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Evaluation of Tacrolimus 0.03% Eye Ointment Versus Standard Antiallergic Drugs in The Treatment of Vernal Keratoconjunctivitis

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Running Title: Antiallergic Drugs in The Treatment of Vernal Keratoconjunctivitis

Abstract

Aim: This study aimed to evaluate the efficacy and safety of tacrolimus eye ointment compared to the standard anti allergic drugs for the management of chronic vernal keratoconjunctivitis (VKC).

Methods: This was a prospective, nonrandomized comparative interventional study that enrolled 50 chronic VKC cases, which were assigned into 2 groups. The first group was treated with 0.03% tacrolimus eye ointment twice daily for 2 months then once daily for 2 months followed by once every other day for another 2 months. The second group was treated with standard anti allergic drugs, topical fluorometholone 0.1% eye drops 3 times daily for 2 weeks and gradually withdrawn for another 2 weeks plus topical olopatadine 0.1% twice daily during the follow up period. The severity of VKC was assessed by a four-point scale of symptoms and signs. The treatment efficacy was assessed by the analysis of changes in symptoms and signs.

Results: Itching was the most common symptom reported and the most observed signs were conjunctival hyperemia and papillary hypertrophy. In both groups, there was a significant improvement in all symptoms and signs after treatment. The tacrolimus group showed a more significant improvement at 3 and 6 months in the mean composite symptom and sign scores. Regarding the complications, there was one case of increased IOP reported in the second group after 2 weeks of steroid treatment while there were no complications in the tacrolimus group only stinging sensation was reported in some cases and well tolerated.

Conclusions: Tacrolimus 0.03%eye ointment was effective and safe and can be used as an alternative to reduce steroid-associated complications.

Keywords: Steroids; Tacrolimus; Vernal keratoconjunctivitis

INTRODUCTION

VKC is a chronic, recurrent, bilateral conjunctival inflammatory disease with seasonal exacerbations.[1] It was seen commonly in boys and may continue to adulthood.[2]

The disease manifests in three types: tarsal, limbal, and mixed. Symptoms include itching, burning, watering, perceived redness, discharge, foreign body sensation, and photophobia. Signs include tarsal papillae, punctate keratitis, inflamed limbus, hyperemia and Horner-Trantas dots.[3]

The IgE and T-cell mediated allergic reaction is responsible for the pathogenesis of VKC. Mast cells, Eosinophils and other inflammatory mediators have an important role in producing tarsal papillae, limbal inflammation, conjunctival hyperemia, and congestion.[4,5]

The treatment includes topical corticosteroids, mast cell stabilizers, antihistaminic agents and immunomodulatory agents.[6] Although steroids are effective in this disease, excessive and prolonged use frequently results in

complications such as cataracts and glaucoma.[7] To avoid steroid-induced complications, immunomodulators like tacrolimus are now being used for treating VKC.[8,9]

Tacrolimus is a macrolide immunomodulator produced by the Streptomyces tsukubaensis.[10] It suppresses calcineurin activity and the production of Th1 and Th2 cytokines. It also inhibits histamine release from mast cells. It is 100-folds stronger compared with cyclosporine.[11] Studies reported that tacrolimus (0.02%–0.1%) ointment is effective in the treatment of VKC, giant papillary conjunctivitis and atopic keratoconjunctivitis.[12-15]

Topical tacrolimus is generally well tolerated. Mild and transient ocular irritation is the most common side effect. As an immunosuppressant, topical tacrolimus use may be associated with increased risk of corneal infections with prolonged use.[13]

The purpose of the current study was to evaluate the efficacy and safety of tacrolimus eye ointment compared to the standard anti allergic drugs for the management of VKC.

PATIENTS AND METHODS

This was a prospective, non-randomized comparative interventional study that enrolled 50 cases with chronic VKC assigned into two groups; the first group was treated with tacrolimus 0.03% eye ointment and the second group was treated with standard antiallergic medications. Ethical Approval for this study was taken from the ethical committee of the Faculty of Medicine of Port Said University (April 22, 2020) and it was conducted at Damietta Ophthalmology Hospital in Damietta, Egypt. The study was registered at the Pan African Clinical Trials Registry (PACTR) with a unique identification number (PACTR202206480800979). We followed the tenets of the Declaration of Helsinki and the written consents were taken from all participants. We included all newly diagnosed and chronic patients with no treatment at least for 1 month regardless of the severity. We excluded patients with history of systemic comorbidities, history of herpes keratitis, history of systemic immunosuppressive drug use, coexisting eye infections, ocular surgery, patients with cataracts or glaucoma, known hypersensitivity to tacrolimus, eyes with congenital anomalies, contact lenses use, and patients younger than 3 years.

All patients were examined by slit-lamp bio microscopy (Photo-Slit Lamp 30 GL; Takagi Seiko Co., Ltd, Japan), measurement of intraocular pressure using a Goldmann applanation tonometer (KAT R-Type Keeler, USA),[16] fluorescein staining and detailed fundus examination during each visit.

