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A comparative study of efficacy, tolerability and safety of 0.03% tacrolimus eye ointment and 0.05% cyclosporin eye drops in the treatment of vernal keratoconjunctivitis

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Abstract
Background: Vernal keratoconjunctivitis (VKC) is a common, chronic, bilateral, recurrent, allergic, inflammatory disease of the ocular surface primarily affecting young males in dry, hot climates such as India.
Objectives: To compare the efficacy, tolerability and safety of 0.03% tacrolimus eye ointment and 0.05% cyclosporin eye drops in the treatment of vernal keratoconjunctivitis.
Methods: A prospective study of 72 patients conducted from December 2017 to February 2021. After having established a diagnosis of VKC and fulfilling inclusion and exclusion criteria, participants were divided into two groups. Group 1 was put on cyclosporin eye drops and group 2 was put on tacrolimus eye ointment. Detailed history and evaluation for symptoms, signs, visual acuity and IOP was done on first visit and subsequently after 6 weeks, 12 weeks and 24 weeks.
Results: 72 patients were diagnosed to have VKC, of whom males were 86% and females 13.9%, all belonging to the age group 5 to 14 years and were divided into two groups. Both the groups showed significant reduction in the symptoms and signs with no significant difference in efficacy between the groups and they maintained normal IOP and visual acuity at 6 weeks, 12 weeks and 24 weeks.
Conclusion: Both the immunomodulators were equally successful in resolving the signs and symptoms of VKC, tolerable with no significant adverse effects and proved to be a safer alternative to steroids as they caused no elevation of intraocular pressure or any complications associated with the use of steroids.

Keywords: Vernal keratoconjunctivitis, cyclosporin eye drops, tacrolimus eye ointment, intraocular pressure

1. Introduction

Vernal keratoconjunctivitis (VKC) is a common, chronic, bilateral, recurrent, allergic, inflammatory disease of the ocular surface, primarily affecting young males in dry, hot climates such as India [1]. Patients with VKC present with itching, redness, photophobia, ocular discomfort, foreign body sensation and lacrimation resulting in visual disturbances. The disease ranges in severity from mild to severe forms. Mild can still interfere significantly with quality of life while severe cases are characterised by potential impairment of vision, especially if the cornea is involved. VKC lasts for about six years in patients with seasonal incidence and longer if the disease is perennial.

Treatment of VKC is with topical antiallergic agents, mast cell stabilizers, decongestants and corticosteroids [2]. Conventionally, steroids are used for all severe kinds of allergic conjunctivitis but chronic, indiscriminate use of corticosteroids may lead to glaucoma, cataract and secondary infections in high steroid responders. Inadequate counselling, unrealistic expectations and free availability of topical steroids without prescriptions often result in overuse, misuse and self-use of steroid, and it is not uncommon to see patients with steroid-related complications, including irreversible optic disc changes and elevated IOP due to steroid-induced glaucoma [3].

Additionally, there is a subset of VKC patients that become refractory to the steroid treatment over a period of time. For refractory cases, oral or subtarsal corticosteroids are indicated, often resulting in the aggravation of the lesion with tapering or discontinuation.

Now, immunomodulatory agents have been introduced to avoid steroid-related complications.

Tacrolimus suppresses Th2 lymphocyte activation, T helper cell-mediated B-cell proliferation and formation of cytokines, and cyclosporin A is effective in controlling ocular inflammation by blocking Th2 lymphocyte proliferation and interleukin 2 production.

Not many studies are available in the evaluation of efficacy, tolerability and safety of these immunomodulatory agents, hence the need for the present study.

2. Aim of the study

To compare the efficacy, tolerability and safety of 0.03% Tacrolimus eye ointment and 0.05% cyclosporine eye drops in vernal keratoconjunctivitis.

3. Materials and methods

This study was conducted in K.R. Hospital, Mysore and Vydehi Institute of Medical Sciences and Research Center, Bangalore, on the subjects of ages 5 years and above who visited the out-patient department of Ophthalmology at K.R. Hospital and VIMS and RC from December 2017 to February 2021 and were clinically diagnosed with vernal keratoconjunctivitis. This was a comparative study with a study population of seventy-two subjects of which thirty-six patients with a diagnosis of vernal keratoconjunctivitis formed the case group with another thirty-six patients forming the control group. All cases satisfied the inclusion and exclusion criteria.

3.1 Inclusion Criteria

All patients aged 5 years and above, both male and female, with a clinical diagnosis of vernal keratoconjunctivitis as the case group from whom written informed consent was taken.

3.2 Exclusion Criteria

(1.) Patients with other ocular disorders such as glaucoma, infectious keratitis and posterior segment abnormalities. (2.) Patients with one blind eye. (3.) Contact lens users. (4.) Patients with congenital abnormalities.

3.3 Study Design

A comparative study was done with purposive sampling. Complete general physical and ophthalmologic examination including visual acuity determination (Snellen chart and near vision chart), slit lamp examination (Zeiss), intraocular pressure measurement (I CARE) and fundoscopy (direct and indirect ophthalmoscope) was conducted. All patients were requested to discontinue all ophthalmologic and oral anti-allergic drugs with the exception of preservative-free artificial tears prior to the study. After 2 weeks run-in period, on the first follow-up visit, complete ophthalmologic examination was done as described above and grading for ocular symptoms (foreign body sensation, itching, discharge, lacrimation, hyperaemia, eye pain and photophobia) and signs (palpebral hyperaemia, bulbar hyperaemia, perilimbal conjunctival hyperplasia and papillae) were done.

