TREATMENT OF VERNAL KERATOCONJUNCTIVITIS: COMPARISON BETWEEN TOPICAL CYCLOSPORINE 0.05% AND FLUOROMETHOLONE 0.1% IN TERMS OF EFFICACY AND SAFETY

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ABSTRACT

Background: *This study was undertaken to evaluate and compare the efficacy and safety of topical solutions of Cyclosporine and Fluorometholone in patients of vernal keratoconjunctivitis***.**
Settings and design: *This was a prospective, double blind, comparative, interventional randomized controlled trial,*
Material and methods: *Patients of vernal kerato-conjunctivitis were included in the study after obtaining their informed consent.Each eye of one patient was prescribed either Cyclosporine eye drops or Fluorometholone eye drops. Patients' vernal keratoconjunctivitis specific symptoms, signs and intraocular pressure were graded and measured repeatedly till 90th day.*
Statistical analysis used: *The intra-group and inter-group changes in symptoms and signs during the course of study were compared using repeat measure ANOVA test.*
Results: *Forty four subjects completed the study, with male preponderance. There was a progressive statistically significant reduction in the symptoms of itching, watering discharge and photophobia from day 7 till day 30 in both the groups.In Cyclosporine group there intra ocular pressure remained unaffected (P=0.17), but, in Fluorometholone group there was a significant increase in intra ocular pressure (P<0.0001). In the patients with mild disease, the improvement was similar in both the groups (P=0.486, Repeated measures ANOVA test).*
Conclusions: *In mild cases of vernal keratoconjunctivitis, topical Cyclosporine is equally effective as topical Fluorometholone, and Cyclosporine is safer as there is no rise in intra ocular pressure.*

Key words: *cyclosporine, Fluorometholone, intra ocular pressure, randomized controlled trial, vernal keratoconjunctivitis*

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic recurrent noninfectious allergic disease that generally affects children and young adults. Its onset is common in spring and summer season nevertheless VKC may occur at any time of the year.

Topical corticosteroids have been in use for treatment of these cases as they provide relief quickly but there is rapid recurrence of symptoms following their discontinuation. Thereis also a potential of adverse effects of corticosteroid. Such as secondary glaucoma, infective condition of ocular surface as well as steroid induced cataract. The menace of glaucoma is under estimated because of practical limitation of intra ocular pressure (IOP) measurement in the affected pediatric population.[1]

In the present scenario search for an effective and safe topical medication is still on for management of vernal keratoconjunctivitis (VKC). Topical cyclosporine has been tried as first line of treatment in some clinical trials on vernal keratoconjunctivitis and has been demonstrated to be effective in both palpebral and limbal forms of vernal keratoconjunctivitis.[1,2]

However, no literature is available on its efficacy in VKC in comparison to topical steroids.This study was undertaken to evaluate the efficacy and safety of cyclosporine ophthalmic solution in comparison to Fluorometholone ophthalmic solution in treatment of patients of vernal keratoconjunctivitis.

AIMS OF THE STUDY

1. To evaluate the efficacy of topical cyclosporine (0.05%) as compared to topical Fluorometholone (0.1%) in treatment of vernal keratoconjunctivitis.
2. To evaluate and compare the safety of topical cyclosporine 0.05% and topical fluorometholone0.1% in patients of vernal keratoconjunctivitis.

METHODS

This was a prospective, double blind, comparative, interventional randomized controlled trial (RCT) comparing the signs and symptoms of vernal keratoconjunctivitis patients receiving topical cyclosporine (0.05%) or topical Fluorometholone (0.1%). Sample size of 43 patients was reached upon using confidence level 95%, sampling error ±10, and population 600. Patients of vernal kerato-conjunctivitis attending the ophthalmic outpatient department of our tertiary care hospital were screened for inclusion and exclusion criteria (**Table 1. and Table 2**.), and included in the study after obtaining their informed consent. The research methodology followed the tenets of the declaration of Helsinki.

Table 1: Diagnostic criteria for Vernal Kerato-conjunctivitis. Any one or more subjective criterion + any one or more objective criteria.