VKC was diagnosed based on seven symptoms [6] (redness, watering, discharge, photophobia, burning, itching, and foreign-body sensations) and five signs [3] (papillary hypertrophy, hyperemia, Horner–Trantas dots, corneal affection and limbal inflammation).

A questionnaire of symptoms was given to all patients and grading was done on a 4-point scale by one constant examiner before starting treatment and at each follow-up visit. Also, clinical signs underwent grading by one constant observer according to a 4-point scale of signs (Tables 1,2).[6,3] Then, the total score was calculated at the start of the treatment, and at each follow-up visit.

The first study group was treated with 0.03% tacrolimus ophthalmic ointment (Entrak Soothe; Entod Pharmaceuticals Ltd., Mumbai, India) twice daily for 2 months and then once daily for 2 months followed by once every other day for 2 months.[2] The second group was treated with topical fluorometholone 0.1% eye drops (Flucon; Novartis Pharma AG, Basel, Switzerland) 3times daily for two weeks plus topical olopatadine 0.1% (Patanol; Novartis Pharma AG, Basel, Switzerland) twice daily then steroids were gradually withdrawn for another two weeks. If symptoms disappeared, maintenance on topical olopatadine 0.1% twice daily during the follow-up period, and if exacerbation occurred, the steroids will be used again. The follow-up visits were at one week, one month, 3 months, and 6 months.

The efficacy of the treatment was assessed by analyzing the changes in symptoms and signs and documented by clinical photography.

Table (1): Scores for symptoms [6]

Symptoms	Score
● **Burning**	
No burning	0
Mild	1
Moderate	2
Marked	3
● **Itching**	
No itching	0
Occasional	1
Frequent	2
Constant	3
● **Discharge**	
No discharge	0
Mucus in the lower fornix	1
Moderate	2
Matted lashes	3
● **Photophobia**	
No photophobia	0
Sensitivity to sunlight with the ability of eye opening	1
Inability to open eyes for a long time	2
Eyes unable to open	3
● **Watering**	
Normal	0
Water logged sensation	1
Infrequent lacrimation	2
Constant lacrimation	3
● **Perceived redness**	
No redness	0
Redness on close observation	1
visible from near	2
visible from far	3
● **Foreign-body sensation**	
No foreign-body sensation	0
Mild	1
Moderate	2
Marked	3

Table (2): Scores for clinical signs [3]

Clinical signs and severity	Score
● **Hyperemia**	
Not-existing	0
Some blood vessels are dilated	1
Several blood vessels are dilated	2
Generalized vascular dilatation	3
● **Horner–Trantas dots**	
Absent	0
1–3	1
4–6	2
>6	3
Limbal inflammation	
Absent	0
Neovascularization in 1 quadrant	1
Neovascularization in 2 quadrants	2
Neovascularization in 3–4 quadrants	3
Punctate keratitis	
Intact epithelium	0
Punctate in one third of the cornea	1
Punctate in two thirds of the cornea	2
Diffuse punctate	3
Papillae	
No papillae	0
Size of papillae: 0.1–0.2 mm	1
0.3–0.5 mm	2
≥0.6 mm	3

Statistical analysis

Data were analyzed using 'IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, N.Y., USA)'. For continuous data, they were tsted for normality by the Shapiro-Wilk test. Quantitative data were expressed as range (minimum and maximum), mean, standard deviation and median for normally distributed quantitative variables Student t-test was used to compare two groups while ANOVA with repeated measures was used to compare between more than

two periods, and followed by Post Hoc test (Bonferroni adjusted) for pairwise comparisons. On the other hand, for not normally distributed quantitative variables Mann Whitney test was used to compare two group while Friedman test was used to compare between more than two periods, and followed by Post Hoc Test (Dunn's) for pairwise comparisons. Significance of the obtained results was judged at the 5% level.

RESULTS

This study included 50 cases of VKC that were assigned into 2 groups. 88% of the tacrolimus group and 84% of the antiallergic group were males. No significant difference according to the mean age of the two groups. The majority of cases in the form of palpebral type except for a nine cases were mixed type (Four cases in the tacrolimus group and five cases in the antiallergic group). (Table 3)

Table (3): Clinical features and demographics of the 2 study groups

	Tacrolimus (n = 25)		**Antiallergic (n = 25)**		**p** value
	No.	**%**	**No.**	**%**	
Gender					
Male	22	88.0	21	84.0	$^{FE}p=$ 1.000
Female	3	12.0	4	16.0	
Age (years)					0.833
Mean ± SD.	16.20 ± 5.10		16.48 ± 4.19		
Type of VKC					
Tarsal Form	21	84.0	20	80.0	$^{FE}p=$ 1.000
Mixed Form	4	16.0	5	20.0	

SD: Standard deviation **FE:** Fisher Exact p value for comparing the studied groups

Table (4,5) shows the mean composite symptom score of the two groups. At baseline and at one month there was no significant difference in the mean composite symptom score between the two studied groups but at 3 months and 6 months there was significant difference ($p = 0.021$, $p < 0.001$ respectively) and the tacrolimus group showed more improvement. Also, there was significant improvement between the all studied periods in both groups. Therefore**,** the improvement in symptoms of the tacrolimus group at three and six months was significantly higher than that of the antiallergic group.

