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TO COMPARE THE EFFICACY OF TACROLIMUS (0.1%) Vs CYCLOSPORINE (0.05%) IN VERNAL KERATO-CONJUNCTIVITIS (VKC)

Ophthalmology

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ABSTRACT

Introduction- The aim of the study was to evaluate and compare the efficacy and safety of topical Tacrolimus (0.1%) as compared to topical Cyclosporine (0.05%) in treatment of vernal keratoconjunctivitis patients.

Methodology- A Prospective, comparative, interventional study was conducted in 142 patients of VKC between February 2020 to august 2021 attending the ophthalmic outpatient department of our hospital. Patients were screened for inclusion and exclusion criteria and included in the study after obtaining informed, written consent from the patients or their guardian. Right eye was be treated with Cyclosporine (0.05%) eye drop twice daily and the left eye was treated with Tacrolimus (0.1%) eye ointment twice daily for 2 months. Patients were followed up on 15th, 30th, 60th day on medication. Then the treatment was withdrawn and patients were reviewed after 4 weeks. At each follow up and at 1st visit patients symptoms were graded, recorded and compared as Total Subjective Symptoms Score (TSSS) and Total Objective ocular sign Score (TOSS).

Result - Both TOSS and TSSS decreased in both the eye consistently without any effect on Intra-ocular pressure. Improvement in scores was more in left eye. But scores increased after the withdrawal of drug, still lower than baseline scores.

Conclusion - Disease has greater propensity in males. Both the drugs were found to be effective and safe, but 0.1% Tacrolimus eye ointment found to be superior than 0.05% Cyclosporine eye drop. Only side effect with tacrolimus eye ointment was stinging sensation on instillation of drug.

KEYWORDS

VKC, Tacrolimus, Cyclosporine, TOSS, TSSSS,

INTRODUCTION

Ocular allergies constitute heterogeneous group of recurrent inflammatory diseases of the ocular surface. VKC and AKC are chronic, bilateral, and the most severe forms of allergic inflammation, due to potential visual impairment.[1] Vernal keratoconjunctivitis (VKC) is a recurrent, bilateral, external, ocular inflammation primarily affecting boys and young adults living in warm, dry climates. Its predominance during the high pollen season lends credence to the widely accepted hypothesis that VKC is an immunologically mediated hypersensitivity reaction to environmental antigens.[2] VKC is characterized by conjunctival hyperaemia, chemosis, photophobia, and mucus discharge. The hallmark of the disease is the presence of giant papillae (cobblestone appearance) at the upper tarsal conjunctiva (tarsal form) or at limbus (bulbar form).[3] Topical and oral antiallergic agents or steroids can be used in treatment of allergic conjunctival disease. The most effective treatment for VKC have been topical corticosteroids, but it carries considerable risk of complications like glaucoma, cataract and secondary infections which may even lead to permanent visual impairment.[4] Both cyclosporine A and tacrolimus have achieved considerable results in the treatment of severe allergic eye diseases, and are well tolerated with negligible side-effects according to many recent studies.[5]

MATERIAL AND METHODS

A prospective, comparative, interventional study conducted on 142 patients of VKC between February 2020 to august 2021 attending the ophthalmic outpatient department of JLN Medical College & Hospital, Ajmer.

INCLUSION CRITERIA:

1. Patients of either sex having vernal keratoconjunctivitis, either symptomatic or asymptomatic or with previous history of treatment with antiallergic drugs. **2**. Willing for regular follow-up&Ready to give written, informed consent for the study.