• Subjective Criteria	• Objective criteria
Itching	Superficial pannus
Redness	Limbal nodule
Watering	Horner Trantas spot
Discharge	Cobblestone appearance or presence of papillae
	Punctuate epithelial keratitis
	Shield `s ulcer

Table 2: Exclusion criteria for patient screened for the study.

Exclusion criteria.
Contact lens wearers during the period of study
Patients with ocular disorders such as glaucoma , blepharitis or uveitis
Those not willing for follow up.
Patients aged less than 5 years or more than 20 years
Previous reported allergy to corticosteroid or to any component of the study.
Ocular trauma or recent surgery in either eyes
Patient taking oral steroid.
Pregnant or lactating mothers

It was ensured that there were no vernal kerato-conjunctivitis targeted therapies for a period of one week before study enrolment (wash out period). After the washout period the patients received a complete ophthalmic examination including vernal keratoconjunctivitis specific evaluation of symptoms and signs and intraocular pressure using rebound tonometer (ICare; TiolatOy, Helsinki, Finland). This tonometer has been evaluated against Goldmann's applanation tonometer in pediatric population and has been found to be useful.[1] These symptoms and signs were graded and a score was calculated using grading system by Akpek EK etal.[2]

The evaluation and anterior segment photography was done on day 0, 7, 14, 30 and day 90 from the date of enrollment. One eye of every patient was randomly assigned to Fluorometholone group (FLAREX 0.1%, Alcon India limited), and the other to Cyclosporine group (CYCLOMMUNE 0.05%, Sun Pharmaceuticals Industries Ltd. (Avesta Division)). The brand labels of these vials were removed and new labels were affixed indicating Rand L respectively for Right eye and Left eye as decided by the

randomization. These drugs were given to the patients without the outer carton. At each consecutive visit, patients were instructed to bring their medications. In all future visits, compliance to therapy was checked by questioning the patient and inspection of the vials given to the patients. During their follow up, the patients were supplied with fresh drugs according to their treatment status.

Statistical analysis was done using MedCalc® Version 11.4.2.0.The intra-group and inter-group changes in symptoms and signs during the course of study were compared using repeat measure ANOVA test. Threshold for statistical significance was fixed at P=0.05.

RESULTS

Participant flow and follow up:

A total of 56 patients were enrolled and 44 patients completed the study over a period of one year. Thus there were 44 eyes in each group. There were 31 male subjects (70.5%) and 13 female subjects (29.5%). Average age of the subjects was 10.6 years (Range 5-20 years, SD 5.2) and the age distribution was not normal (Kolmogorov-Smirnov test for Normal distribution P= 0.01). There was clustering of cases in the age group 5-10 years (~55%), (**Fig. 1**).The age distribution was statistically similar among the male and female subjects (Mann-Whitney test, two tailed probability = 0.52)