Table (4): Composite symptoms score of the 2 groups

Composite symptom score	Tacrolimus (n = 25)	Antiallergic (n = 25)	P value
Baseline			
Mean ± SD.	17.44 ± 2.14	17.52 ± 1.29	0.775
1 Month			
Mean ± SD.	8.60 ± 2.53	7.56 ± 1.26	0.128
3 Month			
Mean ± SD.	4.04 ± 1.95	4.84 ± 1.11	0.021*
6 Month			
Mean ± SD.	1.96 ± 0.73	3.04 ± 0.79	<0.001*

SD: Standard deviation

Significance was done using Mann Whitney test

*: Statistically significant at $p \leq 0.05$

Table (5): Comparison between the different studied periods based on composite symptoms score in each group

	Total symptoms score				P value
	Baseline	1 Month	3 Month	6 Month	
Tacrolimus (n = 25)					<0.001*
Mean ± SD.	17.44 ± 2.14	8.60 ± 2.53	4.04 ± 1.95	1.96 ± 0.73	
p_0		0.006*	<0.001*	<0.001*	
Sig. bet. periods.		p_1=0.003*, p_2<0.001*, p_3=0.028*			
Antiallergic (n = 25)					<0.001*
Mean ± SD.	17.52 ± 1.29	7.56 ± 1.26	4.84 ± 1.11	3.04 ± 0.79	
p_0		0.005*	<0.001*	<0.001*	
Sig. bet. periods.		p_1=0.006*, p_2<0.001*, p_3=0.010*			

SD: **Standard deviation** Significance was done using **Post Hoc test (Dunn's)**

p_0: p value for comparing between **Baseline** and each other periods p_1: between **1** and **3 Months**

p_2: between **1** and **6 Months** p_3: between **3** and **6 Months** *: Statistically significant at $p \leq 0.05$

Tables (6,7) show the mean composite sign score of the two groups. At baseline and at one month there was no significant difference in the mean composite sign score between the two studied groups but at 3 months and 6 months there was significant difference ($p < 0.001$, $p = 0.005$ respectively) and the tacrolimus group showed more improvement. Also, there was significant improvement between the all studied periods in both groups. Therefore**,** the improvement in signs of the tacrolimus group at three and six months was significantly higher than that of the antiallergic group.

Table (6): Composite sign score of the two-study group

Composite sign score	Tacrolimus (n = 25)	Antiallergic (n = 25)	P value
Baseline			0.600
Mean ± SD.	8.76 ± 1.45	8.60 ± 1.41	
1 Month			0.081
Mean ± SD.	4.72 ± 0.98	4.24 ± 1.05	
3 Month			<0.001*
Mean ± SD.	2.52 ± 0.51	3.28 ± 0.74	
6 Month			0.005*
Mean ± SD.	1.32 ± 0.63	1.80 ± 0.65	

SD: Standard deviation Significance was done using Mann Whitney test

*: Statistically significant at $p \leq 0.05$

Table (7): Composite sign score in each group for different studied periods

	Composite sign score				P value
	Baseline	**1 Month**	**3 Month**	**6 Month**	
Tacrolimus (n = 25)					<0.001*
Mean ± SD.	8.76 ± 1.45	4.72 ± 0.98	2.52 ± 0.51	1.32 ± 0.63	
p_0		0.006*	<0.001*	<0.001*	
Sig. bet. periods.		p_1=0.002*, p_2<0.001*, p_3=0.037*			
Antiallergic (n = 25)					<0.001*
Mean ± SD.	8.60 ± 1.41	4.24 ± 1.05	3.28 ± 0.74	1.80 ± 0.65	
p_0		0.002*	<0.001*	<0.001*	
Sig. bet. periods.		p_1=0.037*, p_2<0.001*, p_3=0.004*			

SD: Standard deviation Significance was done using Post Hoc test (Dunn's)

p_0: p value for comparing between Baseline and each other periods p_1: between 1 and 3 Months

p_2: between 1 and 6 Months p_3: between 3 and 6 Months

*: Statistically significant at $p \leq 0.05$

Regarding the mean individual symptom score, the commonest symptoms were redness and itching. All symptoms showed a significant improvement within two weeks in both groups. At 1 month. itching was significantly reduced in antiallergic group in comparison with the tacrolimus group (p= 0.005). But at 6 months the tacrolimus group demonstrated a statistically significant decrease in itching(p=0.039). (Fig.1)

