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Therapeutic Efficacy of 0.05% Topical Cyclosporine - A Eye Drops and 0.1% Topical Tacrolimus Eye Ointment in the Treatment of Refractory Vernal Keratoconjunctivitis

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Abstract

Background: *Vernal keratoconjunctivitis (VKC) is a seasonal, chronic, allergic eye disease involving the bulbar and tarsal conjunctiva. While corticosteroids are very effective, their long term use is restricted due to their side-effects. The above study was conducted to evaluate the therapeutic efficacy of 0.05% topical cyclosporine-A eye drops with 0.1% topical tacrolimus eye ointment.*

Methods *- A prospective, comparative study of randomly selected cases of refractory VKC patients was conducted in Regional institute of ophthalmology, Govt. Medical College, Amritsar after taking approval from thesis and ethical committee of the institute. The study included 60 patients>6 years old. All the patients had active VKC. Patients were randomly assigned to one of the two groups and were given treatment as below:*

> ***Group A:*** *Topical cyclosporine A (0.05%) eye drops twice a day with carboxymethyl cellulose (0.5%) and cold compresses for 04 weeks.*
> ***Group B:*** *Topical tacrolimus (0.1%) eye ointment twice a day with carboxymethyl cellulose (0.5%) and cold compresses for 04 weeks.*

Diagnosis of VKC was made clinically. Patients were evaluated at 0,1,2,3 and 4 weeks. Symptoms and signs observed before and after treatment were recorded and scores were assigned. The main outcome measure was measured in terms of total subjective symptom score (TSSS) and total objective ocular sign score (TOSS) before and after treatment at each visit.

Results *- There was improvement in TSSS in group A and group B after 1st week and was maintained till 4 weeks. The improvement in TSSS between the two groups was observed and was maintained till 4 weeks. Also there was improvement in TOSS within the groups from the 1st week and was maintained till 4 weeks. The beneficial effect of tacrolimus on giant papillae size was also observed. No significant ocular side effects were observed.*

Conclusion *- Both topical cyclosporine and tacrolimus might have the potential to be used as a steroid sparing agent. Effect of tacrolimus is more on papillae and giant papillae size.*

Keyword - VKC, TSSS, TOSS, NCT.

Introduction

Allergic conjunctivitis is the most common allergic eye disease and it occurs when the eye is exposed to antigens in the environment.[1] VKC is a bilateral, recurrent, allergic inflammation of the conjunctiva that tends to occur in children and young adults with a history of atopy. Boys are affected twice as often as girls with a peak incidence between 11-13 years. Its onset is most common in spring and summer months and the inflammation often goes into remission during the colder months.[2] Children usually have a self-limited disease and eventually grow out of the disease in 5-10 years. Some young adults develop more severe manifestations of the disease. Severe and inappropriately

treated VKC can lead to severe ocular complications such as corneal scarring, glaucoma and sometimes even blindness.

The most prominent symptom is intense pruritis. Other complaints include photophobia, burning, tearing, mild ptosis and a thick, ropy, mucoid discharge. Conjuctival signs include hyperaemia, papillary hypertrophy, giant papillae, limbal swelling, Horner Trantas dots (accumulation of gelatinous, inflammatory infiltrates around the limbus), neovascularization of the cornea and corneal epithelial signs.

It is classically thought to be an Ig-E-mediated type I hypersenstivity reaction; however, studies have also noted Th-2 lymphocyte involvement in a type IV Immune reaction.[3] The etiology involves a variety of factors, including environmental allergens, climate, and genetic predisposition. The disease is usually bilateral in 96.7%of the cases; three forms are observed, i.e limbal, tarsal and mixedVKC.[4]

Histopathologically, VKC is characterized by conjunctival infiltration with eosinophils, degranulated mast cells, basophils, plasma cells, lymphocytes and macrophages.

