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COMPARISON OF THE EFFICACY OF 0.1% TACROLIMUS EYE OINTMENT AND 0.05% CYCLOSPORINE EYE DROPS IN PATIENTS OF VARENAL KERATOCONJUNCTIVITIS.

Ophthalmology

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ABSTRACT

BACKGROUND: Vernal keratoconjunctivitis(VKC) is a chronic inflammatory eye disease which can lead to vision threatening corneal complications, coupled with potential iatrogenic side effects makes VKC a concerning ocular surface disorder. In present study we Compare the efficacy of 0.1%tacrolimus eye ointment and 0.05%cyclosporine eye drops in the treatment of vernal keratoconjunctivitis.
METHODS: 42 patients of VKC randomized into 2 groups in 6 months. Group A received 0.1%tacrolimus eye ointment and Group B received 0.05%cyclosporine eye drops twice daily for 8 weeks. Subjective ocular symptoms score(TSSS) and side effects were recorded by patients daily during the entire period. Objective ocular signs score(TOSS) was evaluated and scored at each follow up visit every week. Results analysed using chi square test.
RESULTS: There was a significant decrease in TSSS and TOSS compared to their baselines after 4weeks in both groups. No statistical difference in TSSS and TOSS noted between groups at any time point. Total improvement in TSSS was 97.46% and TOSS was 96.81% after 8 weeks in Tacrolimus group and in cyclosporine group the improvement in TSSS was 97.36% and TOSS was 97.43%. These differences are not statistically significant with pvalue less than0.05. Side effect recorded in both groups were irritation 14% and 9.52% where as burning sensation 9.52% and 19.04% that reduced significantly in both groups at 4weeks.
CONCLUSION: 0.1% tacrolimus eye ointment and 0.05% cyclosporine eye drops are effective in treatment of VKC. 0.1% tacrolimus eye ointment recently introduced in ophthalmic use can become viable option for treatment of VKC.

KEYWORDS

INTRODUCTION:

Vernal keratoconjunctivitis (VKC) is a chronic inflammatory eye disease commonly observed in children and adolescents (1). Seen in regions with hot, humid climate and higher load of airborne allergens (2). Three forms of the disease are observed: limbal, tarsal and mixed VKC. Symptoms of VKC include intense itching, tearing, mucous secretions and severe photophobia.

Conjunctival signs comprise hyperemia, papillary hypertrophy, giant papillae, discharge, and Horner-Trantas dots. Patients with VKC experience significant morbidity which affects the quality of life. Vision threatening corneal complications such as superficial punctate keratopathy, corneal erosion, persistent corneal epithelial defects, corneal ulcers, and corneal plaque in severe and chronic cases(3). Topical steroids are currently the mainstay of therapy in VKC which could produce serious side-effects such as glaucoma, cataracts and ocular infections(4). Thus there is a need for developing better management strategies for these patients. Cyclosporine and tacrolimus inhibit activation of T cells, and also inhibit IgE-dependent histamine release from mast cells and basophils(5). Both drugs act on their target cells via cyclophyllin receptors.

Cyclosporine eye drops are been used in treatment of VKC since long but burning with 0.05% cyclosporine is unacceptable to several patients and could lead to low compliance(5). Tacrolimus is recently introduced in ophthalmic use. It is a macrolide antibiotic that has potent immunomodulatory properties. It acts primarily on T-lymphocytes by inhibiting production of cytokines, particularly IL-2, IL-3, IL-5, TNF-α and IFN γ(6).

In present study, we compared the efficacy of 0.1% tacrolimus ophthalmic ointment to that of 0.05% cyclosporine eye drops in the treatment of VKC.

METHODS:

It is a hospital based prospective interventional study is performed on 42 patients who are diagnosed to have VKC (patients having signs like conjunctival hyperaemia, papilla, giant papilla, corneal infiltration and symptoms like itching, photophobia, tearing, foreign body sensation, burning sensation). The institutional ethical committee had given approval for the project.

All the patients had given their informed consent. They were divided in two groups, each group had 21 patients by using random number table. Their baseline characteristics were similar between groups.

Group A received 0.1% tacrolimus eye ointment twice daily for 8 weeks. Group B received 0.05% cyclosporine eye drops twice daily for the same duration.

Subjective ocular symptoms and side effects was recorded by patients, during the entire period.

Objective ocular signs was evaluated and scored at each follow up visit.

Clinical Scoring System (7)

The main outcome measure is total subjective symptom scores per each day of treatment (TSSS).

