Grade 1	3(18.75%)	4(25%)		
After 1 week				
Grade 0	13(81.25%)	12(75%)	FE=.177	0.674
Grade 1	3(18.75%)	4(25%)		
After 2 weeks				
Grade 0	13(81.25%)	13(81.25%)	.000	1.000
Grade 1	3(18.75%)	3(18.75%)		
After 4 weeks				
Grade 0	16(100%)	16(100%)	.000	1.00
After 6weeks				
Grade 0	16(100%)	16(100%)	.000	1.00
After 8 weeks				
Grade 0	16(100%)	16(100%)	.000	1.00

Chi-square test (X^2), Fisher exact test (FE), *Significant.

In addition, Tanta's dots did not significantly differ among patients who received Tacrolimus and lubricant topical eye drops and those patients who received topical steroids after 1, 2, 4, 6, and 8 weeks of treatment (p>0.05). limbal infiltration did not significantly differ among patients who received Tacrolimus and lubricant topical eye drops and those who received topical steroids after 1, 2, 4, 6, and 8 weeks of treatment (p>0.05), **(Table 4).**

Table (4): Grading of Tanta's dots and limbal infiltration among the studied patients.

Tanta's dots	**On tacrolimus tot N=16**	**On steroid tot N=16**	**X^2 test**	**P-value**
Start				
Grade 0	6(37.5%)	8(50%)	3.39	0.334
Grade 1	4(25%)	5(31.25%)		
Grade 2	5(31.25%)	1(6.25%)		
Grade 3	1(6.25%)	2(12.5%)		
After 1 week				
Grade 0	6(37.5%)	8(50%)	3.39	0.334
Grade 1	4(25%)	5(31.25%)		
Grade 2	5(31.25%)	1(6.25%)		
Grade 3	1(6.25%)	2(12.5%)		
After 2 weeks				
Grade 0	6(37.5%)	8(50%)	4.17	0.243
Grade 1	6(37.5%)	5(31.25%)		
Grade 2	4(25%)	1(6.25%)		
Grade 3	0(0%)	2(12.5%)		
After 4 weeks				
Grade 0	12(75%)	13(81.25%)	3.84	0.147
Grade 1	4(25%)	1(6.25%)		
Grade 2	0(0%)	2(12.5%)		
After 6 weeks				
Grade 0	16(100%)	14(87.5%)	2.13	0.344
Grade 1	0(0%)	1(6.25%)		
Grade 2	0(0%)	1(6.25%)		
After 8 weeks				
Grade 0	16(100%)	14(87.5%)	FE=2.06	0.151
Grade 1	0(0%)	2(12.5%)		
Limbal infiltration				
Start				
Grade 0	7(43.75%)	7(43.75%)	0.277	0.871
Grade 1	6(37.5%)	7(43.75%)		
Grade 2	3(18.75%)	2(12.5%)		
After 1 week				
Grade 0	7(43.75%)	7(43.75%)	0.277	0.871
Grade 1	6(37.5%)	7(43.75%)		
Grade 2	3(18.75%)	2(12.5%)		
After 2 weeks				
Grade 0	9(56.25%)	7(43.75%)	0.530	0.765
Grade 1	6(37.5%)	8(50%)		
Grade 2	1(6.25%)	1(6.25%)		
After 4 weeks				
Grade 0	15(93.75%)	13(81.25%)	FE=1.107	0.293
Grade 1	1(6.25%)	3(18.75%)		
After 6 weeks				
Grade 0	16(100%)	15(93.75%)	FE= 1.00	0.317
Grade 1	0(0%)	1(6.25%)		
After 8 weeks				
Grade 0	16(100%)	16(100%)	.000	1.00

Chi-square test (X^2), Fisher exact test (FE),*Significant

DISCUSSION

Regarding age and sex of patients, our study showed that the age of patients was significantly lower among patients who received Tacrolimus and lubricant topical eye drops compared to those patients who received topical steroids, while sex was matched among the studied groups. Similarly, **Chatterjee *et al.*** [12] evaluated the efficacy of tacrolimus in the treatment of corticosteroid-refractory VKC. Thirty VKC patients who had not responded to topical corticosteroid therapy for at least four weeks were recruited for this open-label trial. Preservative-free artificial tears, 0.05% ketotifen eye drops twice daily, and 0.03% tacrolimus eye ointment three times a day were administered to all patients. In terms of patient demographics, **Chatterjee *et al.*** [12] showed that the mean age of the group was 14.766.4 years, with 9(39%) females and 14(61%) males.

Regarding the clinical types and prior treatments, **Chatterjee *et al.*** [12] showed that 11(48%) of the patients had mixed-type VKC, 6 (26%) had pure palpebral type, and 6 (26%) had pure limbal type. Three individuals had a familial history of atopy, and nine patients had a positive personal history of the condition. A few topical medications were being used by the patients at the time of enrollment, including cromolyn sodium (3 patients), olopatadine (6 patients), and ketotifen (14 patients). Prior to starting therapy, all patients had at least four weeks of topical 1% prednisolone acetate.