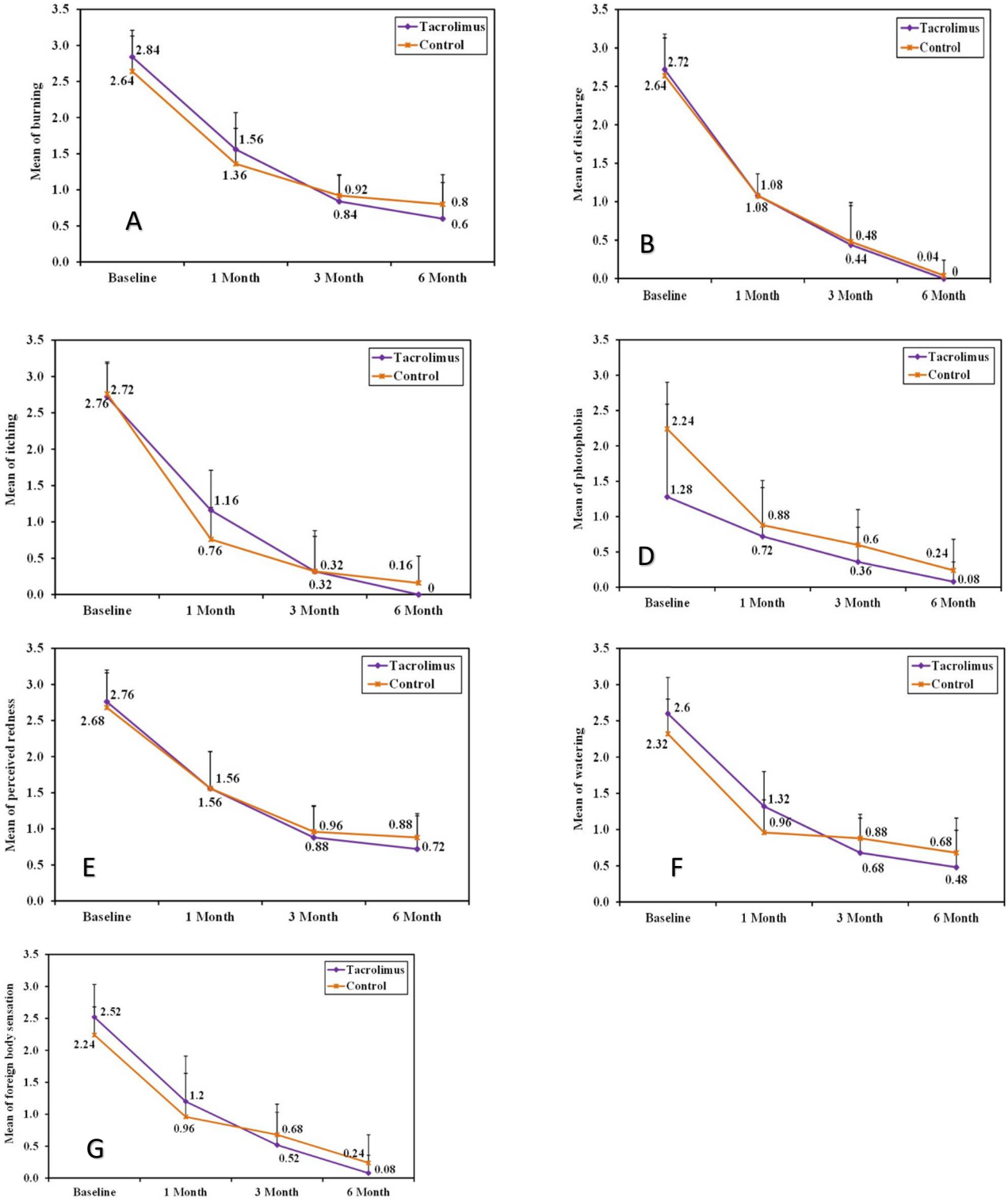

Fig.1. Mean scores of symptoms in tacrolimus and antiallergic group

Concerning the mean individual sign score, the most observed signs were papillary hypertrophy and conjunctival hyperemia, which were present in all patients. Papillae were significantly reduced in the tacrolimus group in comparison with the antiallergic at 3 months and 6 months (p= <0.001, and 0.039, respectively). Limbal inflammation was significantly reduced in the tacrolimus group in comparison with the antiallergic at 6 months (p=0.020). (Fig. 2)