Exacerbations of VKC are often controlled by topical steroids which could produce serious side-effects such as glaucoma, cataracts and ocular infections. Steroid induced glaucoma is not uncommon and could lead to blindness.[5]

Cyclosporine and Tacrolimus (FK-506) inhibit activation of T cells and also inhibit IgE-dependent histamine release from mast cells and basophils.[6] Both drugs act on their target cells via cyclophyllin receptors. Cyclosporine eye drops are found to be effective in treating severe VKC.[7] However burning with 2% cyclosporine was unacceptable to several patients and could lead to low compliance.[8] Tacrolimus is a macrolide antibiotic that has potent immunomodulatory properties.[9] Adverse effects from 0.1% tacrolimus ointment includes transient stinging sensation only. Systemic absorption of tacrolimus from conjunctival surface is also found to be minimal.[10]

Methods

A prospective, comparative study of refractory VKC patients selected randomly from OPD of Regional Institute of Ophthalmology, Government Medical College, Amritsar was taken up for study after obtaining through written consent. The study was conducted after taking due permission from thesis and ethical committee of the institution.

60 patients were selected after excluding 12 patients who were lost after the first follow up. All patients had active VKC on enrolment. Diagnosis of VKC was made clinically according to the commonly accepted criteria. Patients complete history, duration of illness, chief complaints and treatment taken was recorded. Complete general, physical and ophthalmologic examination was done. The patients were advised to discontinue all topical and oral allergic drugs for two weeks. After two weeks the patients were examined and their baseline symptoms (TSSS) as well as baseline signs (TOSS) were recorded. The patients were randomly assigned to one of the two groups and were given treatment as below:-

Group A: Topical cyclosporine A (0.05%) eye drops twice a day along with carboxymethyl cellulose (0.5%) and cold compresses for 04 weeks.
Group B: Topical tacrolimus (0.1%) eye ointment twice a day along with carboxymethyl cellulose (0.5%) a preservative free artificial tears and cold compresses for 04 weeks.

Inclusion Criteria:

1. Refractory cases of Vernal Keratoconjunctivitis on treatment for more than one year:
   - Cases not responding to conventional therapy of VKC
   - Cases having a recent relapse after cessation of steroids

Exclusion Criteria:

1. Patients with known hypersensitivity to medications used in study.
2. Active infective disease of the cornea and conjunctiva including viral, fungal or mycobacterial infection of eye.
3. Patients with history of any ocular pathology or medical condition that could result in patient's inability to complete the study.
4. Children less than 6 years of age.
5. Patients not willing to participate.

Study protocol

All the patients were evaluated with a detailed history of VKC, family history and general history. Detailed history of any previous treatment taken was also recorded.

Clinical examination

All the patients were subjected to a detailed general physical examination, external examination of the eye, visual acuity by Snellens chart, examination of anterior segment and measurement of intraocular pressure by NCT (non contact tonometry).

The findings were recorded in the prescribed performa.

Clinical scoring system

Clinical Scoring System Grading of Symptoms (Bleik et. al.)[11]

Symptoms of itching, tearing, photophobia, discharge and foreign body sensation were recorded before and after treatment.

Symptoms were graded as follows
0 - indicating no symptoms
1+ - mild symptoms of discomfort which were just noticeable.
2 + - moderate discomfort noticed most of the day but did not interfere with daily routine activities.
3+ - severe symptoms interfering with daily routine activities

Grading of Signs

Conjunctival hyperemia
0 - no evidence of bulbar hyperemia.
1+ - mild bulbar hyperemia.
2+ - moderate bulbar hyperemia.
3+ - severe bulbar hyperemia.

Palpebral conjunctival papillae
0 - no papillary hypertrophy of the palpebral conjunctiva.
1+ - mild papillary hypertrophy
2+ - moderate papillary hypertrophy (hazy view of the deep tarsal vessels).
3+ - severe papillary hypertrophy (deep tarsal vessels not visible in more than 50% of the surface).

Punctate keratitis
0 - no evidence of punctate keratitis.
1+ -one quadrant of punctate keratitis.
2+ - two quadrants of punctate keratitis.
3+ - three or more quadrants of punctate keratitis.

Trantas'dots were graded as follows
0 - no evidence of dots.
1 + - 1 to 2 dots.
2 + - 3 to 4 dots.
3 + - more than 4 dots.

Limbal infiltration
0 - no evidence of limbal infiltrates.
1 + - less than 900 of limbal infiltrates.
2 + - less than 1800 of limbal infiltrate but more than 90^0.
3 + - more than 1800 of limbal infiltrate.
6 symptoms and 9 clinical signs were analyzed for the study

Follow up: Follow up was done every week for four weeks with treatment. The main outcome measure was measured in terms of total subjective symptom score (TSSS) and total objective ocular sign score (TOSS) before and after treatment at each visit.