EXCLUSION CRITERIA:

1. Patient with associated ocular disease (corneal degeneration or dystrophies or uveitis, strabismus, subluxated or dislocated lens and glaucoma etc).
2. H/o previous ocular surgery or any structural abnormalities (lid scarring, entropion),
3. Contact lens users
4. Using topical medication other than artificial tears & some immunosuppressive systemic therapy or taking antibacterial treatment within 30 days of participating in study
5. Any systemic disease other than co-existing allergic rhinitis, asthma.
6. Reported hypersensitivity to FK- 506 or cyclosporine

Patients of VKC attending the OPD of our department, were screened for the inclusion and exclusion criteria and included in the study after obtaining informed consent either from the patients or their guardian. All patients received a thorough comprehensive ophthalmic examination. Specific symptoms and signs of VKC were graded and recorded in the proforma. Intraocular pressure was recorded using schiotz tonometer.

Right Eye was treated with Topical Cyclosporine 0.05% eye drop and left eye with Topical Tacrolimus 0.1% eye ointment twice daily per day for 2 months along with artificial tear (preservatives free)

The patients were followed up, symptoms and sign scores were recorded on 15th , 30th, 60th day. The treatment was then withdrawn for 30 days and patients were reviewed after 1 month(12th week) and symptoms and sign scores were recorded.

Clinical scoring system

Grading of Symptoms[6,7]

Four clinical symptoms were evaluated and graded according to severity score from 0 to 3.

- **Itching:**

Score 0- no symptoms
Score 1- Occasional itching
Score 2- Frequent itching with tendency to rub eye
Score 3- Continuous itching , frequent rubbing of eye

- **Tearing:**

Score 0- Absent
Score 1- Occasional with no complain of discomfort
Score 2- Frequent, patient felt as discomfort
Score 3- Persistent

- **Photophobia:**

Score 0- Absent
Score 1- Occasional with no complain of discomfort
Score 2- Continuously photopobic
Score 3- eye responds with blepharospasm on exposure to light

- **Fb Sensation:**

Score 0- Absent
Score 1- Slight
Score 2- Moderate
Score 3- Severe

Grading of signs[6,7]

Four clinical signs were evaluated and graded according to severity score from 0 to 3.

- **Hyperemia:**

Score 0- Absent
Score 1- Slightly dialated vessels, color of vessels is pink
Score 2- More apparent dialatation of vessels
Score 3- Numerous and obvious dialated vessels

- **Punctate Keratitis:**

Score 0- none
Score 1- one quadrant of cornea affected
Score 2- Two quadrant affected
Score 3- Three or more quadrant affected

- **Horner Tranta's dots:**

Score 0- none
Score 1- one or two
Score 2- three or four
Score 3- More than four dots

- **Papillae:**

Score 0- Nil
Score 1- Flat, topped mosaic (hyperemic scattered papillae)
Score 2- Macro Papillae
Score 3- Cobblestone appearance

STATISTICALANALYSIS

The data was tabulated using SPSS version of Microsoft Excel and expressed as percentage and mean scores. Both the eyes were compared and analyzed. P value <0.05 was considered as statistically significant.

RESULTS

149 patients of VKC were enrolled into this study but 142 patients appeared and completed the study during the study period. Total subjective symptoms scores and total ocular sign scores of both the eyes were evaluated and compared.

Demographic distribution

We obtained demographical information from patients, and found that the minimum age of presentation was 3 years and maximum age of patient was 20 years of age. The data conferred mean age with 10.09 with standard deviation3.955 (Range 9-14 years, Table 1)

Table 1: Showing mean age, standard deviation

	Minimum	Maximum	Mean	Std. Deviation
Age	3	20	10.09	3.955

We found higher propensity of VKC among males in our study results. Urban patients were observed to be more 128(90.1%) than rural patients 14 (9.9%) (Table 2).

Table : showing gender and residential area predisposition-

	Frequency	Percent
Female	43	30.3
Male	99	69.7
Urban	128	90.1
Rural	14	9.9

Outcome Measures

Total subjective symptoms score (TSSS)

Itching was found to be the major complaint that patients presented with, followed by tearing. The pre (Day 1) , post (2^{nd}, 4^{th}) treatment and after drug withdrawal (12^{th} week) total subjective symptom scores of both the eyes are summarized Table 3. There was reduction in mean TSSS in both the eyes from 2^{nd} weeks onward but improved was evident higher in Left eye(being treated with Tacrolimus) as compared to right eye (on Cyclosporine).

