ORIGINAL ARTICLE

A STUDY TO EVALUATE AND COMPARE THE EFFICACY AND SAFETY OF TOPICAL CYCLOSPORINE-A 0.5% WITH TOPICAL PLACEBO (ARTIFICIAL TEARS) IN ALLEVIATING THE CLINICAL FEATURES ASSOCIATED WITH VERNAL KERATOCONJUNCTIVITIS

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ABSTRACT

Introduction: Vernal keratoconjunctivitis is a severe, typically seasonal recurrent ocular inflammatory disorder. Topical cyclosporine-A is inhibitory to many T-cell dependent inflammatory mechanisms which are likely to play role in treatment of vernal keratoconjunctivitis.

Methodology: The study was conducted on 100 patients of vernal keratoconjunctivits selected from Ophthalmology out patients Department of Dr. D.Y Patil Hospital, Pune. Patients were divided in two groups of 50 each, group I and group II. It was double masked comparison study to assess and compare the efficacy of 0.5% topical Cyclosporine-A and topical placebo in the treatment of vernal keratoconjunctivits.

Results: Comparing therapeutic response of symptoms in two groups at day 28 of the study shows topical cyclosporine was better and favored over placebo. Patients showed improvement in following symptoms accordingly. Itching: 49 in group I, 33 in group II. Discharge: 33 in group I, 4 in group II. Photophobia: 32 in group I, 1 in group II. Foreign body sensation: 35 group I, 11 in group II. Patients showed improvement in following signs accordingly: Conjunctival inflammation: 40 in group I, 11 in group II. Papillary hypertrophy: 15 in group I, none in group II. Limbal changes: 7 in group I, none in group II.

Conclusion: The use of topical cyclosporine for treatment of vernal keratoconjunctivitis should be encouraged to prevent complications associated with the natural course of the disease and prolonged topical use of corticosteroids.

Keywords: Vernal keratoconjunctivitis, Cyclosporine-A, Papillary hypertrophy, Limbal changes, Itching

INTRODUCTION

Vernal keratoconjunctivitis(VKC) is defined as "recurrent, bilateral, interstitial, inflammation of the conjunctiva of periodic seasonal incidence, self limiting in character and (as yet) of unknown aetiology, characterized by flat topped papillae usually on the tarsal conjunctiva resembling cobblestones in appearance, a gelatinous hypertrophy of the limbal conjunctiva, either discrete or confluent and a distinctive type of keratitis associated with itching, redness of the eyes, lacrimation and a mucinous or lardaceous discharge usually containing eosinophils.VKC has a seasonal predilection for spring time, with peak incidence between April and August, for some individuals, the disease can manifest itself year round.[1]

Pathologically, there is hypertrophy of adenoid layer of conjunctiva with infiltration of eosinophils. There is marked eosinophilia of inflammatory exudates as well as raised tear and serum IgE. IgE mediated reactions involve mast cell degranulation and release of prostaglandins, chemical mediators as histamine, slow reacting substances of anaphylaxis and serotonin. These vasoactive amines cause increased capillary permeability, cellular infiltration, increased serum neutrophil chemotactic activity and exudation.[2]

Recent studies have shown prevalence of local helper T-cell type 2 response in vernal keratoconjunctivitis, with the presence of helper T-cell type 2 like cells in tears and conjunctival biopsy specimens. Interleukin (IL) – 3, IL-5, IL-6 and granulocyte – macrophage colony-stimulating factor are particularly expressed in conjunctival eosinophils of vernal keratoconjunctivitis patients. High levels of tear IL-5 and eosinophil cationic protein (ECP) have also been found in patients with vernal keratoconjunctivitis.So, T-cell mediated inflammation appears to play central role in pathogenesis of vernal keratoconjunctivitis.[3]

Topical cyclosporine-A is inhibitory to many T-cell dependent inflammatory mechanisms. It has unique ability to selectively suppress the synthesis and pro-

duction of interleukins. Cyclosporine-A also has direct and indirect inhibitory effects on mast cell activation and mediator release, which are likely to play role in treatment of allergic inflammation. It is anti-apoptotic, immunomodulatory and anti-inflammatory.[4]

Topical cyclosporine-A has been successfully used in vernal keratoconjunctivitis, with an improvement in symptoms and clinical signs. The aim of our study is to compare efficacy of topical cyclosporine A drops with placebo in steroid resistant cases of vernal keratoconjunctivitis.[5,6]

METHODOLOGY

Selection of Cases:

- Hundred patients having bilateral signs and symptoms of vernal keratoconjunctivitis were selected of any age, sex and habitat attending out patients department of Ophthalmology, Dr. D.Y Patil Hospital, Pune. Patients were studied to evaluate and compare the efficacy of topical cyclosporine A 0.5% with topical placebo (artificial tears CMC 0.5%) in treating vernal keratoconjunctivitis. All these patients were in contact with clinician prior to the study, so that they were using topical steroids for atleast 2 weeks and remained refractory, with persistent or progressive inflammation.