All the finding related to each case were recorded in the prescribed proforma and the data was compiled and analysed.

Statistical analysis: Data was analyzed by a statistical software package (SPSS version 17). Chi-square was used to compare sex and age rates between the two groups. In addition, paired T test was used for comparison of TSSS and TOSS within the group. For inter-group comparison, unpaired T test was used. p value of <0.05 was considered statistically significant.

Result

An open, prospective, observational and comparative study was conducted at Regional institute of ophthalmology, Govt. Medical College, Amritsar after taking approval from thesis and ethical committee of the institute. 72 consecutive patients of VKC presenting from December 2015 to July 2017 were enrolled into the study but only 60 patients completed the above study. Mean age for group A was 8.96±2.76 and for group B was 9.50±3.52 with range (6-17 years). Mean age in both the group was 9.23±3.12. Most of the patients were male (n=48) with only 12 female patients. Majority of patients were from rural background (n=36) as against (n=24) from urban background showing that VKC was more common in dusty environment of rural areas in our study.

Mixed VKC was the most common form of presentation (n=30) followed by tarsal variant (n=26) and limbal variant (n=4).

The five major complaints recorded were itching (60 patients, 100%), lacrimation (59 patients, 98.3%), redness (58 patients, 96.7%), discomfort (53 patients, 88.3%), photophobia (50 patients, 83.3%) and eye discharge (46 patients, 76.77%). Hence itching was the most common symptom in both the groups.

There was improvement in TSSS (Total subjective symptom scores) in group A (cyclosporine-A) and group B (tacrolimus) after 1stweek itself and this improvement was maintained till 4weeks in both the groups. Also the improvement in TSSS between the two groups (inter-group) was statistically significant from 1st week onwards and was maintained till the final follow-up i.e. 4thweeks.

Table No.1: Age Distribution

Age group (years)		Group A	Group B	Total
5-10	No.	22	20	42
	%	73.3%	66.7%	70.0%
6-15	No.	7	7	14
	%	23.3%	23.3%	23.3%