Patients were then categorized into 2 groups I and II. Group I was requested to use 0.03% tacrolimus eye ointment twice daily and group II was requested to use 0.05% cyclosporin eye drops 4 times daily. A complete ophthalmologic assessment was done again at 15 days, 1month, 3 months and 6months. During follow up visit, all patients were evaluated for improvement in subjective symptoms, objective signs and ocular safety based on changes in visual acuity, intraocular pressure and fundus examination. Subjective and objective assessments of the symptoms (itching, photophobia and tearing) and signs (papillae, bulbar hyperaemia and palpebral hyperaemia) of vernal keratoconjunctivitis were done using standard scoring methodologies as follows:

Scoring of symptoms:

Itching	
Grade 0	**No itching**
Grade 1	Occasional sensation of itching
Grade 2	Frequent sensation but occasional rubbing
Grade 3	Sensation of rubbing is almost always and frequent rubbing any time of the day

Photophobia	
Grade 0	**None**
Grade 1	Outdoors only
Grade 2	Indoors-bright light (TV, computer etc.)
Grade 3	Indoors, prefers darkened room

Watering	
Grade 0	**None**
Grade 1	Mild (eye feels slightly watery)
Grade 2	Moderate (blows nose occasionally)
Grade 3	Severe (tears overflow)

Scoring of Signs:

Papillae	
Grade 0	**Absent**
Grade 1	A few papillae of less than 0.2 mm
Grade 2	Papillae of 0.3 to 1 mm on the tarsal conjunctiva
Grade 3	Papillae of 1 to 3 mm throughout the tarsal conjunctival area

Hyperemia (bulbar conjunctiva)	
Grade 0	**None**
Grade 1	Mild (dilation of a few blood vessels)
Grade 2	Moderate (dilation of many blood vessels)
Grade 3	Severe (dilation of all blood vessels, Eyes look congested)

Hyperemia (palpebral conjunctiva)	
Grade 0	**None**
Grade 1	Mild (dilation of a few blood vessels in part of palpebral conjunctiva)
Grade 2	Moderate (dilation of many blood vessels in entire palpebral conjunctiva)
Grade 3	Severe (redness of entire palpebral conjunctiva; individual blood vessels cannot be distinguished)

Patient's clinical responses (i.e., scoring of signs and symptoms) and tolerability to medication was assessed by evaluating IOP at initial presentation and 14 (week 2), 28 (week 4), 90 (week 12) and 180 (week 24) days post treatment, through appropriate follow-up visits.

3.4 Statistical Methods

The data was analyzed using SPSS (Statistical Presentation System Software) for windows (version 20.0). The statistical methods adopted for the study were (i) descriptive statistics and (ii) inferential statistics (crosstab procedure) and Cramer's V. Sample size was calculated based on the prevalence of 4% using the formula $S\text{-}Z^2pq/d^2$ with Z value of 1.96 and proportion of prevalence as 0.04 and margin of error as 0.05. The estimated sample size was 60, and a total of 72 patients were included in this study.

4. Results

The majority of VKC cases were seen in the 5-9 years group (59%), followed by the 10-14 years group (39%). The above

15 years group constituted 10% of the VKC cases. The youngest patient in this study was 5 years old and the oldest was 25 years old. (Table 1)

Table 1: Age distribution of VKC cases

			groups		Total
			Group I	Group II	
Ages	5-9	Count (%)	20 (55.6%)	13 (36.1%)	33 (45.8%)
	10-14	Count (%)	12 (33.3%)	21 (58.3%)	33 (45.8%)
	15 +	Count (%)	4 (11.1%)	2 (5.6%)	6 (8.3%)
Total		Count (%)	36 (100%)	36 (100%)	72 (100%)

Table 2: Symmetric measurements of age distribution of VKC cases

		Value	Approx. Sig.
Nominal by Nominal	Phi	.253	.100
	Cramer's V	.253	.100
N of Valid Cases		72	
(Using the asymptotic standard error assuming the nul hypote)			

In the study group, 86% were males and females constituted 14%. The ratio of M:F was 9:1. This picture is also seen in both the individual treatment groups. The gender wise distribution of VKC cases is presented in Table 3.

Table 3: Gender-wise distribution of VKC cases

			groups		Total
			Group I	Group II	
sex	Male	Count (%)	30 (83.3%)	32 (88.9%)	62 (86.1%)
	Female	Count (%)	6 (16.7%)	4 (11.1%)	10 (13.9%)
Total		Count (%)	36 (100%)	36 (100%)	72 (100%)

Table 4: Symmetric measures

		Value	Approx. Sig.
Nominal by Nominal	Phi	-.080	.496
	Cramer's V	.080	.496
N of Valid Cases		72	

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the null hypothesis

Table 5: T-test (group statistics)

	groups	N	Mean	Std. Deviation	Std. Error Mean
age	Group I	36	9.81	4.091	.682
	Group II	36	10.50	2.249	.375

Table 6: t-test for Equality of Means (Independent Samples Test

	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
age	-.893	70	.375	-.694	.778

The changes in the itching scores during the treatment period for the cyclosporin and tacrolimus group are provided in Table 7, while the results of statistical analysis for the two groups vis-a-vis the effect of treatment on itching scores is presented in Table 8. Figure 1 graphically shows the mean itching scores as was present in the two groups at various intervals of time. The itching scores in both the treatment groups improved over the 24-week observation period.