- Patients with other active ocular disease or infection, a history of ocular surgery, serious medical illness and concurrenttreatment for other allergic conditions like rhinitis were excluded from the study.

Ethical committee permission was taken prior to the study and written informed consent was taken from each patient.

Diagnosis of Vernal Keratoconjunctivitis: This was done on the basis of history and examination. Prior to initiation of therapy, relevant history and clinical details were recorded according to proforma. A detailed history was recorded with special reference to history of swollen eye, burning/stinging sensation, discharge/tearing, foreign body sensation, photophobia, itching and any past ocular history.

History of allergic symptoms elsewhere in body and family history of allergy was taken. Detailed examination of both the eyes under diffuse illumination and slit lamp examination was done to confirm the conjunctival, limbal and corneal signs such as lid edema, conjunctival chemosis, conjunctival inflammation, conjunctival discharge, papillary hypertrophy, limbal changes and also to rule out any other ocular pathology. Visual acuity of the patients was also recorded.

Grading of Patients: Allergic ocular symptoms i.e. itching, swollen eyes, burning/ stinging, discharge/tearing, foreign body sensation, photophobia and allergic signs i.e. lid edema, conjunctival chemosis, conjunctival inflammation/injection, papillary hypertrophy and limbal changes were rated using a scale from 0-3 i.e. allergic symptoms were rated as 0 for none, I for mild, II for moderate and III for marked, while signs were rated as 0 for none, I for mild, II for moderate and III for severe.

Grouping of Patients: Hundred patients of vernal keratoconjunctivitis were included in the study. They were randomly divided into two groups of fifty each, 50 receiving cyclosporine A and other 50 receiving placebo drops.

Treatment Regime: In this masked paired study, patients were randomly assigned either to have topical cyclosporine A 0.5% or topical placebo (artificial tears CMC 0.5%) 2 times daily for 4 weeks. Both the eye drops were dispensed to the patients in identical sterile vials coded I for cyclosporine-A & II for placebo,by masked health personnel unassociated with the study. Thus, the nature of the drug in each vial was masked.

Follow up: After the initial baseline assessment, treatment was started and every patient was subsequently examined after 7 days, 14 days, 21 days and 28 days of initiation of therapy. At each visit, the signs and symptoms were graded as already explained. Response to therapywas measured for each sign and symptom in relation to vernal keratoconjunctivitis and rated +2 for much improved, +1 for improved, 0 for no change, 1 for worse and –2 for much worse.

RESULT

Itching

Gradewise distribution of group I and group II treated eyes for itching at day 0: In group I, 45 (90%) patients and in group II, 47(94%) patients presented with severe, grade 3 itching. 5(10%) patients and 3 (6%) patients in group I & II respectively had mean baseline score of 2 on day 0.

Therapeutic response at day 28 of group I and II for itching: At the end of study, 49 patients in group I had much improved symptoms while in group II, 30 patients reported with much improved symptoms and 17 had +1 (improved) response. Ocular itching improved almost 100% in group I patients as compared to group II patients.

Discharge

Gradewise distribution of group I and group II treated eyes for discharge/tearing at day 0: 28 patients (56%) in group I had severe discharge/tearing while 11 had moderate and 1 had

mild discharge. In group II, 26 patients presented with severe discharge, 13 with moderate and 1 with mild discharge/watering.

Therapeutic response at day 28 of group I and II for discharge/tearing: Evaluation for therapeutic response at the end of study showed that 33 patients in group I were much improved, with 7 patients having improved symptoms. In group II, only 4 patients had improvement of ocular discharge while 46 had no change in discharge or tearing.

Photophobia

Gradewise distribution of group I and II treated eyes for photophobia at day 0: Most of the patients 32(64%) in group I and 28(56%) in group II presented with moderate photophobia. 3(6%) patients in group I and 5(10%) in group II had marked photophobia at baseline evaluation. Mild photophobia was seen in 5(10%) patients in group I and 6 (12%) in group II.

Therapeutic response at day 28 of group I and II for photophobia: At the end of study, 32 patients had much improved photophobia with 8 patients improved and 10 patients had no change in group I. In comparison, 47 patients in group II had no change .

Foreign body sensation

Gradewise distribution of group I and II treated eyes for foreign body sensation: At the day 0 in group I,27 patients(54%) and 26 patients(52%) in group II had marked foreign body sensation. 8 (16%) in group I and 9(18%) in group II presented with moderate foreign body sensation. Mild foreign body sensation was reported in 6 (12%) in group I and 7(14%) in group II vernal keratoconjunctivits patients.

Therapeutic response at day 28 of group I and II for foreign body sensation: At the end of the study in group I, 35 patients had much improved symptoms with 6 improved and 9 had no change while in group II, 27 patients reported improvement in foreign body sensation, 11 cases had much improved and no improvement in 12 cases.