16-20	No.	1	3	4
	%	3.3%	10.0%	6.7%
Total	No.	30	30	60
	%	100.0%	100.0%	100.0%

X^2: 1.09; df: 2; p=0.578

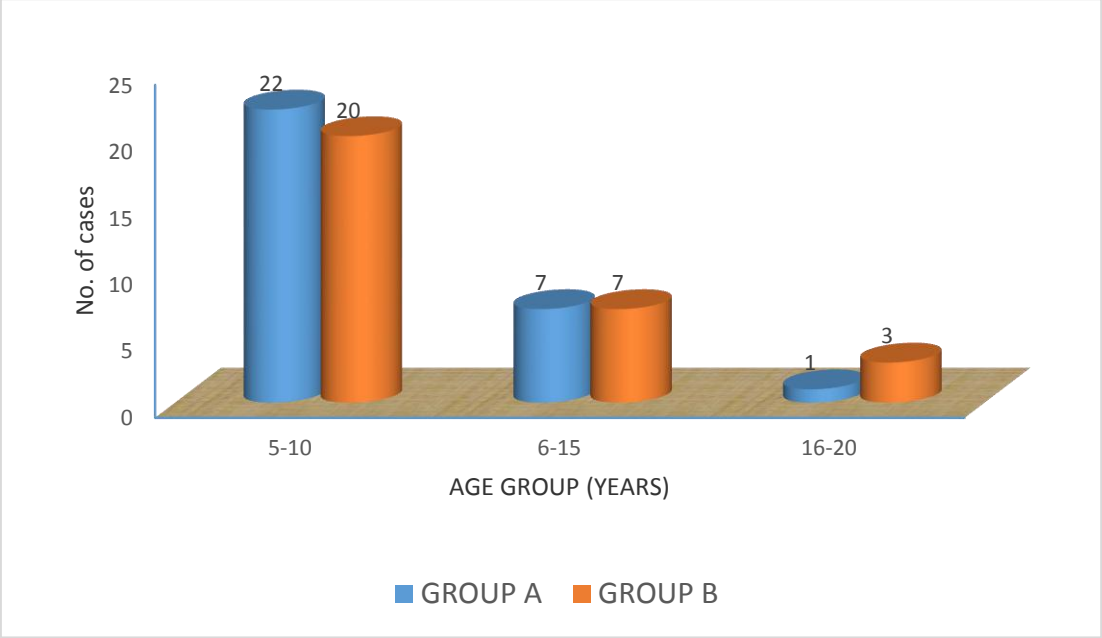


Fig 1: Showing Age Distribution

Table No.2: Gender Distribution of Patients

Sex		Group A	Group B	Total
Male	No.	23	25	48
	%	76.7%	83.3%	80.0%
Female	No.	7	5	12
	%	23.3%	16.7%	20.0%
Total	No.	30	30	60
	%	100.0%	100.0%	100.0%

X^2: 0.417; df: 1; p=0.519

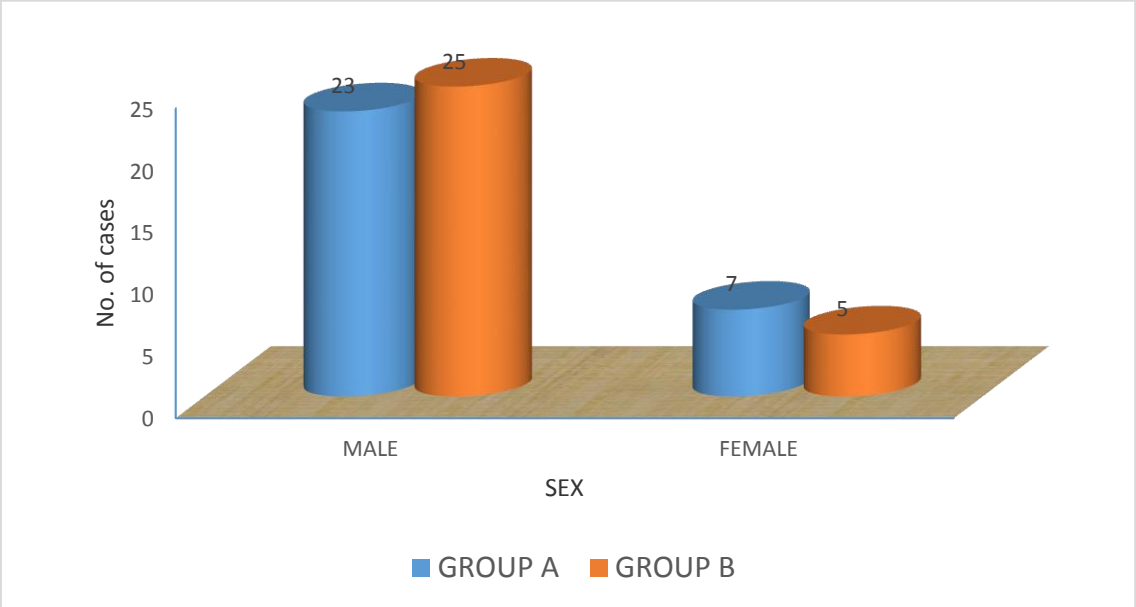


Fig 2: Showing Gender Distribution of Patients

Table No.3: Mean Change in Symptoms TSSS (Total Subjective Symptom Score)

Symptoms	Group A		Change from baseline		p-value	Group B		Change from baseline		p-value	Group A v/s B (p=value)
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		
Baseline	12.90	2.39				13.63	1.45				0.150
1st week	10.77	2.37	2.13	1.81	0.00	9.43	1.56	4.20	1.91	0.00	0.013
2nd week	7.63	1.93	5.26	2.36	0.00	5.73	1.36	7.90	1.98	0.00	0.000
3rd week	4.77	1.52	8.13	2.66	0.00	2.87	1.04	10.76	1.81	0.00	0.000
4th week	2.43	1.69	10.45	2.88	0.00	0.63	0.89	13.00	1.72	0.00	0.000