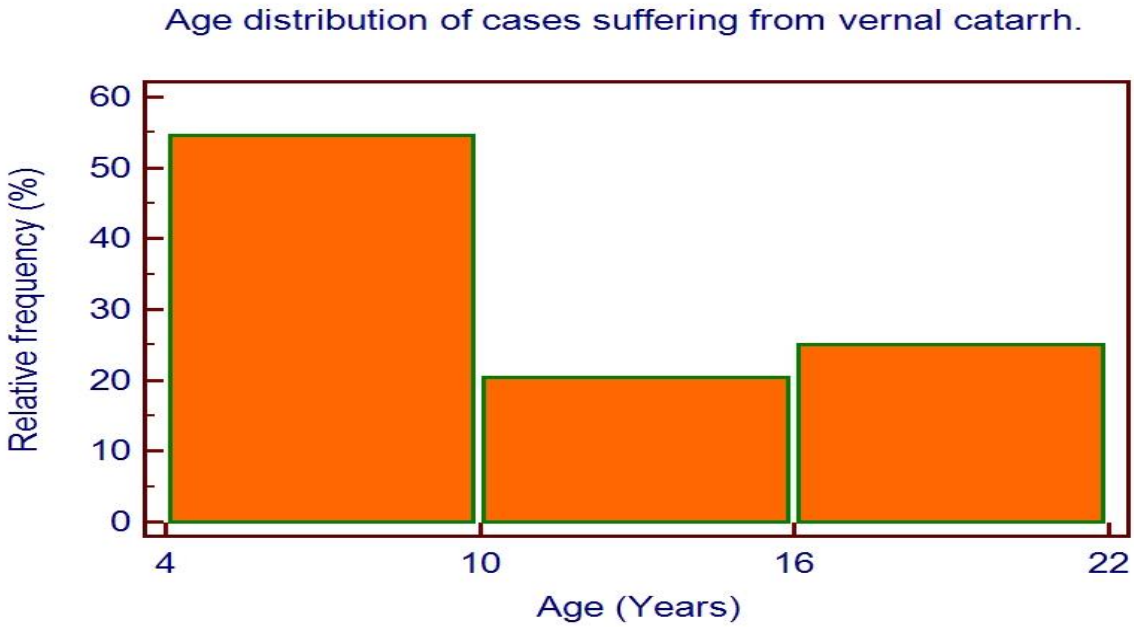
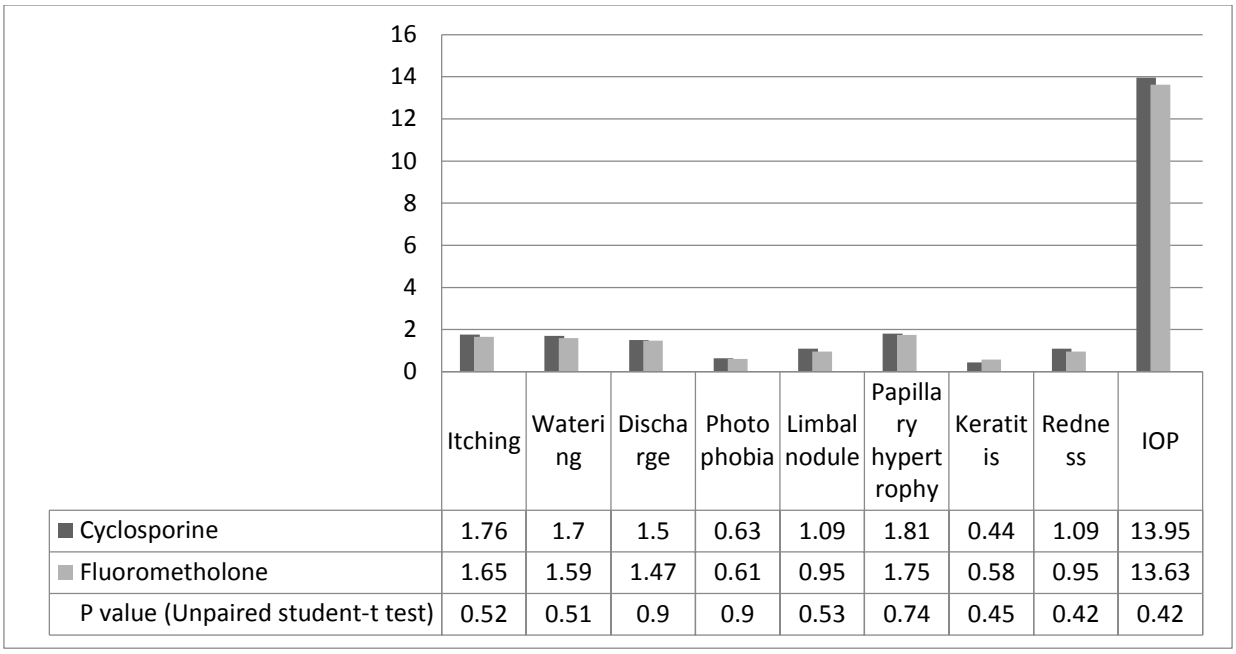


Figure 1: Age distribution of cases of Vernal Kerato Conjunctivitis (VKC) included in the study

The symptom and sign scores including the Intra Ocular Pressure (IOP) in the two groups (Cyclosporine and Fluorometholone) at the time of enrolment were statistically similar, thus displaying the congruence among the groups regarding the disease severity at baseline (P=0.65, Independent samples student-ttest). **Figure 2.**



	Itching	Watering	Discharge	Photophobia	Limbal nodule	Papillary hypertrophy	Keratitis	Redness	IOP
Cyclosporine	1.76	1.7	1.5	0.63	1.09	1.81	0.44	1.09	13.95
Fluorometholone	1.65	1.59	1.47	0.61	0.95	1.75	0.58	0.95	13.63
P value (Unpaired student-t test)	0.52	0.51	0.9	0.9	0.53	0.74	0.45	0.42	0.42

Fig. 2. Comparison of symptoms and signs score between the groups at the time of enrolment with the P value for unpaired student t-test.