Table 7: Itching scores in both the treatment groups during treatment period

Groups		No. of patients with complaints of itching (count with percentage)				Total
		G 0	G 1	G 2	G 3	
I	Initial visit	0 (0%)	12 (33.3%)	21 (58.3%)	3 (8.3%)	36 (100%)
	1st visit	9 (25%)	17 (47.2%)	9 (25%)	1 (2.8%)	36 (100%)
	2nd Visit	21 (58.3%)	14 (38.9%)	1 (2.8%)	0 (0%)	36 (100%)
	3rd visit	34 (94.4%)	2 (5. 6s%)	0 (0%)	0 (0%)	36 (100%)
	4th visit	35 (100%)	0 (0%)	0 (0%)	0 (0%)	35 (100%)
	Total	99 (55.3%)	45 (25.1%)	31 (17.3%)	4 (2.2%)	179 (100%)
II	Initial Visit	0 (0%)	2 (5.6%)	34 (94.4%)		36 (100%)
	1st visit	0 (0%)	25 (69.4%)	11 (30.6%)		36 (100%)
	2nd visit	19 (52.8%)	17 (47.2%)	0 (0%)		36 (100%)
	3rd visit	35 (97.2%)	1 (2.8%)	0 (0%)		36 (100%)
	4th visit	36 (100%)	0 (0%)	0 (0%)		36 (100%)
	Total	90 (50%)	45 (25%)	45 (25%)		180 (100%)
Total	Initial visit	0 (0%)	14 (19.4%)	55 (76.4%)	3 (4.2%)	72 (100%)
	1st visit	9 (12.5%)	42 (58.3%)	20 (27.8%)	1 (1.4%)	72 (100%)
	2nd visit	40 (55.6%)	31 (43.1%)	1 (1.4%)	0 (0%)	72 (100%)
	3rd visit	69 (95.8%)	3 (4.2%)	0 (0%)	0 (0%)	72 (100%)
	4th visit	71 (100%)	0 (0%)	0 (0%)	0 (0%)	71 (100%)
	Total	189 (52.6%	90 (25.1%)	76 (21.2%)	4 (1.1%)	359 (100%)

Table 8: Chi-Square Tests

Groups		Value	df	Asymp. Sig. (2-sided)
Group I	Pearson Chi-Square	134.819	12	.000
Group II	Pearson Chi-Square	224.111	8	.000
Total	Pearson Chi-Square	345.372	12	.000

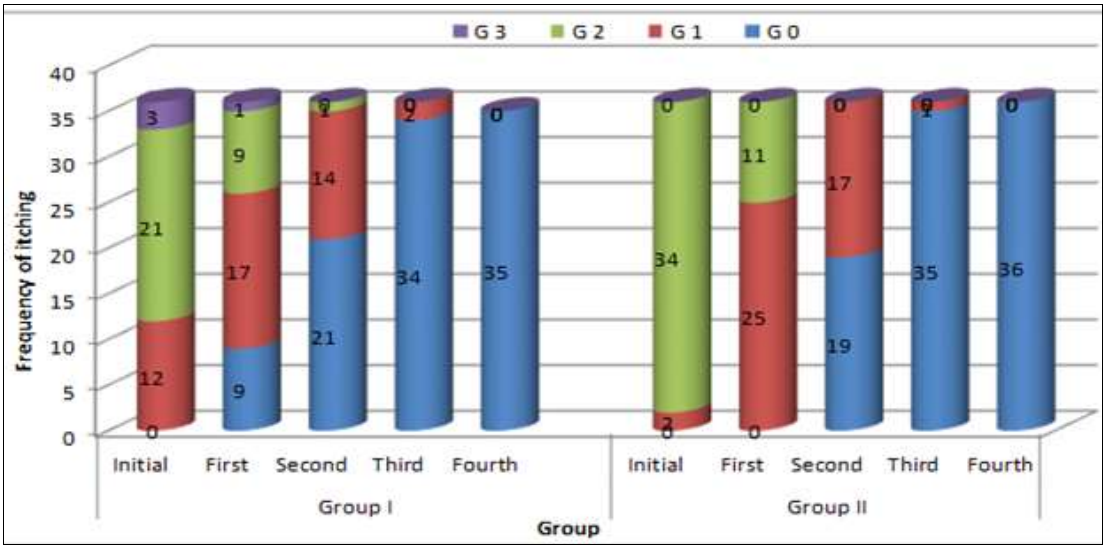

Fig 1: Itching scores in both the groups

The changes in the photophobia scores during the treatment period for cyclosporin and tacrolimus group are provided in Table 9 while the results of statistical analysis for the two groups vis-a-vis the effect of treatment on photophobia scores is presented in Table 10. Figure 2 graphically shows the mean photophobia scores as was present in the two groups at various intervals of time. The photophobia scores in both the treatment groups improved over the 24-week observation period.

Table 9: Photophobia changes in both groups during treatment period

Groups		No. of patients with photophobia changes during treatment period (count with percentage)				Total
		G 0	G 1	G 2	G 3	
I	Initial visit	0 (0%)	14 (38.9%)	21 (58.3%)	1 (2.8%)	36 (100%)
	1st visit	0 (0%)	23 (63.9%)	13 (36.1%)	0 (0%)	36 (100%)
	2nd visit	21 (58.3%)	14 (38.9%)	1 (2.8%)	0 (0%)	36 (100%)
	3rd visit	34 (94.4%)	1 (2.8%)	1 (2.8%)	0 (0%)	36 (100%)
	4th visit	34 (97.1%)	1 (2.9%)	0 (0%)	0 (0%)	35 (100%)
	Total	89 (49.7%)	53 (29.6%)	36 (20.1%)	1 (0.6%)	179 (100%)
II	Initial Visit	0 (0%)	13 (36.1%)	23 (63.9%)		36 (100%)
	1st visit	0 (0.0%)	23 (63.9%)	13 (36.1%)		36 (100%)
	2nd visit	8 (22.2%)	27 (75%)	1 (2.8%)		36 (100%)
	3rd visit	29 (80.6%)	6 (16.7%)	1 (2.8%)		36 (100%)
	4th visit	34 (94.4%)	2 (5.6%)	0 (0%)		36 (100%)
	Total	71 (39.4%)	71 (39.4%)	38 (21.1%)		180 (100%)
Total	Initial visit	0 (0%)	27 (37.5%)	44 (61.1%)	1 (1.4%)	72 (100%)
	1st visit	0 (0%)	46 (63.9%)	26 (36.1%)	0 (0%)	72 (100%)
	2nd visit	29 (40.3%)	41 (56.9%)	2 (2.8%)	0 (0%)	72 (100%)
	3rd visit	63 (87.5%)	7 (9.7%)	2 (2.8%)	0 (0%)	72 (100%)
	4th visit	68 (95.8%)	3 (4.2%)	0 (0%)	0 (0%)	71 (100%)
	Total	160 (44.6%)	124 (34.5%)	74 (20.6%)	1 (0.3%)	359 (100%)