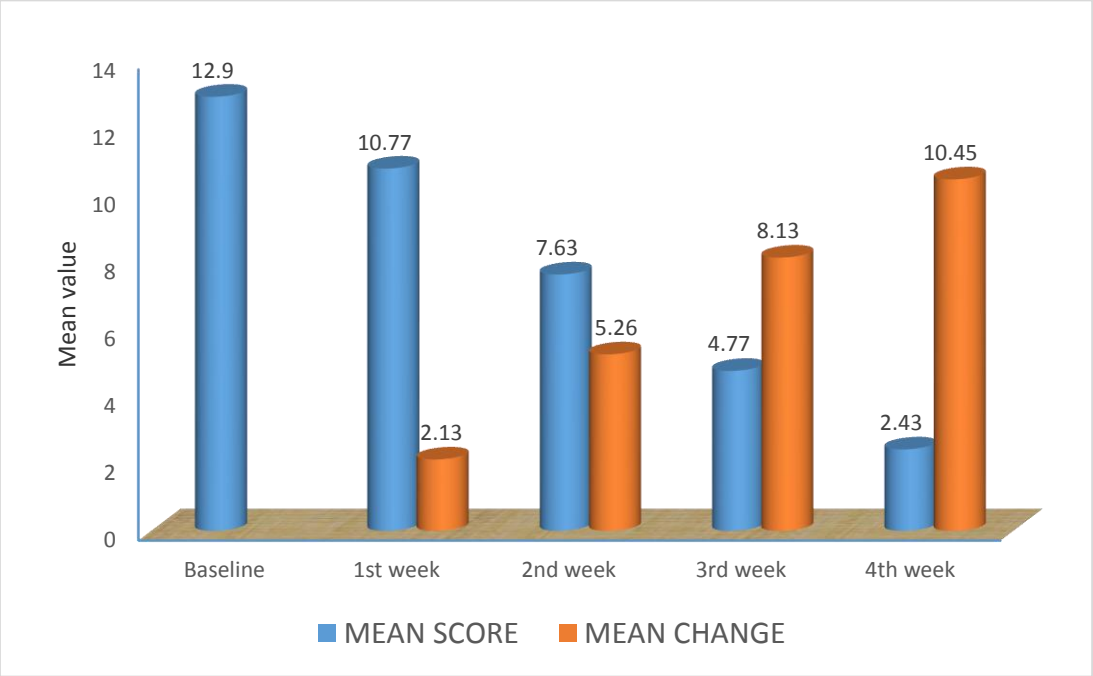


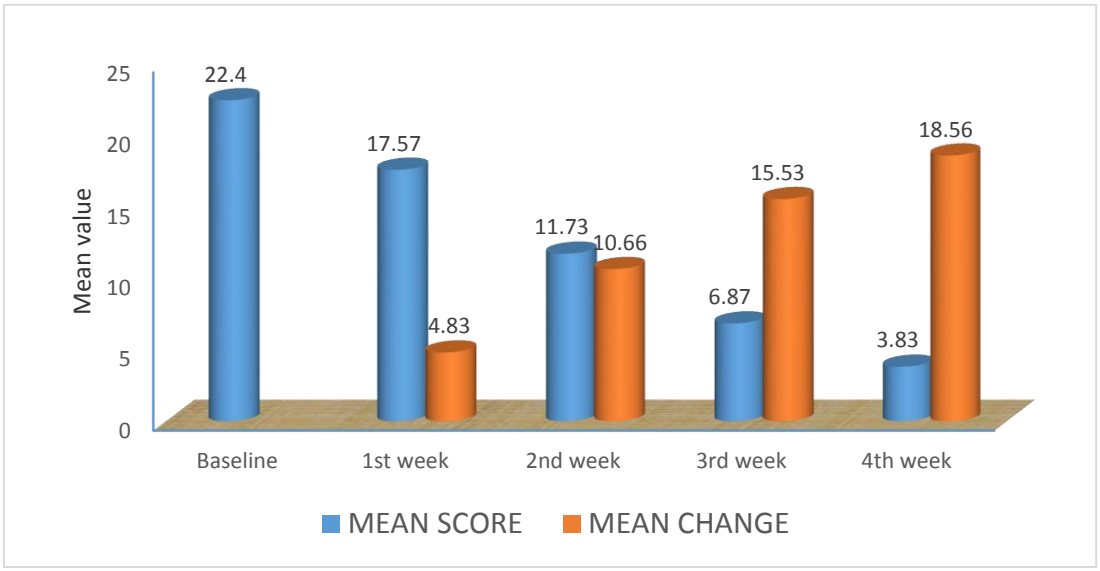
Fig 1: Showing Mean Change in Symptoms TSSS (Total Subjective Symptom Score)