Secondary outcomes include changes in total objective ocular sign score (TOSS) at each visit and in side effects of medications.

Each patient recorded subjective symptoms and scored at every follow up. (itching, photophobia, watering, foreign body sensation and burning sensation)

Each variable was graded as follows: (7)
0 = absent, 1 = mild, 2 = moderate or 3 =severe.

These scores was summed and average was yield total score/day (TSSS).

Total objective ocularsigns (TOSS) was recorded at each visit. These scores comprised hyperemia of bulbar and palpebral conjunctiva, papillae, giant papillae, and corneal infiltration.

Palpebral and bulber conjunctival Hyperemia:
0 = absent
1 = Dilatation of several vessels
2 = Dilatation of many vessels
3 = Impossible to distinguish individual blood vessels

Papillae were graded according to their numbers and sizes;
0 = absent,
1 = a few papillae of less than 0.2 mm,
2 = papillae of 0.3 to 1 mm on the tarsal conjunctiva,
3 = papillae of 1 to 3 mm throughout the tarsal conjunctival area.

Giant, cobblestone-like papillae (>3 mm) of the superior tarsal conjunctiva were also graded according to their numbers and sizes;

1 = few giant papillae of 3 to 4 mm,
2 = giant papillae of 3 to 4 mm throughout the tarsal conjunctival area, or a few papillae of 4 to 6 mm,
3 = giant papillae of 4 to 6 mm throughout the tarsal conjunctival area, or papillae = 6 mm.

Corneal infiltrates were scored based on epithelial defects;
0 = no corneal involvement,
1 = fine superficial epithelial defects involving less than half of the cornea,
2 = diffuse fine superficial epithelial defects involving more than half of the cornea,
3 = confluent epithelial defects, mucous plaque formation or oval corneal ulcers.

The eye with higher severity at baseline was selected.

Objective ocular signs at each were summed (TOSS). Maximal values of TSSS and TOSS were 15.

These scores were used for comparison within and between groups. Results were analysed by using chi square test.

RESULT:

Forty two consecutive VKC patients presented to ophthalmic department of our institute during 6 months period who were enrolled (without any drop out) in present study. Their mean age was 9.61 ± 2.55 years (median 8.90 ±2.55 years; range 5.42 -14.05 years).

There were 29 males and 13 females. Male:Female ratio was 2.3:1 Five patients had used some form of treatment for VKC before enrollment (topical steroid, olopatadine, lodoxamine and 0.5% cyclosporine). Thirty seven patients were newly diagnosed VKC cases which had not been previously treated with any drug at entry.

Tarsal VKC was the most common form of presentation (n = 24, 57.14%) followed by mixed (n = 10, 23.80%) and limbal type VKC (n = 8, 19.04%).

Mixed type had the highest TSSS and TOSS (means = 6.57 ± 5.10 and 8.00 ± 1.22) followed by tarsal type (means = 6.10 ± 2.62 and 7.13 ± 2.69) and limbal type (means = 5.63 ± 3.63and 5.00 ± 1.62).

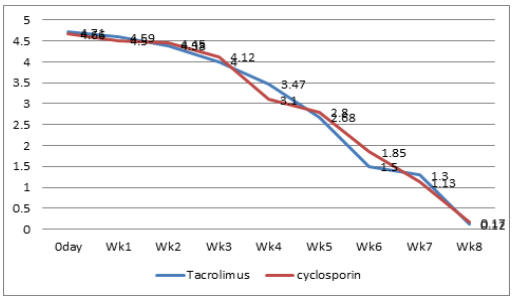
The five major complaints recorded by patients were itching (40 patients, 95.83%), foreign body sensation (40 patients, 95.8%), tearing (38 patients, 83.3%), photophobia(35 patients, 79.1%) and burning sensation (35 patients, 79.1%).

Reduction of TSSS within group (compared to their baselines at the end of run-in period) became statistically significant at week 4 for both the tacrolimus and cyclosporine groups. Such reductions were maintained in both groups throughout the 8 week period. (TABLE 1) Plots of data from the two groups, at each time point, are slightly overlapped to allow better appreciation of data distribution. Here vertical exes show TSSS (Mean) at each time point of the two treatment groups (at entry, after run-in, and at various weeks of treatment). TSSS significantly decreased from baselines at 4th and 8TH weeks in both groups. No difference was observed between groups at any time point. (GRAPH 1) When individual symptom was examined (itching, irritation, watery eye, photophobia and burning), improvements were observed in both groups at varying degrees.