Scores became statistically significant at 4 weeks i.e p< 0.05 and remained significant thereafter. On 4^{th} follow-up i.e. at 12^{th} week (post 1 month of withdrawal) mean TSSS scores were found to be higher when compared to TSSS scores of 3^{rd} follow-up(on treatment), but was still lower than that of baseline scores and remained significant(p-value<0.05).

Table 3: Showing TSSS on consecutive follow-ups

Day 1(Baseline)				
	Itching	**Fb Sensation**	**Tearing**	**Photophobia**
RE (Cyclosporine)	1.8±0.63	0.68±0.78	1.3±0.94	0.56±0.64
LE(Tacrolimus)	1.8±0.63	0.66±0.807	1.29±0.92	0.55±0.64
p-value	0.92	0.82	0.94	0.85
1st Follow-up (2nd week)				
RE (Cyclosporine)	0.91±0.68	0.49±0.702	0.63±0.66	0.3±0.56
LE(Tacrolimus)	0.76±0.6	0.38±.69	0.57±0.68	0.21±0.41
p-value	0.69	0.2	0.43	0.15
2nd Follow-up (4th week)				
RE(Cyclosporine)	0.35±0.56	0.13±0.34	0.17±0.37	0.08±0.27
LE(Tacrolimus)	0.23±0.42	0.05±0.21	0.17±.37	0.08±0.27
p-value	0.04(S)	0.01(S)	--	--
4th Follow-up(12 week)- post withdrawl				
RE(Cyclosporine)	0.3±0.502	0.11±0.31	0.19±0.39	0.09±0.28
LE(Tacrolimus)	0.14±0.34	0.04±0.202	0.06±0.24	0.03±0.16
p-value	0.003(S)	0.02(S)	0.001(S)	0.02(S)

Total objective sign scores (TOSS)

The pre (Day 1) , post (2^{nd}, 4^{th}) treatment and after drug withdrawal (12^{th} week) total ocular sign scores of both the eyes are summarized Table 4. There was reduction in mean TOSS in both the eyes from 2^{nd} weeks onward and was found to have similar effect on signs but improvement was evidenced little higher in Left eye (being treated with Tacrolimus) as compared to right eye(on Cyclosporine). Improvement in papillae and conjunctival hyperemia were seen in both the eyes with the mean papillae in RE and LE was 0.56±0.69 and 0.35±.53 respectively and mean Redness in RE and LE was 0.59±.66and 0.37±0.62 respectively, which became statistically significant at week 2(p<0.05).

On 12^{th} week,1 month post drug withdrawal the mean Papillae in RE and LE was 0.11±0.308 and 0.04±0.18 respectively, followed by meanHorner \Tranta's Spotin RE and LE was 0.06±0.23 and respectively, similarly, the mean Redness in RE and LE was 0.012±0.32 and 0.03±0.16, which were higher when compared to TOSS of 3^{rd} follow-up but still were much lower than that of baseline scores and conferred statistical significance with p-value<0.05.