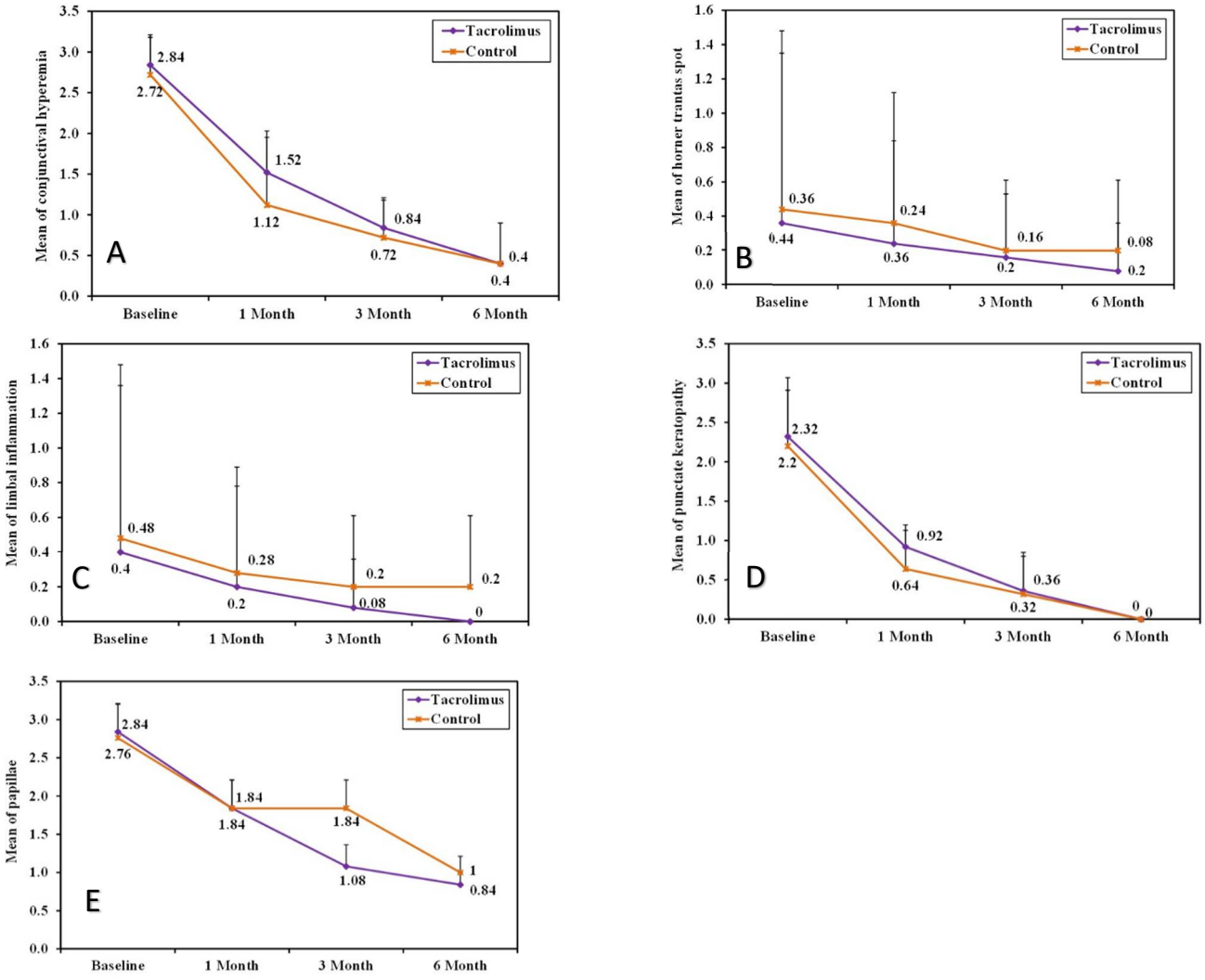

Fig.2. Mean scores of signs in tacrolimus and antiallergic group

Table (8) show IOP in both groups, there was no significant difference between both groups.

Table (8): Comparison between the two studied groups according to IOP

		Tacrolimus (n = 25)	Antiallergic (n = 25)	p
IOP	**Baseline**			
	Mean ± SD.	14.8 ± 2.8	15.6 ± 2.9	0.322
	1 month			
	Mean ± SD.	15 ± 2.8	15.6 ± 2.7	0.479
	3 months			
	Mean ± SD.	15 ± 2.9	15.6 ± 2.7	0.486
	6 months			
	Mean ± SD.	15.1 ± 2.6	15.6 ± 2.7	0.462

SD: Standard deviation

p: p value for comparing between the studied groups

Figures (3-6) showed photos of a cases of tarsal and mixed VKC pre- and post-treatment in the tacrolimus group and in the control group.