Table No.4: Mean Change in Signs (TOSS or Total Ocular Sign Score)

Signs	Group A		Change from baseline		p-value	Group B		Change from baseline		p-value	Group A v/s B (p=value)
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		
Baseline	22.40	5.08				23.63	6.22				0.150
1st week	17.57	4.52	4.83	1.70	0.00	17.24	5.27	6.36	1.99	0.00	0.013
2nd week	11.73	3.49	10.66	2.65	0.00	10.40	3.76	13.23	3.38	0.00	0.000
3rd week	6.87	2.76	15.53	3.45	0.00	5.43	2.58	18.20	4.78	0.00	0.000
4th week	3.83	1.76	18.56	3.91	0.00	1.47	1.59	22.16	5.63	0.00	0.000

Table no.2 showing TOSS for group A and B:-
There was improvement in TOSS (Total objective ocular sign score) within the groups (intra-group) from the 1st week itself and was maintained till 4th weeks. On comparison between the two groups, the p-value of TOSS was statistically significant from 1st week onwards and was maintained till the final follow-up i.e. 4th weeks.

GROUP A



GROUP B

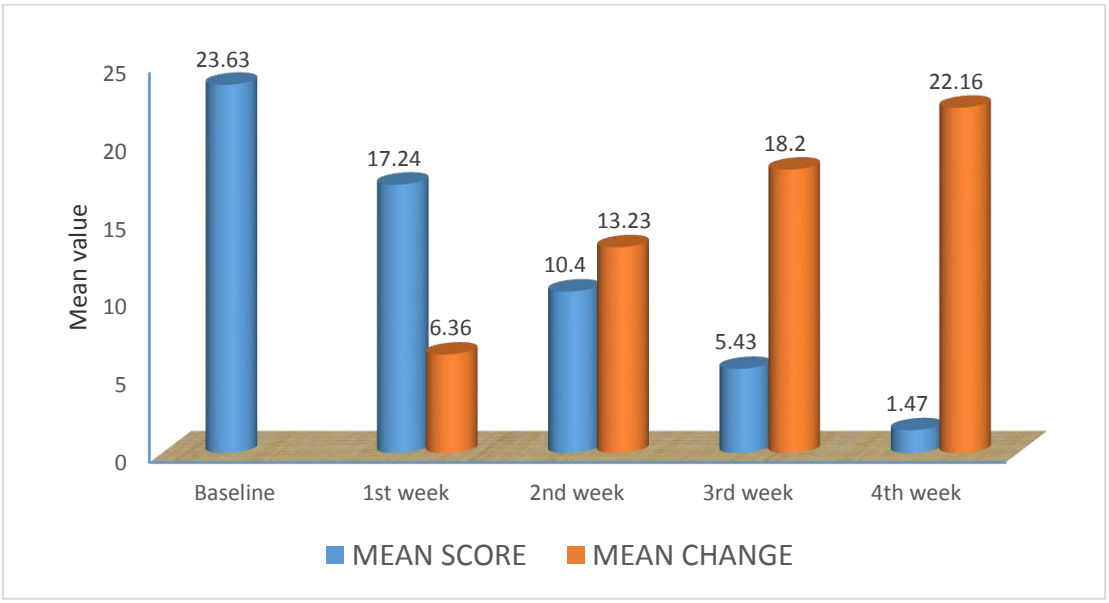


Fig 2: Showing Mean Change in Signs TOSS or Total Ocular Sign Score

The reduction in size of papillae (OD) on inter group comparison was statistically significant from 1st week (p=0.019) and was maintained till 2nd weeks (p=0.027). The reduction in size of giant papillae in both eyes was statistically significant from 1st week (p=0.012 in OD, p=0.000 in OS) and was maintained till 4 weeks on intergroup comparison (p=0.00 in OD, p=0.019 in OS).

Side effects

No ocular or systemic side effects were observed in either group.