The changes in the symptoms and signs in the Cyclosporine and Fluorometholone group are shown in the **Table 3**, which shows that there was a progressive statistically significant reduction in the symptoms of itching, watering discharge and photophobia from day 7 till day 30 in both the groups. At day 90 both groups had some increase in the symptoms which was statistically insignificant (repeated measures ANOVA test). There was a statistically significant negative linear trend in the symptoms studied in both the groups.

On comparing the two groups, the improvements seen in the symptoms of itching, watering, discharge and photophobia was statistically similar in both the groups at day 7, 14, and day 30. At the final evaluation at day 90 the symptom scores of itching and watering were significantly better in Fluorometholone group as compared to Cyclosporine group.

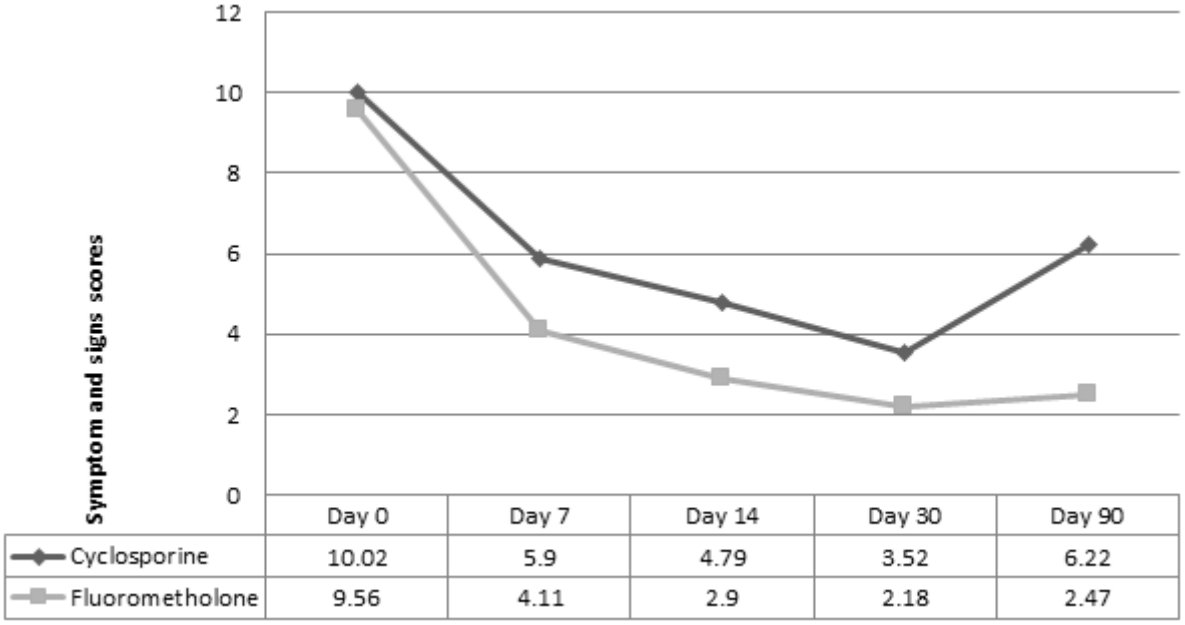
The signs studied were limbal nodule, papillary hypertrophy, punctate keratopathy, and conjunctival hyperemia. Looking at the **Table 3**, one can see that there was a progressive reduction in signs from day 7 till day 30 in both cyclosporine and Fluorometholone groups. There was a negative linear trend in severity of signs studied, from day 7 to day 90 in all the groups except conjunctival hyperemia in the cyclosporine group.