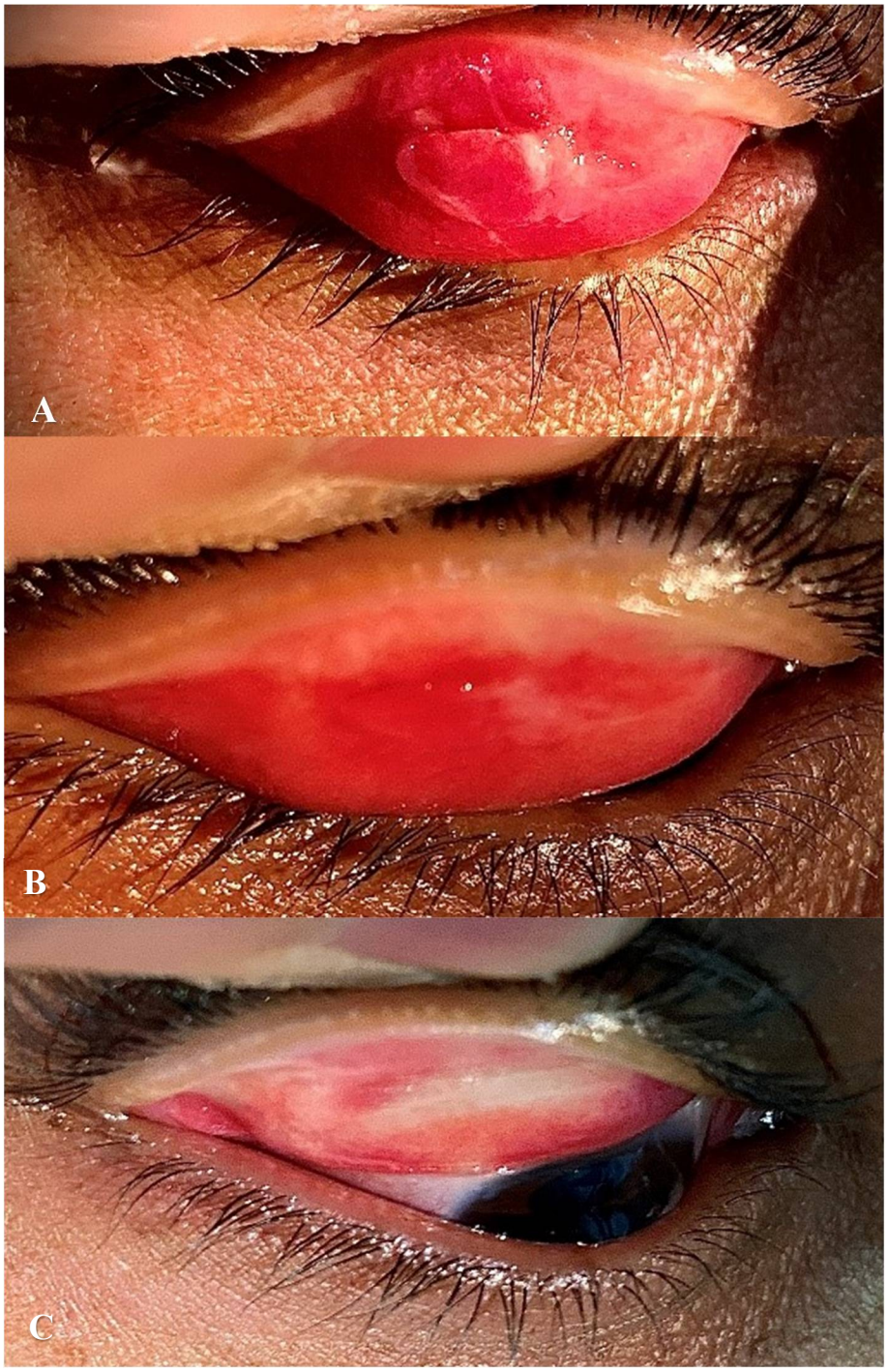

Fig.3: (A) A case of tarsal VKC at pretreatment with notable large papilla (B) the eye after 1 month of tacrolimus 0.03% treatment (C) the eye after 6 months treatment with notable complete resolution of the papilla.

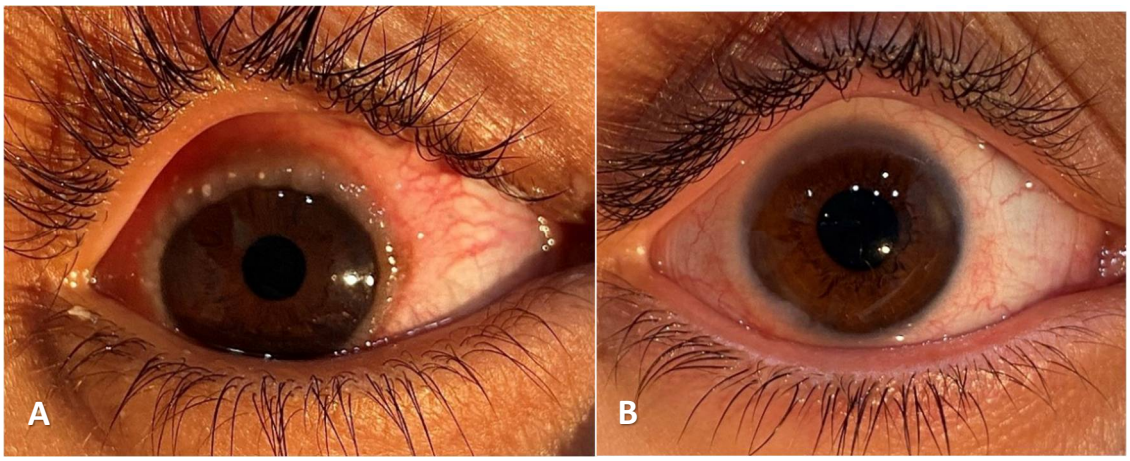

Fig.4: (A) Limbal inflammation in a case of mixed VKC at pretreatment (B) the eye after 1 month of tacrolimus 0.03% treatment with notable complete resolution.