Table 10: Chi-Square Tests

Groups		Value	df	Asymp. Sig. (2-sided)
Group I	Pearson Chi-Square	152.743	12	.000
Group II	Pearson Chi-Square	160.556	8	.000
Total	Pearson Chi-Square	302.875	12	.000

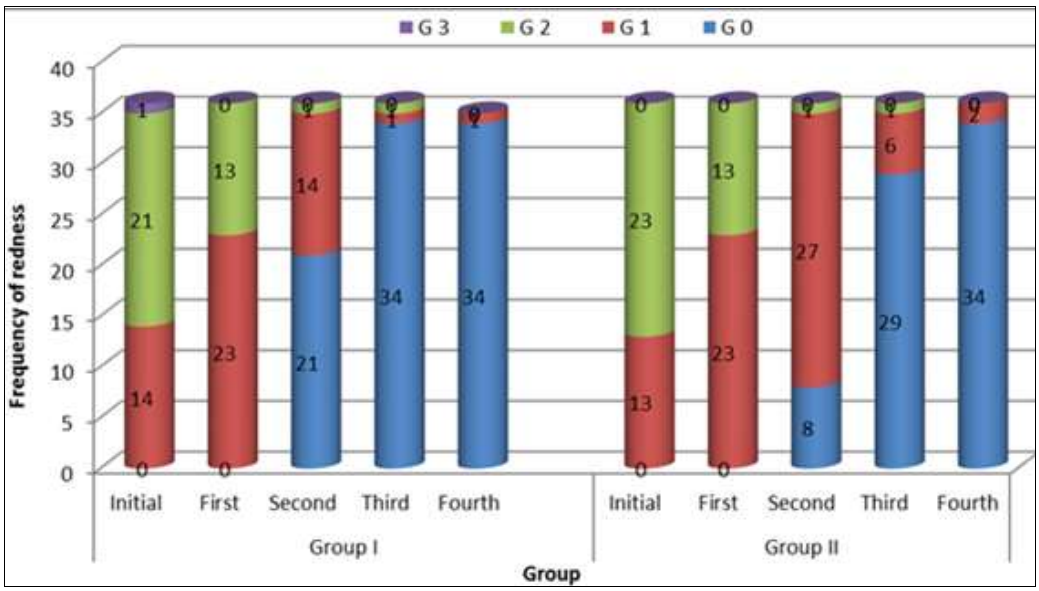

Fig 2: Photophobia changes in both the groups during treatment

The changes in watering scores during the treatment period for the cyclosporin and Tacrolimus group are provided in Table 11 while the results of statistical analysis for the two groups vis-a-vis the effect of treatment on watering scores is presented in Table 12. Figure 3 graphically shows the mean watering scores as was present in the two groups at various intervals of time. The watering scores in both the treatment groups improved over the 8-week observation period.

Table 11: Watering scores in both the groups during treatment period

Groups		No. of patients with photophobia changes during treatment period (count with percentage)				Total
		G 0	G 1	G 2	G 3	
I	Initial visit	6 (16.7%)	10 (27.8%)	19 (52.8%)	1 (2.8%)	36 (100%)
	1st visit	7 (19.4%)	18 (50%)	11 (30.6%)	0 (0%)	36 (100%)
	2nd Visit	29 (80.6%)	7 (19.4%)	0 (0%)	0 (0%)	36 (100%)
	3rd Visit	36 (100%)	0 (0%)	0 (0%)	0 (0%)	36 (100%)
	4th visit	36 (100%)	0 (0%)	0 (0%)	0 (0%)	36 (100%)
	Total	113 (63.1%)	35 (19.6%)	30 (16.8%)	1 (0.6%)	179 (100%)
II	Initial Visit	8 (22.2%)	23 (63.9%)	5 (13.9%)		36 (100%)
	1st visit	11 (30.6%)	24 (66.7%)	1 (2.8%)		36 (100%)
	2nd visit	23 (63.9%)	13 (36.1%)	0 (0%)		36 (100%)
	3rd visit	36 (100%)	0 (0%)	0 (0%)		36 (100%)
	4th visit	36 (100%)	0 (0%)	0 (0%)		36 (100%)
	Total	114 (63.3%)	60 (33.3%)	6 (3.3%)		180 (100%)
Total	Initial visit	14 (19.4%)	33 (45.8%)	24 (33.3%)	1 (1.4%)	72 (100%)
	1st visit	18 (25%)	42 (58.3%)	12 (16.7%)	0 (0%)	72 (100%)
	2nd visit	52 (72.2%)	20 (27.8%)	0 (0%)	0 (0%)	72 (100%)
	3rd visit	72 (100%)	0 (0%)	0 (0%)	0 (0%)	72 (100%)
	4th visit	71 (100%)	0 (0%)	0 (0%)	0 (0%)	71 (100%)
	Total	227 (63.2%)	95 (26.5%)	36 (10%)	1 (0.3%)	359 (100%)