Table 3: Mean scores (Standard Errors) of Symptoms and Signs scores of Patients of vernal catarrh over time in the two groups (Topical Cyclosporine Vs Topical Fluorometholone)

Mean scores (Standard Errors) of Symptoms and Signs of Patients of vernal catarrh over time in the two groups (Topical Cyclosporin Vs Topical Fluorometholone)										
Observed symptom or sign	Group		Baseline	1 Week	2 Week	4 Week	12 Week	Repeated measures ANOVA for each group from day 0 to day 90 (P value or Significance level)	Trend analysis for linearity (Reported only when statistically significant)	Repeated measures ANOVA comparing the two groups from day 0 to day 90 (P value)
Itching	Cyclosporine	Mean	1.70	0.82	0.61	0.57	1.02	<0.001	-4.3	0.001
		Standard Error	0.12	0.12	0.09	0.09	0.13			
	Fluorometholone	Mean	1.66	0.61	0.32	0.16	0.27	<0.001	-10.9	
		Standard Error	0.12	0.09	0.07	0.06	0.08			
Watering	Cyclosporine	Mean	1.70	0.70	0.59	0.32	0.77	<0.001	-7.3	0.031
		Standard Error	0.14	0.12	0.10	0.07	0.13			
	Fluorometholone	Mean	1.59	0.50	0.34	0.23	0.23	<0.001	-8.758	
		Standard Error	0.13	0.10	0.09	0.07	0.07			
Discharge	Cyclosporine	Mean	1.50	0.68	0.64	0.39	0.64	<0.001	-4.90	0.137
		Standard Error	0.17	0.11	0.12	0.10	0.13			
	Fluorometholone	Mean	1.48	0.55	0.36	0.23	0.30	<0.001	-6.40	
		Standard Error	0.18	0.11	0.09	0.06	0.08			
Photophobia	Cyclosporine	Mean	0.64	0.32	0.14	0.11	0.16	<0.001	-4.9	0.277
		Standard Error	0.12	0.08	0.06	0.05	0.07			
	Fluorometholone	Mean	0.61	0.18	0.05	0.05	0.05	<0.001	-4.9	
		Standard Error	0.12	0.06	0.03	0.03	0.03			
Limbal nodule	Cyclosporine	Mean	1.09	0.52	0.45	0.43	0.84	<0.001	-1.70	<0.001
		Standard Error	0.15	0.11	0.11	0.10	0.14			
	Fluorometholone	Mean	0.95	0.14	0.14	0.00	0.05	<0.001	-5.10	
		Standard Error	0.16	0.08	0.08	0.00	0.05			
Papillary hypertrophy	Cyclosporine	Mean	1.82	1.80	1.70	1.64	1.61	0.02	-2.7	0.362
		Standard Error	0.14	0.14	0.14	0.14	0.14			
	Fluorometholone	Mean	1.75	1.64	1.50	1.48	1.39	<0.001	-3.50	
		Standard Error	0.12	0.13	0.13	0.14	0.13			
Punctate keratopathy	Cyclosporine	Mean	0.48	0.30	0.14	0.07	0.11	<0.001	-2.6	0.659
		Standard Error	0.13	0.11	0.06	0.05	0.06			
	Fluorometholone	Mean	0.57	0.20	0.05	0.05	0.05	<0.001	-3.6	
		Standard Error	0.14	0.10	0.05	0.05	0.03			
Conjunctival Hyperemia	Cyclosporine	Mean	1.09	0.77	0.52	0.66	1.0682	<0.001	Insignificant	<0.001
		Standard Error	0.13	0.13	0.11	0.12	0.15			
	Fluorometholone	Mean	0.9545	0.30	0.16	0.16	0.16	<0.001	-5.3	
		Standard Error	0.12	0.08	0.06	0.06	0.06			
Intra Ocular Pressure	Cyclosporine	Mean	13.95	14.09	14.20	14.41	14.30	0.65	Insignificant	<0.001
		Standard Error	0.33	0.29	0.33	0.26	0.27			
	Fluorometholone	Mean	13.64	14.77	15.57	17.32	18.34	<0.001	14.23	
		Standard Error	0.23	0.24	0.31	0.36	0.37			

