ORIGINAL RESEARCH PAPER

Volume-7 | Issue-6 | June-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

TO COMPARE EFFICACY OF TOPICAL CYCLOSPORIN 0.1% , TACROLIMUS OINTMENT O.1% THERAPY WITH FLUROMETHALONE 0.1% FOR VERNAL KERATOCONJUNCTIVITIS.

Ophthalmology

Narinder Pal Singh Md Consultant and Head of Department, Dr Baba Saheb Ambedkar Medical and Hospital, New Delhi, India

Daljeet Kaur Ms* Senior specialist and Head of Department, Babu Jagjivan Ram Hospital, New Delhi, India. *Corresponding Author

ABSTRACT

Background : Vernal keratoconjunctivitis is a conjunctival inflammatory disorder caused by Type 1, hypersensitivity reaction.1It is treated effectively by topical steroids, but their prolonged use subjects these patients to steroid induced side effects. Hence there is a need to evaluate an alternative treatment like immunomodulators. AIM : To compare the effects of cyclosporine,,tacrolimus,and fluoromethalone in management of moderate to severe VKC in terms of efficacy& safety.

Materials and Methods : 60 cases of moderate to severe VKC were divided into 3 groups with 20 patients each,and treated with cyclosporine 0.1% ,tacrolimus 0.1% ointment , and flurometholone 0.1% eye drops. All the patients were studied for symptoms of Itching, tearing, foreign body sensation, photophobia and signs of red eye, papillary hypertrophy, chemosis, & infiltration of cornea .

RESULTS;Flurometholone showed earliest and maximum relief of symptoms and signs(after 7 days of treatment) , followed by Tacrolimus(after 14 days of treatment) and Cyclosporine(after 30 days of treatment). Flurometholone also caused rise in Intra ocular pressure , which is not seen in case of Tacrolimus and Cyclosporine.

CONCLUSION; All the three drugs ,Flurometholone, Tacrolimus, and Cyclosporin were effective in treating symptoms and signs of VKC, but had different peaks of effect. Considering IOP rise with Flurometholone one can safely use , tacrolimus and cyclosporine in patients of moderate to severe VKC.

KEYWORDS

Vernal Keratoconjunctivitis(VKC) , Immunomodulators, Papillary Hypertrophy, Chemosis.

INTRODUCTION

Vernal Keratoconjunctivitis a form of seasonal exacerbated allergic Conjunctivitis[1] is treated effectively with steroids like Fluoromethalone but this therapy carries a definite risk of developing steroid related side effects including Glaucoma[4] ,and rapid recurrence of symptoms following their discontinuation . So there is a need for standardised therapeutic approach on the basis of grading the disease and subsequent safe and effective treatment modality.[1, 5] Immunomodulators have been investigated for VKC treatment including ocular preparations of Cyclosporine and Tacrolimus [6 ,7] .Pathogenesis of VKC involves role of IGE , mast cell mediated process ,along with cytokines, chemokines, and inflammatory cells. Cyclosporine by virtue of inhibitory effect on production of cytokines, chemokines from effector cells including T- helper cells[3], could cause clinical improvement. Tacrolimus is found to inhibit the release of histamine and production of inflammatory mediators , such as LTC4 from human basophils[4]thus beneficial in various inflammatory disorders of anterior segment like severe atophic blephro-conjunctivitis,atopic kerato-conjunctivitis, and papillary conjunctivitis.[9,10]

METHODS AND MATERIALS

Studydesign This was a Prospective and Interventional Randomised Comparative double Blinded study for efficacy of Tacrolimus, and Cyclosporine , with Fluoromethalone eye drops forvernalkeratoconjuctivitis.The study was conducted in Department of Ophthalmology, Dr. Baba Saheb Ambedkar Medical college and Hospital, Rohini, New Delhi, India. It is a tertiary care hospital catering both urban and rural population.

Subjects60 cases were studied and divided into 3 groups with 20 patients per group.Group A: Diagnosed cases of moderate to severe VKC treated with cyclosporine 0.1% eye drops.Group B: Diagnosed cases of moderate to severe VKC treated with tacrolimus 0.1% ointment.Group C: Diagnosed cases of moderate to severe VKC treated with flurometholone 0.1% eye dropsPatients were excluded if their age was <5 years and >20 years, if they had any coexisting ocular disease like glaucoma, uveitis, corneal disease, or if they had reported hypersensitivity to tacrolimus, cyclosporine or flurometholone.

Methodology The 3 groups were assigned medication through Block randomization technique. In this technique patients were randomized in a series of blocks of 15 ,that is, for every 15 patients randomized five received Group A treatment , five received Group B treatment and other five received Group C treatment. Neither patient nor evaluator were aware which label represents which group , making the study double blinded.Pre and post treatment assessments were performed by one ophthalmologist. The clinical notes were made inaccessible to the evaluating ophthalmologist.The dosage of medication given in each group during period of 90 days of study was as such: Group A : cyclosporine 0.1% eye drops in dosage of one drop every 12 hours in both eyesGroup B: tacrolimus 0.1% eye ointment twice a day in both eyes.Group C : fluorometholone 0.1% eye drops four times day in both eyes.