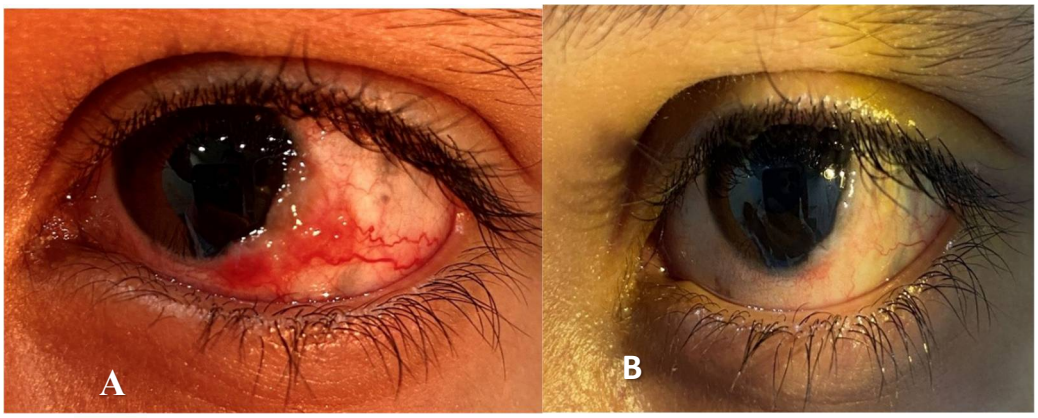

Fig.5: (A) limbal inflammation in a case of mixed VKC pretreatment (B) the same eye after 1 month of Flurometholone and Olopatadine treatment note nearly complete resolution.

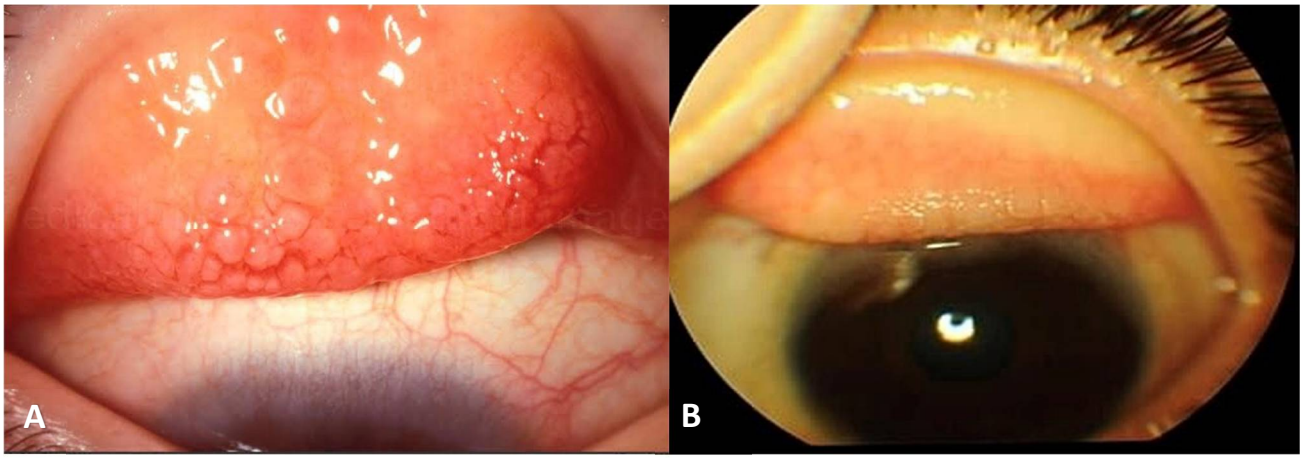

Fig.6: (A) a case of tarsal VKC pretreatment (B) the same eye after 6 months of Flurometholone and Olopatadine treatment note improvement in papillae and conjunctival hyperemia.

According to the complications, one case of increased IOP among the antiallergic group was reported after 2 weeks of treatment and treated. In the tacrolimus group, no complications were observed except the stinging sensation in some cases which was lasted for a few days and well tolerated.