Table 4: Showing TOSS On Consecutive Follow-ups

Day 1(Baseline sign score)				
	Papillae	**Horner\ Tranta's Spot**	**Redness**	**Keratopathy /Punctate**
RE (Cyclosporine)	0.77±0.75	0.53±0.905	1.04±0.68	0.28±0.58
LE (Tacrolimus)	0.73±0.84	0.56±0.95	1.04±0.68	0.32±0.32
p-value	0.65	0.79	0.93	0.63
1st Follow-up (2nd week)				
RE (Cyclosporine)	0.56±0.69	0.45±0.69	0.59±.66	0.28±0.55
LE (Tacrolimus)	0.35±.53	0.21±0.45	0.37±0.62	0.1±0.29
p-value	0.001(S)	0.001(S)	0.001(S)	0.001(S)
2nd Follow-up (4th week)				
RE (Cyclosporine)	0.08±0.27	0	0.16±0.37	0
LE(Tacrolimus)	0.01±0.08	0	0.05±.21	0
p-value	0.002(S)	0	0.002(S)	0
4th Follow-up (12th week) post withdrawl				
RE (Cyclosporine)	0.11±0.30	0.06±0.23	0.12±.32	0
LE (Tacrolimus)	0.04±0.18	0	0.03±0.16	0
p-value	0.02(S)	0.004(S)	0.003(S)	0

Effect on Intra-ocular pressure

Graph 1: Showing mean IOP on various follow-up during study period

The baseline mean IOP in RE (0.05% Cyclosporine) was 13.63 mm of Hg and in LE (0.1% Tacrolimus) 13.44 mm of Hg. The change in IOP in both the eyes from baseline to last follow-up was neither statistically different nor there was any effect of both the drugs on intraocular pressure.

DISCUSSION

In this study both tacrolimus 0.1% eye ointment and cyclosporine 0.05% eye drops were found to be effective for the treatment of VKC, but improvement in symptom scores were found to more in eye being treated with tacrolimus. Improvement in sign scores were almost similar in both the eyes with little higher evident in left eye. A similar comparative study was conducted by Pucci et al,2015 which included a totalof 30subject and treated them with1% Cyclosporine in one eye and 0.1% Tacrolimus in the other eye for 3 weeks. A significant improvement was observed in the eyes treated with 0.1% oftacrolimus.[8] One more study conducted by Labcharoenwongsat el 2012compared the efficacy of 0.1% tacrolimus (FK-506) ophthalmic ointment with 2% cyclosporine eye drops in the treatment of VKC. This study concluded that there was similar efficacy for 0.1% tacrolimus ophthalmic ointment and 2% cyclosporine eye drops for the treatment ofVKC.[9]

The disease had a greater prevalence in males (69.7%) as compared To females (30.3%). Collum MT et al said that, VKC usually occurs before 10 years of age with a male-female ratio about 2:1, which means that males are more susceptible to this VKC[10].

The Mean age of presentation was 10.09 years(3.955 SD) with clustering of cases in the age group 9-14 yrs, this is also in corcondance with the literature. Our study findings are supported by a study done by Hakak B et al[11], who conducted a cross-sectional study on 424 eyes of 212 patients of 5 to 20 years of age. In another study, Sabooetal[12] studied a retrospective chart analysis of 468 patients of VKC, observed that, the mean age at presentation was 12 ±6.63SD years .

The most frequent side effect complained by our study population was burning sensation on in stilling the drug but it was not severe enough to stop the drug. Both the drugs were well tolerated. No one developed elevation of intraocular pressure, infectious keratitis or cataract. A study conducted by Samyuktaetal2019,Patients were treated with tacrolimus 0.03% ointment and were followed for 8months. Apart from a transient stinging sensation, no participant experienced adverse effects throughout this study. [13]A similar study Wan et al 2017 conducted to study the efficacy and safety of 0.1% tacrolimus eye drops and found no significant changes in visual acuity,cataracts, elevation of intraocular pressures were found during the follow up period.[14]

CONCLUSION

This study suggests that both Cyclospoirne 0.05% & Tacrolimus 0.1% has demonstrated its efficiency and safety in the management of VKC along with having a non-significant change in intra-ocular pressure. But 0.1% Tacrolimus found to be more effective. Hence, it can be considered as a first-line treatment for patients with VKC, but has a side effect of stinging sensation on instillation of drug. **Lacunae** of our study was that it was a Double Masked Prospective Interventional comparative study, which reduced the scope of larger sample size and study criteria, thereby limiting the major out-comes of the study.

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