In another study, **Kheirkhah *et al.*** [13] investigated the effectiveness and safety of a topical 0.005% tacrolimus eye drop in the treatment of refractory VKC. This prospective research comprised 20 eyes from ten individuals with refractory VKC who had active symptoms despite traditional treatments such as topical prednisolone. After stopping all other drugs, patients were given a topical 0.005% tacrolimus eye drop four times each day. The changes in subjective symptoms and objective indicators following therapy were reviewed, and the development of potential consequences was assessed.

Their findings indicated that **Kheirkhah *et al.*** [13] showed that the research comprised twenty eyes from ten patients (9 males and 1 female) with refractory VKC, all of whom had bilateral VKC involvement. Furthermore**, Shoughy *et al.*** [14] showed that assessing the safety and effectiveness of topical low-dose tacrolimus (0.01%) solution in patients with VKC was the aim of the present study. Retrospectively, 62 consecutive VKC patients who were unresponsive to standard therapy were considered. Patients were given tacrolimus 0.01% ophthalmic solution twice a day following the cessation of all prior topical medicines. Treatment lasted anywhere from one month to twenty-nine months. About demographics, **Shoughy *et al.*** [14] showed that 13 (21%) and 49 (79%) of the 62 individuals with refractory VKC were females. Twelve years old was the median age.

Regarding BCVA and IOP, our study found that the best corrected visual acuity and intraocular pressure were matched among the studied groups. In comparison, **Chatterjee *et al.*** [12] found that the improvement in distant visual acuity following therapy almost achieved statistical significance. Tacrolimus treatment has been shown to improve corneal staining scores, which explains this. Consequently, schoolchildren receiving tacrolimus therapy may anticipate a return to their regular activities as their clinical severity of VKC decreases and their visual acuity improves at 12 weeks. Likewise, **Kheirkhah *et al.*** [13] showed that two out of four eyes with corneal stromal opacity improved by one score. At the conclusion of the follow-up period, BSCVA improved by more than two Snellen lines in two eyes, two lines in two eyes, and one line in four others. Any attempt to cease tacrolimus eye drop resulted in a return of patients' symptoms and indicators. However, continuing the medication resulted in an instantaneous improvement of symptoms. Similarly, **Shoughy *et al.*** [14] demonstrated that the mean visual acuity at presentation, and the mean visual acuity on the last visit.

Regarding grading symptoms, our study found that there were statistically significant differences among the studied groups regarding grading symptoms after 1, 2, and 4 weeks of treatment, it was significantly lower frequent among patients who received Tacrolimus (0.03%) and lubricant topical eye drops compared to those patients who received topical steroids after 1, 2, and 4 weeks of treatment. However, it started to gradually become absent and matched after 6 and 8 weeks of treatment. Similarly, **Chatterjee *et al.*** [12] showed that compared to a baseline, the total symptom score decreased. Itching, redness, watering, discharge, and photophobia all saw a substantial decline in scores. Between baseline and the visits at 4 and 12 weeks, although the decline in scores between the latter two visits was not statistically significant. In support of this, **Chatterjee *et al.*** [12] showed that the itching and other symptoms subsided after four weeks of therapy. The decrease in clinical indicators, namely corneal epithelial staining, limbal inflammation, and bulbar conjunctival injection, coincided with the healing of our patients' complaints. The most dangerous symptom is itching because it causes eye rubbing, which can result in keratoconus [15].

Another study by **Heikal *et al.*** [16] also demonstrated that at the first week of follow-up, the tacrolimus group performed significantly better than the cyclosporine group in terms of redness, burning, photophobia, and foreign body feeling. In particular, the tacrolimus group saw a substantial reduction in burning and foreign body feeling at the fourth week, as well as redness and burning sensation at the twelfth week. This comparative favorable impact might be explained by the fact that tacrolimus in ointment form has a long-lasting effect as compared to cyclosporine A administration, which minimizes ocular surface

exposure duration due to the accompanying stinging sensation. Finally, **Heikal *et al.*** [16] showed that within the first week, both groups had considerable relief from their problems, while **Kheirkhah *et al.*** [13] observed that tacrolimus alleviated itching as the initial symptom.