Table 12: Chi square tests

Groups		Value	df	Asymp. Sig. (2-sided)
Group I	Pearson Chi-Square	126.270	12	.000
Group II	Pearson Chi-Square	92.833	8	.000
Total	Pearson Chi-Square	213.413	12	.000

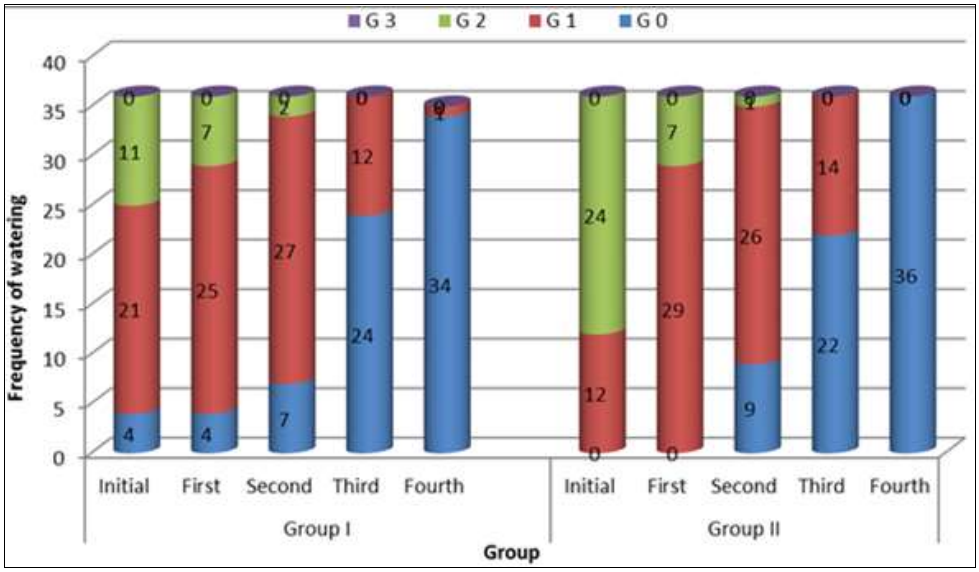

Fig 3: Watering changes in both the groups during treatment period

The changes in the bulbar hyperemia scores during the treatment period for the cyclosporin and tacrolimus group are provided in Table 13, while the results of statistical analysis for the two groups vis-a-vis the effect of treatment on bulbar hyperemia scores is presented in Table 14. Figure 4 graphically shows the mean bulbar hyperemia scores as was present in the two groups at various intervals of time. The bulbar hyperemia scores in both the treatment groups improved over the 24-week observation period.

Table 13: Hyperaemia changes in both the groups during treatment period

Groups		No. of patients with photophobia changes during treatment period (count with percentage)				Total
		G 0	G 1	G 2	G 3	
I	Initial visit	0 (0%)	13 (36.1%)	22 (61.1%)	1 (2.8%)	36 (100%)
	1st visit	0 (0%)	30 (83.3%)	6 (16.7%)	0 (0%)	36 (100%)
	2nd visit	21 (58.3%)	15 (41.7%)	0 (0%)	0 (0%)	36 (100%)
	3rd Visit	34 (94.4%)	2 (5.6%)	0 (0%)	0 (0%)	36 (100%)
	4th visit	34 (97.1%)	1 (2.9%)	0 (0%)	0 (0%)	35 (100%)
	Total	89 (49.7%)	61 (34.1%)	28 (15.6%)	1 (0.6%)	179 (100%)
II	Initial Visit	0 (0%)	11 (30.6%)	25 (69.4%)		36 (100%)
	1st visit	0 (0%)	32 (88.9%)	4 (11.1%)		36 (100%)
	2nd visit	9 (25%)	26 (72.2%)	1 (2.8%)		36 (100%)
	3rd visit	30 (83.3%)	6 (16.7%)	0 (0%)		36 (100%)
	4th visit	34 (94.4%)	2 (5.6%)	0 (0%)		36 (100%)
	Total	73 (40.6%)	77 (42.8%)	30 (16.7%)		180 (100%)
Total	Initial visit	0 (0%)	24 (33.3%)	47 (65.3%)	1 (1.4%)	72(100%)
	1st visit	0 (0%)	62 (86.1%)	10 (13.9%)	0 (0%)	72 (100%)
	2nd visit	30 (41.7%)	41 (56.9%)	1 (1.4%)	0 (0%)	72 (100%)
	3rd visit	64 (89.9%)	8 (11.1%)	0 (0%)	0 (0%)	72 (100%)
	4th visit	68 (95.8%)	3 (4.2%)	0 (0%)	0 (0%)	71 (100%)
	Total	162 (45.1%)	138 (38.4%)	58 (16.2%)	1 (0.3%)	359 (100%)

Table 14: Chi-square tests

Groups		Value	df	Asymp. Sig. (2-sided)
Group I	Pearson Chi-Square	179.849	12	.000
Group II	Pearson Chi-Square	194.214	8	.000
Total	Pearson Chi-Square	365.743	12	.000