Intergroup comparison showed that Fluorometholone group had greater reduction in the signs as compared to cyclosporine group at day 90(Repeated measures ANOVA). However of the four signs studied this difference was statistically significant for limbal nodule and conjunctival hyperemia only. In cyclosporine group there was no significant increase in intra ocular pressure (statistically insignificant positive linear trend 1.40, P=0.17). However, in Fluorometholone group there was a significant increase in intra ocular pressure (positive linear trend of 14.23, P<0.0001). Inter group comparison showed that although there was no significant difference in intra ocular pressure of both groups at base line but later there was significant increase in IOP in Fluorometholone group as compared to cyclosporine group (Repeated measures ANOVA P<0.001). The total cumulative

scores over the study period are depicted in the **Figure 3**. There was a progressive reduction in the symptoms and signs scores from day 7 till day 30. The relief in symptoms and signs was more in the Fluorometholone group as compared to cyclosporine group from day 7 till day 90 when all the patients were included and analyzed (P=0.001, Repeated measures ANOVA test).



	Day 0	Day 7	Day 14	Day 30	Day 90
Cyclosporine	10.02	5.9	4.79	3.52	6.22
Fluorometholone	9.56	4.11	2.9	2.18	2.47

Figure 3: Effects of Cyclosporine and Fluorometholone on symptoms and signs scores in the patients of Vernal Kerato-conjunctivitis (VKC) during the study period of 90 days.

When only patients with mild disease (total cumulative score 0-8, at the time of enrolment, n=32, cyclosporine group=15, Fluorometholone group=17) were analyzed for their symptoms and signs during the study period, the improvement was similar in both the groups (P=0.486, Repeated measures ANOVA test). Thus patients with mild disease had similar relief in both Cyclosporine and Fluorometholone groups, none of the patients opted to quit the study because of inconvenience or discomfort due to the treatment.

DISCUSSION

In our study it was observed that the disease has greater prevalence in males (70.45%) as compared to females (29.54%) this is in concordance with other studies.[1,2,3] Cyclosporine 0.05% eye drops have fast onset of action observable at 1 week and increasing relief in signs and symptoms (itching, watering, discharge, limbal nodule, punctate keratitis, redness) is seen till 4 week time, when there is maximum effect. After 4 weeks the effect seems to plateau off (but does not dip) as seen in other studies.[1,2]

Cyclosporine eye drops used have no effect on intra ocular pressure, is well tolerated and does not cause any increase in punctate keratitis. One of the important observations regarding the safety of cyclosporine eye drops is its neutrality on intra ocular pressure. Fluorometholone also have maximum effect in most of the symptoms and signs at 4 week time, except redness and photophobia on which maximum effect was earlier (at day 14) and no recurrences found during the period of the study. The analysis of total signs and symptoms score (excluding the IOP) showed that eyes receiving Fluorometholone eye drops did better at all the observation points when compared to cyclosporine and this difference was pronounced and statistically significant on day 30 and day 90. Before that there was no statically significant difference between the two groups. In patients with mild disease (total cumulative score at enrollment, range 0-8) responded equally well in both the groups.

One of the safety concerns with the use of steroid eye drops is tendency to increase intra ocular pressure[1] as seen in the Fluorometholone group in our study. This IOP rise had a positive linear trend of 14.23 ($P<0.001$) with maximum IOP seen at the end of study duration at day 90. Average increase in IOP was 4.7 mm Hg (Range 4.0-5.3). Possibility of further rise in IOP with continuous use cannot be ruled out and hence development of vision threatening steroid induced glaucoma may be there. Additional problem in the scenario is that in the affected pediatric population it is not possible to measure the IOP easily and reliably. This adds to the problem of indiscriminate prolonged use of steroid drops due to unyielding nature of the disease which needs maintenance therapy for long periods of time. Other safety concerns are development of cataract and local infective lesions due to use of steroid drops, which we did not see in any of our patients due to short study period.

Thus according to our study cyclosporine may be a first line drug for treatment of vernal keratoconjunctivitis to avoid the sight threatening side effects of steroid. Cyclosporine provides prompt and adequate relief comparable to Fluorometholone with no rise in intraocular pressure, in mild disease, which constitutes the majority of patients. Thus it can be the first line of treatment for vernal keratoconjunctivitis and steroid drops to be reserved for moderate and severe cases.

Further study may be done to evaluate the combination or sequential use of cyclosporine and Fluorometholone for patients of vernal keratoconjunctivitis to decide the dose titration of these two individual drugs to reach to an optimum, safe and effective therapeutic regime.

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