Concerning grading conjunctival hyperemia, our study showed that grading conjunctival hyperemia was less common among patients who received Tacrolimus and lubricant topical eye drops compared to those who received topical steroids after 1, 2, and 4 weeks of treatment. However, the differences between the groups did not reach statistical significance. Over time, the differences gradually diminished, and by 6 and 8 weeks of treatment, the grading of conjunctival hyperemia had matched between the groups. In agreement with our findings, **Chatterjee *et al.*** [12] reported a significant decline in the overall sign score. Conjunctival injection, limbal inflammation/hypertrophy, and corneal staining scores, in particular, all drastically declined from baseline to the 4- and 12-week visits; however, the difference between the latter two visits was not statistically significant. Additionally, even while the papillary hypertrophy score decreased during the 4-week visit, it wasn't until 12 weeks that it reached statistical significance. Interestingly, at neither time point did the decline in cobblestone papillae scores reach statistical significance. Similarly, **Kheirkhah *et al.*** [13] showed that conjunctival hyperemia was the first clinical symptom to improve after tacrolimus treatment. Prior to therapy, hyperemia was severe in 12 and moderate in 8 eyes. By one month, 4 eyes showed no hyperemia, while 16 showed moderate hyperemia. Consistent with our results, **Kheirkhah *et al.*** [13] observed that all eight eyes with moderate to severe large papillae improved, with three eyes showing noticeable alterations as early as two weeks and four eyes completely disappearing by the conclusion of the follow-up period. Improvements were also observed in related symptoms such as limbal hypertrophy, punctate epithelial erosions, and corneal pannus. Supporting this, **Shoughy *et al.*** [14] demonstrated that a statistically significant decrease in conjunctival papillary hypertrophy was seen in 34 (55%) participants at the final follow-up visit following tacrolimus medication. The tacrolimus group had substantially reduced scores for tarsal conjunctival papillary hypertrophy in the first and 12th weeks, as well as punctuation erosions and cobblestone papillae in the first week, as compared to the cyclosporine A group. Notably, they observed that by the 12th week, the tacrolimus group had completely resolved cobblestone papillae.

Concerning punctate keratitis, our study showed that punctate keratitis was less frequently observed among patients treated with tacrolimus and lubricant eye drops compared to those receiving topical steroids after one week of treatment; however, this disparity wasn't statistically noteworthy. By the 2nd, 4th, 6th, and 8th weeks of follow-up, the condition had gradually resolved and was similarly absent in both groups. These findings agree with **Shoughy *et al.*** [14] who reported that superficial punctate keratitis was present in 27% of patients at baseline, and that after using tacrolimus eye drops, there was a statistically significant decrease in its intensity at the last follow-up appointment. Additionally, **Marquezan *et al.*** [17] in their study evaluating tacrolimus ointment for Thygeson's superficial punctate keratitis noted that patients showed good tolerance to treatment, with no significant local side effects such as toxic punctate keratitis, and without developing complications like herpes simplex keratitis or ocular surface malignancies.

Regarding the presence of Trantas dots, our study showed that the presence of Trantas dots did not significantly differ between patients treated with tacrolimus and lubricant eye drops and those who received topical steroids throughout the follow-up period at 1, 2, 4, 6, and 8 weeks. In contrast, **Shoughy *et al.*** [14] reported a statistically significant decrease in the intensity of Trantas dots at the last appointment after using tacrolimus eye drops, indicating the potential efficacy of tacrolimus in resolving this specific clinical sign of VKC. Similarly, **Azeem *et al.*** [18] in a prospective study assessing the efficacy and safety of 0.1% tacrolimus ointment in children with VKC. They found that Trantas dots were present in 76% of patients at baseline. They observed a statistically significant improvement in all clinical signals including Trantas dots particularly in mild cases, where improvements began by the end of the first week, and in severe cases by the fourth week of therapy. The differing outcomes between our study and the referenced literature may be attributed to variations in baseline severity, treatment formulations, duration, or patient characteristics. Further controlled studies are warranted to confirm the temporal response of Trantas dots to tacrolimus therapy across different patient populations.

Concerning limbal infiltration, our study demonstrated that limbal infiltration did not significantly differ between patients treated with tacrolimus and lubricant eye drops and those who received topical steroids at 1, 2, 4, 6, and 8 weeks of treatment. In contrast, **Wan *et al.*** [19] showed that treatment with 0.1% tacrolimus eye drops led to a statistically significant reduction in limbal inflammation as early as one week after initiation, suggesting a rapid anti-inflammatory effect. Their study also reported continued improvements in other clinical signs, including corneal staining and papillary hypertrophy, over subsequent weeks.

CONCLUSION

Both treatment modalities significantly improved clinical signals and symptoms. However, Tacrolimus showed a more rapid and sustained reduction in symptom scores (TSSS and TOSS) during the early treatment phase (weeks 1–4), particularly in ocular

irritation and conjunctival hyperemia, without significantly increasing adverse effects or intraocular pressure. Although certain individual signs (e.g., Transat dots, punctate keratitis, limbal infiltration) did not differ significantly between groups at most follow-up points, the consistent early improvement observed in the Tacrolimus group supports its non-inferiority and, in some domains, potential superiority over topical steroids. Importantly, Tacrolimus did not demonstrate steroid-related risks such as IOP elevation, positioning it as a safer long-term option.

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