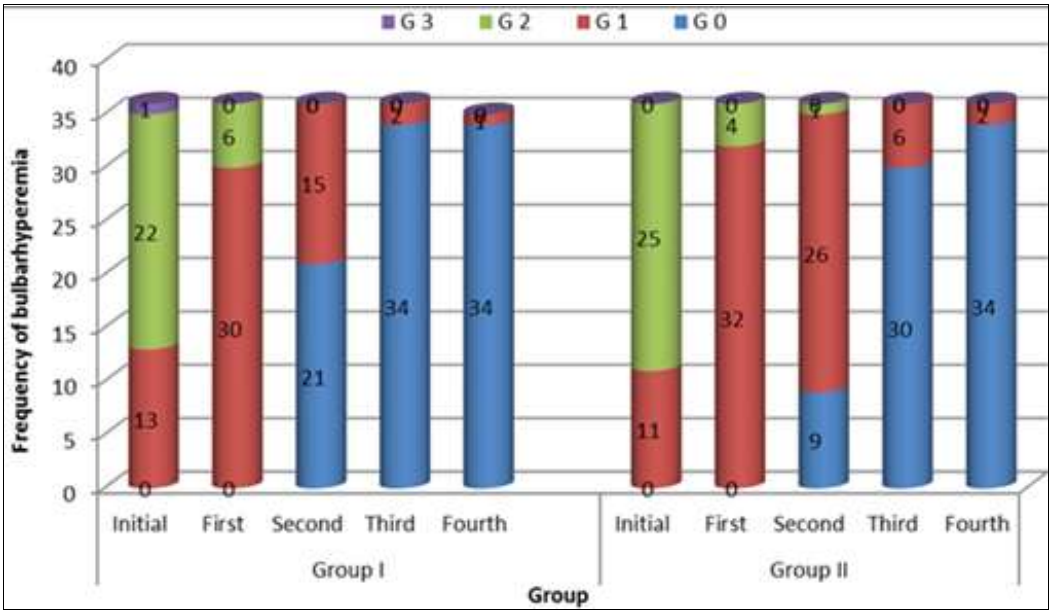

Fig 4: bulbar hyperaemia changes during treatment period in both the groups

The changes in the palpebral hyperemia scores during the treatment period for the cyclosporin and tacrolimus group are provided in Table 15 while the results of statistical analysis for the two groups vis-a-vis the effect of treatment on palpebral hyperemia scores is presented in Table 16. Figure 5 graphically shows the mean palpebral hyperemia scores as was present in the two groups at various intervals of time. The palpebral hyperemia scores in both the treatment groups improved over the 24-week observation period.

Table 15: palpebral hyperaemia scores in both the groups during treatment period

Groups		No. of patients with palpebral hyperaemia changes during treatment period (count with percentage)				Total
		G 0	G 1	G 2	G 3	
I	Initial visit	0 (0%)	13 (36.1%)	21 (58.3%)	2 (5.6%)	36 (100%)
	1st visit	0 (0%)	34 (94.4%)	2 (5.6%)	0 (0%)	36 (100%)
	2nd visit	15 (41.7%)	20 (55.6%)	1 (2.8%)	0 (0%)	36 (100%)
	3rd visit	34 (94.4%)	1 (2.8%)	1 (2.8%)	0 (0%)	36 (100%)
	4th visit	34 (97.1%)	1 (2.9%)	0 (0%)	0 (0%)	35 (100%)
	Total	83 (46.4%)	69 (38.5%)	25 (14.0%)	2 (1.1%)	179 (100%)
II	Initial Visit	0 (0%)	33 (91.7%)	3 (8.3%)		36 (100%)
	1st visit	0 (0%)	32 (88.9%)	4 (11.1%)		36 (100%)
	2nd visit	15 (41.7%)	20 (55.6%)	1 (2.8%)		36 (100%)
	3rd visit	30 (94.4%)	2 (5.6%)	0 (0%)		36 (100%)
	4th visit	36 100%)	0 (0%)	0 (0%)		36 (100%)
	Total	85 (47.2%)	68 (37.8%)	27 (15%)		180 (100%)
Total	Initial visit	0 (0%)	26 (36.1%)	44 (61.1%)	2 (2.8%)	72 (100%)
	1st visit	0 (0%)	67 (93.1%)	5 (6.9%)	0 (0%)	72 (100%)
	2nd visit	30 (41.7%)	40 (55.6%)	2 (2.8%)	0 (0%)	72 (100%)
	3rd visit	68 (94.4%)	3 (4.2%)	1 (1.4%)	0 (0%)	72 (100%)
	4th visit	70 (98.6%)	1 (1.4%)	0 (0%)	0 (0%)	71 (100%)
	Total	168 (46.8%)	137 (38.2%)	52 (14.5%)	2 (0.6%)	359 (100%)

Table 16: chi-square tests

Groups		Value	df	Asymp. Sig. (2-sided)
Group I	Pearson Chi-Square	198.260	12	.000
Group II	Pearson Chi-Square	199.491	8	.000
Total	Pearson Chi-Square	397.487	12	.000