DISCUSSION

VKC is a disease which is documented to lead to complications as shield ulcer and can cause blindness.[7] The commonly used drugs for the management of VKC include steroids, antihistamines and immunomodulators like tacrolimus and the main purpose is to relief patients from uncomfortable symptoms like watering, itching, and burning without complications.[17]

In our study, fifty cases of VKC were assigned into 2 groups with both eyes per subject involved. Both groups responded well to therapy. No complications reported in the tacrolimus group, the stinging sensation was the only side effect encountered and it was well-tolerated by most patients and lasted for a few days. However, one case of increased IOP was reported in the antiallergic group after 2 weeks of steroid treatment. Chatterjee and co-workers [9] reported that the mild transient stinging for a few days was observed in their study. Also, Vadivelu et al.[18] studied 30 patients randomized into 2 groups (tacrolimus group and steroid group) and reported that 4 cases in the tacrolimus group experienced mild irritation and 4 patients in the steroid group developed a high intraocular pressure at the end of 6 weeks.

In the tacrolimus group, the mean composite symptom score at the base line was 17.44 ± 2.14, and it improved significantly to 1.96 ± 0.73 after 6 months ($p < 0.001$), and in the antiallergic group, the mean composite symptom score at the base line was 17.52 ± 1.29, and it improved significantly to 3.04 ± 0.79 after 6 months ($p < 0.001$). However, tacrolimus group showed a significantly more improvement at 3 and 6 months ($p=0.021$, $p=0.001$ respectively).

Our results coincide with those of Vadivelu et al.[18] who reported a significant improvement in symptoms after 28 days of tacrolimus treatment. Rathore et al.[19] randomized 69 patients into 2 groups; tacrolimus and olopatadine group which showed that after 3 months the mean symptom score reduced significantly from 9.0 ± 2.04 to 0.11 ± 0.32 in the tacrolimus group ($p < 0.001$) and reduced significantly from 8.88 ± 2.18 to 1.70 ± 0.77 in the olopatadine group ($p < 0.001$) and difference of the mean symptom score of the tacrolimus group was significantly higher than that of the olopatadine group at 3 months ($p < 0.001$) that was similar to our finding.

In our study, the mean composite sign score in the tacrolimus group was 8.76 ± 1.45, and it improved significantly to 1.32 ± 0.63 after 6 months ($p < 0.001$) and in the allergic group, the mean composite sign score was 8.60 ± 1.41, and it improved significantly to 1.80 ± 0.65 after 6 months ($p < 0.001$). However, tacrolimus group showed a significantly more improvement at 3 and 6 months ($p <0.001$, $p=0.005$ respectively). Our results coincide with that of Vadivelu et al.[18] who reported a significant improvement in signs after 28 days of tacrolimus treatment. Also, Rathore et al.[19] study showed that after 3 months the mean sign score reduced significantly from 3.93 ± 1.93 to 0.08 ± 0.28 in the tacrolimus group ($p < 0.001$) and reduced significantly from 4.36 ± 1.90 to 0.64 ± 0.55 in the olopatadine group ($p < 0.001$) and difference of the mean sign score of the tacrolimus group was significantly higher than that of the olopatadine group at 3 months ($p < 0.001$) that was similar to our finding.

Itching was the most encountered symptom in our study and first responded to treatment within one month. Samyukta et al.[3] also stated that itching was the first symptom that responded to treatment.

The most encountered signs in this study were conjunctival hyperemia and tarsal papillae which were present in all patients in both groups. Tacrolimus group showed a more significant improvement of the tarsal papillae at 3 months and 6 months of treatment compared to the antiallergic group ($p<0.001$, $p=0.039$, respectively). Similarly, more significant improvement in limbal inflammation in the tacrolimus group was noted at 6 months ($p=0.020$). There was delayed improvement in limbal inflammation and tarsal papillae in the antiallergic group. Kymionis and colleagues [20] revealed a complete reduction in giant papillae in patients having giant papillae conjunctivitis treated with tacrolimus within one month, while we detected nearly complete resolution of papillae in tacrolimus group at 6 months. On the other hand, other studies found delayed reduction in upper tarsal conjunctival papillae and cobblestone papillae.[8, 13, 21]

The main limitations of our study were the non-randomization and the small sample size. Our strength was that, by using a single agent (tacrolimus 0.03 % ointment) for the management of VKC with a high success rate, we avoid the need for corticosteroids with its related complications. Future double-blinded clinical trials with more patients and longer follow-up periods should be conducted to confirm our findings.

CONCLUSION

Treatment with tacrolimus 0.03 % eye ointment show more improvement in both symptoms and signs at 3 and 6 months compared to the antiallergic drugs without any complications. So, tacrolimus eye ointment is effective and safe and can be utilized as an alternative in steroid responders to avoid steroid-related complications.

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DATA AVAILABILITY

All data are included in this article.

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Ethics declarations

Conflict of interest

Mahmoud Eltagoury, Waleed Abou Samra, Ehab Ghoneim. all authors have no conflicts of interest that are directly relevant to the content of this review.

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