Conclusion

In our study, at baseline, itching was the most common symptom in both the groups. There was improvement in TSSS (Total subjective symptom scores) in group A (cyclosporine-A) and group B (tacrolimus) after Ist week itself and this improvement was maintained till 4weeks in both the groups. Also the improvement in TSSS between the two groups (inter-group) was statistically significant from 1st week onwards and was maintained till the final follow-up i.e. 4thweeks. There was improvement in TOSS (Total objective ocular sign score) within the groups (intra-group) from the Ist week itself and was maintained till 4th weeks. On comparison between the two groups, the p-value of TOSS was statistically significant from Ist week onwards and was maintained till the final follow-up i.e. 4th weeks.

Topical cyclosporine of various concentrations has been investigated for treatment of VKC with different results. In a 2 week, double masked, placebo-controlled trial done in 2002 by Pucci et al,[12] 2% cyclosporine resulted in about 40% reduction subjective and objective scores by the end of randomization period. 2% cyclosporine eye drops were tried in a large number of children with VKC from Rawanda,

Africa.[13] In this study, 2% cyclosporine eye drops were shown to be as effective as topical dexamethasone during the 4 weeks study period. In a longer open trial done in 2006 by Spadavecchiet al,[14] on using a lower concentration of cyclosporine (1.25% and 1%) for 4 months, a higher degree of benefit in subjective & objective signs was observed. Recently the use of 1% topical cyclosporine in VKC resulted in improvement of subjective symptoms and objective signs after 2 weeks & 4 months. Difference in efficiency of cyclosporine in various publications could be due to difference in methods for cyclosporine preparation and also due to difference in the severity of the disease.

Our study too showed significant effectiveness of cyclosporine at 1st week in TSSS and TOSS scores. The concentration of the drug used was (0.05%). This concentration was selected for our study as it is commercially available. Cyclosporine is also notorious for causing a stinging sensation but we did not get such complaints in our study due to lower concentration of the drug used. It also might be responsible for relapse of symptoms within 2 weeks of stopping the treatment.

A study was done in 2012 by Labcharoenwongs P et al[15]with 24 patients: 12 patients received 0.1% tacrolimus eye ointment twice daily and other 12 patients received 2% cyclosporine eye drops four times daily. It showed a significant decrease in TSSS compared to their baseline at 4 weeks and 8 weeks in both the treatment groups. TSSS between the 2 groups was not statistically significant. Total ocular sign score (TOSS) in the FK-506 group decreased significantly at 4 weeks and 8 weeks as compared to the baseline. Although there was decrease in TOSS in the cyclosporine group, the difference did not reach statistical significance.

A prospective double masked, randomized comparative study was conducted in 2016 by Kumari R and Saha CB.[16]In this study, 19 patients received 0.03% tacrolimus eye ointment daily for 6 weeks and other 15 received 0.5% cyclosporine eye drops four times daily for 6 weeks. This study reported that tacrolimus brought about an improvement of the signs and symptoms of VKC similar to that of cyclosporine A. Objective ocular signs (or TOSS) were found to be more improved with tacrolimus treatment even though this was not statistically significant. At the same time, there were no ocular side effects in either group.

Also the beneficial effect of tacrolimus on signs especially on papillae and giant papillae size was seen in our study two as mentioned in other studies.

There was a difference in our observations from the above studies. This is so because that the concentration of the drugs used in our study and the number of times of instillation of the drugs was different from the studies mentioned above. We used topical cyclosporine (0.05%) twice a day in group A and topical tacrolimus (0.1%) twice a day in group B. No significant side effects were observed in our study except for occasional stinging sensation caused by cyclosporine use. The period of our study was also short i.e 4 weeks only as compared to the study period of above studies.

No literature at present mentioned about the course of the disease after stopping the treatment with respect to concentration and duration. The limitations of our study are a small sample size and a short course of treatment of 4 weeks only. Also since 16 out of 76 patients were lost to follow-up, much cannot be commented on the side effects of the drugs but the beneficial effects of both the drugs was seen in our study. So both topical cyclosporine (0.05%) and topical tacrolimus (0.1%) can be used as a drug for refractory type of VKC.

The present study confirmed that both topical cyclosporine and topical tacrolimus can be used as first line drugs for refractory type of VKC.Effect of tacrolimus is more on clinical signs as decrease in size of papillae and giant papillae.

Both topical cyclosporine and tacrolimus might have the potential to be used as a steroid sparing agent as there was significant reduction in TOSS at 1st week itself. However, the initial concentration and duration of treatment needs to be investigated further in a larger study group.

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