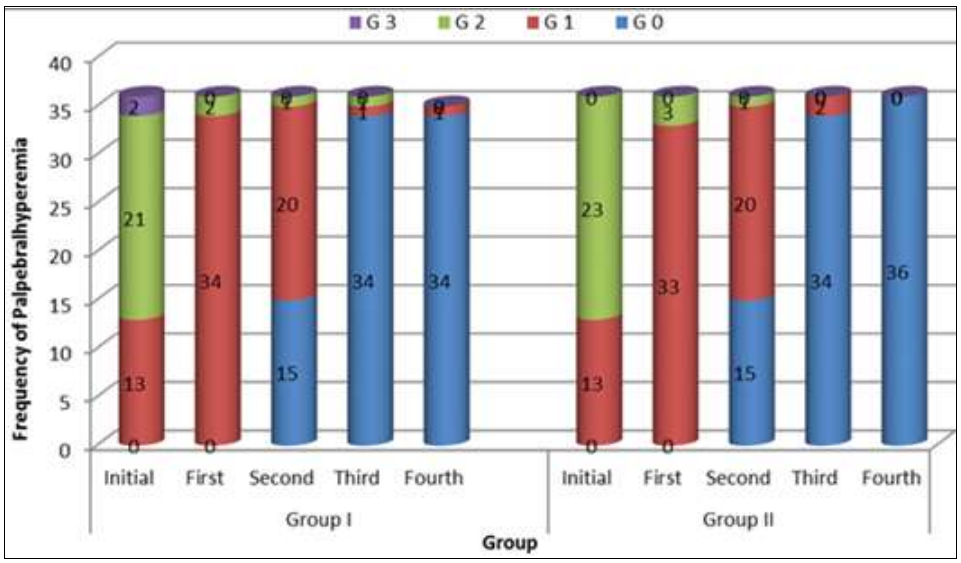

Fig 5: palpebral hyperaemia scores in both groups during treatment period

The changes in the papillae scores during the treatment period for cyclosporin and tacrolimus group are provided in Table 17, while the results of statistical analysis for the two groups vis-a-vis the effect of treatment on papillae scores is presented in Table 18. Figure 5 graphically shows the mean papillae scores as was present in the two groups at various intervals of time. The papillae scores in both the treatment groups improved over the 24-week observation period.

Table 17: Papillae scores in both the groups during treatment period

Groups		No. of patients with papillae during treatment period (count with percentage)			Total
		G 0	G 1	G 2	
I	Initial visit	0 (0%)	12 (33.3%)	24 (66.7%)	36 (100%)
	1st visit	0 (0%)	30 (83.3%)	6 (16.7%)	36 (100%)
	2nd visit	1 (2.8%)	31 (86.1%)	4 (11.1%)	36 (100%)
	3rd visit	12 (33.3%)	23 (63.9%)	1 (2.8%)	36 (100%)
	4th visit	34 (97.1%)	1 (2.9%)	0 (0%)	35 (100%)
	Total	47 (26.3%)	97 (54.2%)	35 (19.6%)	179 (100%)
II	Initial Visit	0 (0%)	18 (50%)	18 (50%)	36 (100%)
	1st visit	0 (0%)	22 (61.1%)	14 (38.9%)	36 (100%)
	2nd visit	14 (38.9%)	22 (61.1%)	0 (0%)	36 (100%)
	3rd visit	27 (75%)	9 (25%)	0 (0%)	36 (100%)
	4th visit	36 (100%)	0 (0%)	0 (0%)	36 (100%)
	Total	77 (42.8%)	71 (39.4%)	32 (17.8%)	180 (100%)
Total	Initial visit	0 (0%)	30 (41.7%)	42 (58.3%)	72 (100%)
	1st visit	0 (0%)	52 (72.2%)	20 (27.8%)	72 (100%)
	2nd visit	15 (20.8%)	53 (73.6%)	4 (5.6%)	72 (100%)
	3rd visit	39 (54.2%)	32 (44.4%)	1 (1.4%)	72 (100%)
	4th visit	70 (98.6%)	1 (1.4%)	0 (0%)	71 (100%)
	Total	124 (34.5%)	168 (46.8%)	67 (18.7%)	359 (100%)

Table 18: Chi-square tests

Groups		Value	df	Asymp. Sig. (2-sided)
Group I	Pearson Chi-Square	181.433	8	.000
Group II	Pearson Chi-Square	142.161	8	.000
Total	Pearson Chi-Square	294.078	8	.000

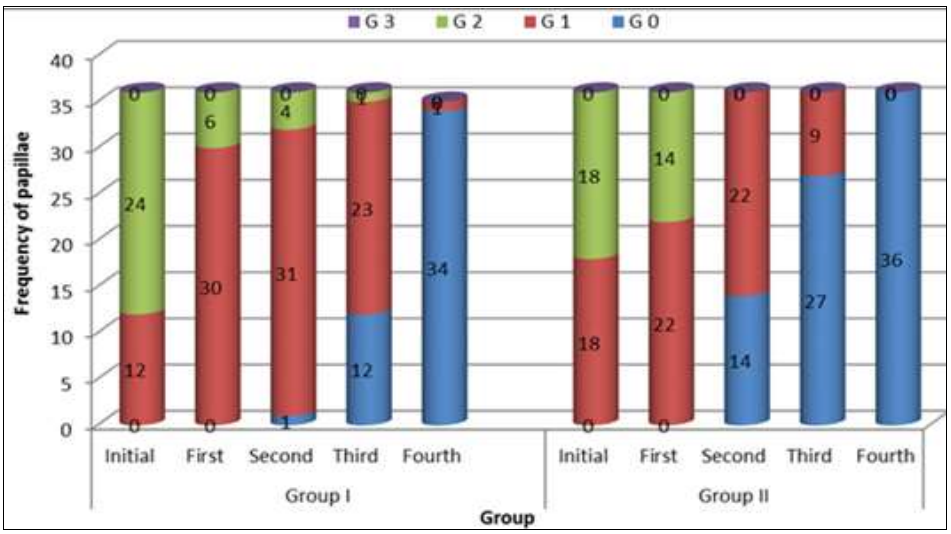

Fig 6: Papillae scores in both the groups during treatment period

5. Discussion

In this study, the majority of VKC cases were seen in the 5-15 years group (86%). 14% of the VKC cases were above 15 years of age. The youngest patient in this study was 5 years old while the oldest was 25 years old. The findings as far as the age of occurrence and distribution of VKC cases in different age groups concurs with such studies done in other parts of the world. In a case series of 406 vernal keratoconjunctivitis patients studied by Leonardi A *et al* in Padua, Italy, it was found that at the time of diagnosis, 83% of patients were under 10 years of age, with the average age of onset in males and females being 7.0 $\pm$ 5 and 7.5 $\pm$ 6 years respectively [4]. When patients were divided into smaller age subgroups, the highest prevalence of VKC was found in the 6–10 years group (56.3%). In a study by Al-Akily SA and Bamashmus MA done in Yemen, the majority of cases with VKC examined in this study were younger than 10 years. (49.2%) [5]. The highest number of cases were found in the 5–9 years group (180 cases, 41.76%), followed by the 10–14 years group (144 cases, 33.41%).