Table:1 Changes in TSSS at every follow up

TSSS(Mean)	0day	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8
Tacrolimus	4.71	4.59	4.38	4	3.47	2.68	1.5	1.3	0.12
Cyclosporine	4.66	4.5	4.45	4.12	3.1	2.8	1.85	1.13	0.17

Graph:1 Changes in TSSS at every follow up



No difference in TOSS between the two treatment groups was observed at any time points.(TABLE 2) Plots of data from the two groups, at each time point, are slightly overlapped to allow better appreciation of data distribution.(GRAPH 2) After treat of 8 weeks total improvement in TSSS among Tacrolimus group was 97.46% and in Cyclosporine group is 96.36%.

Table:2 Changes in TOSS at every follow up

TOSS(Mean)	0day	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8
Tacrolimus	11.57	10.29	9.oo	7.58	4.47	2.68	1.4	1.3	0.37
Cyclosporine	11.66	10	9.15	7.12	4.1	2.89	1.85	1.03	0.3

Graph:2 Changes in TOSS at every follow up

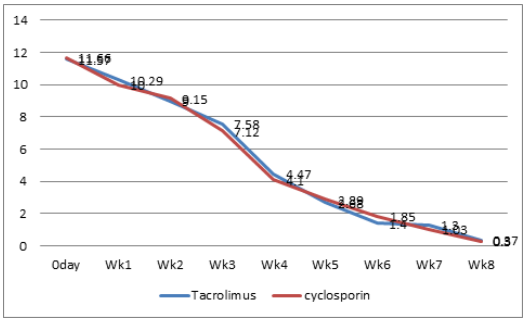


TABLE 3 is showing the comparison of improvement in TSSS after 8 weeks in both groups.

Table:3 Improvement in TSSS after 8 weeks

Group	% Improvement in TSSS	% No improvement in TSSS
Tacrlolimus	97.46	2.54
Cyclosporine	96.36	3.64

The chi-square statistic is 0.2052.
The *p*-value is 0 .650571.
This result is not significant at *p* > .05.

After treatment of 8 weeks total improvement in TOSS among Tacrolimus group was 96.81% and in Cyclosporine group is 97.43%.

TABLE 4 is showing the comparison of improvement in TOSS after 8 weeks in both groups.

Table:4 Improvement in TSSS after 8 weeks

Group	% Improvement in TOSS	% No improvement in TOSS
Tacrlolimus	96.81	3.19
Cyclosporine	97.43	2.57

The chi-square statistic is 0.2136.
The *p*-value is 0.696238.
This result is not significant at *p* > 0.05.

Comparison of side effect scores between groups was not significantly different any time point.

Side effect scores reduced with time and became statistically significant in both groups.

No serious adverse effect requiring withdrawal from the study was noted in either group. No patients developed any exacerbation of the disease during the treatment. No adjunctive therapy was required during the entire study.

CONCLUSION AND DISCUSSION:

In present study majority of the patients belong to age group of 5 to 20 years of age (71.42%). The mean age was 9.61 ±2.55years. The male:female ratio was 2.3:1. Tarsal VKC was the most common form of presentation (n = 24/ 57.14%) followed by mixed (n = 10/23.80%) and limbal type VKC (n = 8/19.04). After treatment of 8 weeks total improvement in TSSS among Tacrolimus group was 97.46% and in Cyclosporine group is 96.36%. After treatment of 8 weeks total improvement in TOSS among Tacrolimus group was 96.81% and in Cyclosporine group is 97.43%.

These differances are not statistically significant with p value >0.05.

To conclude, we reported 0.1%tacrolimus ophthalmic ointment twice daily brought about an improvement of symptoms of VKC similar to that of 0.05%cyclosporine eye drop twice daily.

Cyclosporine and Tacrolimus both were associated with burning sensation and irritation on application but it decreased gradually.

So. In countries like india where the climate is more prone for VKC along with polluted environment it is really important to use drugs having less side effects as steroid can cause glaucoma, cataracts and ocular infections which can lead to ocular morbidity and as this disease is more prevalent in children and adolescent vision threatening side effects should be looked for.

The limitation of our study is a small sample size. With this reason, the result of our study could be subjected to a lower statistical power (type-II error). A difference of the efficacy between the two medications in VKC will have to be further studied in a larger trial and with standard preparation of drugs.

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DICLARATION:
The authors have no financial interest in any materials used and discussed in this article.

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