Clinical Examination : The basal examination was carried out 7 days before start of study. Demographic information, clinical history, and specific symptoms were noted . A complete ophthalmic examination including visual acuity using Snellen Chart , Slit lamp biomicroscopy and Shiotz tonometery was done on 7, 14 ,30 ,60 , 90 days after start of the Study. These patients underwent fundoscopy under pupillary dilation (only on day 30 and 90).Follow up was done on days 7, 14,30,60,90.Diagnosis was done on basis of signs and symptoms of VKC and severity was graded[4] as mild, moderate and severe, with uniform treatment modalities as planned ,for moderate and severe cases of VKC.[3]

Table-1. Classification for severity of Vernal Keratoconjuctivitis

SYMPTOMS	NORMAL	MILD	MODERATE	SEVERE
Itching (desire to rub or stretch eye)	No desire	Occasional desire	Frequent need	Constant need
Tearing	Normal tear production	Positive sensation of fullness of conjuctival sac without tears spilling over lid margins	Intermittent, infrequent, spilling of tears over lid margin	Constant spilling of tears over lid margin
Foreign body sensation	Absent	Mild (fine dust sensation)	Moderate(sand like sensation with mild tearing)	Severe sensation (with constant tearing and blepharospasm)
Photophobia	absent	Mild difficulty with light , causing squeezing .	Moderate, necessitating use of dark glasses.	Severe, causing patient to stay indoors

Stinging	absent	Mild	Moderate	Severe
Red eye	Absent	Mild(patient cannot observe his red eye but is told that he/she has it)	Moderate(patient can observe his red eye from 30cm in a mirror)	Severe(patient can observe his red eye from more than 30cms in a mirror).
Conjunctival Hyperemia	Absent	Mild(<25% of total conjunctival surface)	Moderate	Severe
Conjuctival discharge	Absent	Small amount(translucent or whitish)	Moderate amount(yellow or greenish yellow)	Severe (with traces of Blood in lower cul-de-sac).
Tarsal conjuctival papillary hypertrophy	Absent	Mild papillary hypertrophy	Moderate papillary hypertrophy with conjunctival edema.	Severe papillary hypertrophy with obscuration of deep Tarsal vessels.
Chemosis	Absent	Mild	Moderate	severe
Corneal Infilterates	Absent	Fine superficial epithelial defects involving <1/2 cornea	Diffuse fine epithelial defects involving >1/2 cornea	Confluent epithelial defects, mucous plaque formation or oval corneal ulcers

Statistical analysis

Statistical analysis was performed as :

1. Quantitative variables were compared using ANOVA/Kruskal Wallis test between three groups and paired t-test/Wilcoxon ranked sum test across follow up within group.
2. Qualitative variables were compared using Chi-Square test /Fisher's exact test.

Ap value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results and Observation.

120 eyes of 60 patients of moderate to severe VKC were examined .The patients age ranged from 5-15 years in Group A (mean age : 10.1±2.2) , in Group B mean age was 10.75±1.97 and in Group C mean age was 9.4±1.93. all groups were statistically comparable with regard to age distribution and gender distribution with no significant difference (p>0.05)

1) After treatment with three drugs, improvement was seen in the symptoms of itching, tearing, photophobia earliest at 7 days in all the groups which was statistically significant for each group(p<0.05) but intergroup variations were not significant. In Group B and Group C , foreign body sensation started improving after two weeks of treatment, but in Cyclosporine treated (group A), this improvement started after 30 days. This trend was then maintained till the end of study. Maximum improvement of symptoms following drug therapy was seen in patients of Group C (patients using Flurometholone eye drops) followed by Group B(patients using Tacrolimus ointment) and then Group A(patients using cyclosporine eye drops).

POST TREATMENT DAY	IMPROVEMENT IN SYMPTOMS
DAY 7	Group C>Group B>Group A
DAY 14	Group c>Group B>Group A
DAY 30	Group C=Group B> Group A
DAY 60	Group C>Group B>Group A

Table-2. Post treatment analysis of improvement in symptoms in Group A,B and C

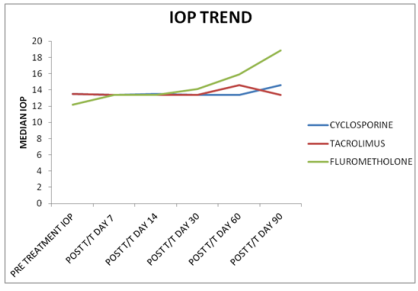
2) Following treatment with the three drugs, improvement in all signs (conjuctival hyperemia, conjuctival discharge, chemosis) except papillary hypertrophy was seen earliest at 7 days and this improvement was progressive till the end of study. Papillary hypertrophy started improving after 30 days of treatment in Group A,and Group B , while in Group C this improvement started after 14 days of treatment . After 90 days of treatment , papillary hypertrophy was significantly improved in all groups p<0.05 (Group C=Group B> GroupA) but intergroup variations were not significant.