VKC is commoner in males, with the male to female ratio in different studies varying from 4:1 to 2:1. In this study group (72 patients) 90% were males and females constituted 20%. The ratio of M:F was 9:1. This picture is also seen in both the individual treatment groups. In the Yemeni study, the majority of VKC patients (n=431) were males (n=327) and females (n= 104) with a male:female ratio of 3.1:1 [5]. In the Italian study, the vast majority of VKC patients (n=311) were male (76%), with a male:female ratio of 3.3:1. In this study, the baseline characteristics were similar between the groups. Cyclosporine eye drops 0.05% resulted in an approximately 97% reduction in symptoms and signs of VKC by the end of 24 weeks of treatment, as there were no similar studies of same duration and concentration of drug available for comparison, the response of 35% reduction in symptoms and signs at 2 weeks has been compared with a similar study done by Pucci N *et al*. in a double masked trial where in cyclosporine 2% resulted in an approximately 40% reduction in symptoms and signs which was in concurrence [6].

However, in this study, because of low concentration of cyclosporine 0.05%, only 3% of patients reported burning sensation and was better tolerated in the other 97% of patients who were thus able to use it throughout the study period which has resulted in better resolution of symptoms as compared to other studies with cyclosporine eye drops preparation of various concentration (0.1%, 1%, 2% by Pucci N *et al*, Kumar S *et al*., Labcharoenwongs P *et al*. respectively) where many of the patients had discontinued the drugs resulting in recurrence of disease [6-8]. In a longer open trial by Spadavecchia L *et al*. in 2006, utilizing a lower concentration of cyclosporine (1.25% and 1%) for 4 months, a higher degree of benefit in subjective and objective scores were reported which is in concordance with the present study [9].

Throughout the study period, IOP, lens and fundus remained with in normal limits.

Difference in efficacy of cyclosporine in various publications by Spadavecchia L *et al*. [cyclosporine (1.25% and 1%) for 4 months] by De Smedt S *et al*. in 2012 (cyclosporine 2%) could be due to difference in concentration of cyclosporine eye drops and duration of treatment [9-10]. Cyclosporine eye drops caused significant decrease in symptoms and signs from second week onwards which was similar to a prospective, double-masked, randomized comparative study conducted by Labcharoenwongs P *et al*. in 2012 in which twenty-four VKC patients received tacrolimus eye ointment 0.1% twice-daily for 8 weeks, and the other 24 received cyclosporine A eye drops 2% for the same duration. Tacrolimus eye ointment 0.03% resulted in remission in 100% of patients with VKC by the end of 24 weeks of treatment which is in concurrence with the study done by Al Amri AM *et al* in which, after 6 weeks of tacrolimus eye ointment 0.1%, all patients were asymptomatic with minimal adverse effects [11]. In this study, 7% of patients reported mild irritation which was tolerated by the patients who were thus able to continue the drug for the full study period resulting in 100% remission of VKC, which concurs with the study done by Kumar S *et al*. in which 7.4% of patients reported mild irritation with good tolerance and none of the patients discontinued the drug. It has been noted that all the patients have received treatment throughout the study period because of lower concentration of the medication used with negligible adverse effects resulting and good response. It has also been observed that patients on treatment with tacrolimus eye ointment 0.03% did not require any additional medications, which showed its potential role as steroid sparing agent which is in concurrence with the study done by Kumar S *et al*. [7]

In this study, both the drugs (cyclosporine eye drops 0.05% and tacrolimus eye ointment 0.03%) were almost equally efficacious (97% and 100% respectively) in treating VKC and did not show any significant difference between their

efficacy, which concurs with a similar prospective double masked, randomized comparative study done by Kumari R *et al*. in 2016 in which tacrolimus eye ointment 0.03% brought about an improvement of the signs and symptoms of VKC similar to cyclosporine eye drops [12]. Also, there were no ocular side effects in either group which is in concordance with the study done by Singla E *et al*. [13]

IOP, lens and fundus of all the patients were with in normal limits throughout the study period in both groups, which concurs with studies done by Kumari R *et al* and Singla E *et al*. [12-13]

The results of this study are in concurrence with another prospective double-masked, randomized, comparative study conducted in 2016 by Kumari R and Saha CB in which 19 patients received tacrolimus eye ointment 0.03% daily for 6 weeks and another 15 received cyclosporine eye drops 0.5% four times daily for 6 weeks, where it was found that tacrolimus brought about an improvement of the signs and symptoms of VKC similar to that of cyclosporine A [12].

6. Conclusion

Both cyclosporine eye drops 0.05% and tacrolimus eye ointment 0.03% were equally efficacious in the treatment of VKC (97% and 100% respectively). The tolerability of both were good with negligible side effects like irritation and burning sensation. There was no evidence of increased IOP, cataract formation or other steroid-related complications. Hence, they proved to be a much safer alternative to steroids.

7. References

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