3) Intraocular Pressure was raised in three patients of Group C after 30 days of treatment which was statistically significant , but no change was seen in patients of Group A and B.(Figure 1.and Table 3.)

Table 3. Median IOP change over period of 90 days in Group A,B and C.

(In mmHg)	CYCLOSPORINE	TACROLIMUS	FLUROMETHOLONE
PRETREATMENT IOP	13.5	13.5	12.3
POST TREATMENT IOP DAY 7	13.4	13.4	13.4
POST TREATMENT IOP DAY 14	13.5	13.4	13.4
POST TREATMENT IOP DAY 30	13.4	13.4	14.1
POST TREATMENT IOP DAY 60	13.4	14.6	15.9
POST TREATMENT IOP DAY 90 DAY 90	14.6	13.4	18.9

Figure 1. Trend of IOP over period of 90 days in Group A B and C.



As seen from the results, all three drugs were effective in reliving symptoms and signs in patients of moderate to severe VKC. However, there was a difference in time for maximum effect among three drugs , earliest effect seen with fluorometholone followed by tacrolimus and cyclosporine. Significant rise in IOP was only seen with flurometholone eye drops but there were no fundus changes attributing to raised IOP seen during the period of study.

DISCUSSION

Vernal Keratoconjunctivitis(VKC) is chronic form of seasonal allergic Conjunctivitis, having three forms, limbal, tarsal and mixed1,2. .Effective and safe therapy for VKC is needed to improve signs and symptoms and to prevent complications. Most of the patients use topical steroids for long duration , resulting in complications like Cataract, Glaucoma, superimposed infections etc. Present study was aimed at analyzing efficacy and safety of topical Cyclosporin6 and Tacrolimus5 in comparision to Flurometholone in treatment of moderate to severe VKC.

The patients who received Cyclosporine showed improvement in all symptoms except foreign body sensation at the earliest 7 days of treatment , maximum effect was at 30 days, and this trend continued till the end of study. Foreign body sensation started to improve after 14 days of treatment and improvement persisted till the end of study. All the Signs improve at 7 days after treatment with Cyclosporine , except Papillary hypertrophy which takes 30 days.

In the Group of Tacrolimus treated patients all the symptoms, and signs started to improve 7 days after the treatment with peak effect after14 days. However Papillary hypertrophy showed maximum effect at 60 days of treatment.

In Flurometholone group significant improvement in all symptoms was observed earliest after 7 days , peak effect was seen after 14 days

,and improvement was progressive till the end of study. Three patients in this group also showed a significant rise of intraocular pressure .

The inter group comparison showed improvement of signs and symptoms earliest and maximum in fluromethalone treated eyes followed by Tacrolimus and this improvement was almost equivalent in these two groups. Cyclosporine treated group showed a delayed onset and peak effect in improvement of signs and symptoms.8

CONCLUSION

All the three drugs Cyclosporine ,Tacrolimus and Fluromethalone are effective in relieving signs and symptoms of moderate to severe VKC. Fluromethalone shows earliest and maximum effect , followed by tacrolimus and cyclosporine. With significant rise of IOP with Fluromethalone , the other two drugs Tacrolimus and Cyclosporin can be used as an alternative .

REFERENCES

1. Buckley RJ .Vernal Keratoconjuctivitis. Int Ophthalmol Cllin. 1988; 28 (4): 303-308.
2. Bonini S ,Coassin M , Arnni S, Lambiase A Vernal Keratoconjunctivitis. Eye (Lond) (2004) 18:345-351.
3. Sunil Kumar.,Vernal Keratoconjunctivitis: a major review. Acta Ophthalmol.2009; 87:133-147
4. Bonini, Stefano,Sacchetti, Marta, Mantelli, Flavio, et al. Clinical Grading of Vernal Keratoconjunctivitis. Curr Opin Allergy ClinImunlol 2007oct; 7(5):436-41
5. Cheng AC, Yuen K, Chan W. Topical Tacrolimus ointment for treatment of refractory anterior segment inflammatory disorders. Cornea. 2006;25:634.
6. Lambiase A, Leonardi A, Sacchetti M, et al. Topical Cyclosporine prevents seasonal recurrence of Vernal Keratoconjunctivitis in a randomized , dauble masked , controlled 2 year study. J Allergy Clin Immunol. 2011;128:896-7.
7. Fairburn WD, Thorson JC, Fluromethlone anti- inflammatory and intraocular pressure effects. Arch Ophthalmol. 1971;86: 138-41.
8. Sanjiv Kumar Gupta, Ajay Kumar, Amit Verma, Siddharth Aggarwal, Vishal Katiyar. Indian Journal of Clinical and Experimental Ophthalmology, January-March 2015;1(1):22-28.