Conjunctival Inflammation

Gradewise distribution of group I and II treated eyes for conjunctival inflammation at day 0: In group I, 12(24%) patients & in group II, 11 (22%) patients had severe conjunctival inflammation at day 0, while 19(38%) in group I and 22(44%) in group II patients presented with moderate conjunctival inflammation. Mild conjunctival inflammation was seen in 19(38%) patients in group I and 17(34%) in group II.

Therapeutic response at day 28 of group I and II for conjuntival inflammation: Evaluation for therapeutic response at the end of study showed that 40 patients had much improved cojunctival inflammation and 9 improved in cyclosporine treated eyes. 11 patients had improvement in their condition while 39 patients had no change in placebo treated eyes.

Table 1: Comparision of symptoms and it's severity in group 1 and Group 2.

Symptoms	Group 1			Group 2		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Itching	-	5	45	-	3	47
Discharge	1	11	28	1	13	26
Photophobia	5	3	32	6	5	28
Foreign body sensation	6	8	27	7	9	26
Conjunctival inflammation	12	19	19	11	22	17
Papillary hypertrophy	2	18	9	1	19	10
Limbal changes	18	8	3	17	9	2

Papillary Hypertrophy

Gradewise distribution of group I and II treated eyes for Papillary hypertrophy at day 0: Baseline evaluation showed that 9(18%) patients in group I and 10(20%) patients in group II presented with grade 3 papillae. Moderate papillary hypertrophy was present in 18(36%) patients in group I and 19(38%) patients in group II. Mild papillary reaction was present in 2 patients (4%) in group I and 1patient (2%) in group II, while no papillae were present in 21(42%) in group I and 20 (40%) in group II patients.

Therapeutic response at day 28 of group I and II for papillary hypertrophy: At the end of study, papillary hypertrophy was much improved in 15 patients and improved in 14 , while 21 patients had no change in papillary reaction group I. In placebo treated eyesiegroupII, 16 patients had improved papillae while 34 patients had no change in papillary reaction.

Limbal Change

Gradewise distribution of group I and II treated eyes for Limbal changes at day 0: 62% of patients in both groups presented with limbal

changes on baseline evaluation, 5% patients in both cyclosporine treated and placebo treated eyes had severe limbal changes (grade 3), while 8(16%) in group I and 9(18%) in group II presented with (grade 2) moderate limbal changes 18(36%) in group I and 17 (34%) in group II had mild limbal changes. No limbal changes were seen in 19 (38%) patients of both groups.

Therapeutic response at day 28 of group I and II of limbal changes: 7 patients showed much improvement and 21 patients had improvement in limbal changes with topical cyclosporine treated while 22 presented with no improvement at the end ofstudy. 13 patients showed improvement and 37 patients had no improvement in placebo treated eyes.

DISCUSSION

The present study was conducted on hundred patients to compare the effects of topical cyclosporine and topical placebo (artificial tears CMC 0.5%) in vernal keratoconjunctivitis in the department of Ophthalmology, Dr.D.YPatil Medical College, Pune. Topical cyclosporine 0.5% and topical placebo (CMC 0.5%) were used, one drop 2 times a day for 4 weeks. Most of the patients in the study were males i.e. 39 males in group I and 37 in group II with 11 (22%) females in group I and 13 (26%) in group II 66% in group I and 78% in group II were from rural areas. The maximum number of patients, 18 in group I and 25 (50%) in group II were of 10-12 years age group. The disease was seen to have a chronic, recurrent form with a majority of patients 28 (56%) in group I and 20 (40%) in group II having history of 1 to 3 years. Most of these patients had exacerbation in summer. The mixed form of disease was most common, found in 50% in group I and 46% in group II patients.

In the present study, topical cyclosporine 0.5% have been found to be safe and effective in alleviating prominent ocular symptoms of itching, discharge, photophobia and foreign body sensation on day 7, 14 21 and 28 of the study. Among the signs, conjunctival inflammation was reduced significantly with topical cyclosporine in comparison to topical placebo but papillary hypertrophy and limbal changes remained largely unaffected probably due to shorter duration of time.

Comparing therapeutic response of symptoms in two groups at day 28 of the study shows topical cyclosporine was better and favoured over placebo.

Total 49 patients showed improvement in itching in group I and 33 in group II. 33 patients showed improvement in discharge in group I and only 4 in group II. 32 patient showed improvement in photophobia in group I and 1 in group II. 35 patient showed improvement in foreign body sensation in group I and 11 in group II. Greater numbers of patients, at the end of study, were improved for signs of vernal keratoconjunctivitis with topical cyclosporine than topical placebo. 40 patients showed improvement in conjunctival inflammation in group I and 11 in group II. 15 patients showed improvement in papillary hypertrophy in group I and none in group II. 7 patients showed improvement in limbal changes in group I and none in group II.

CONCLUSION

The study suggests that topical cyclosporine -A is safe and effective in treatment of severe vernal keratoconjunctivitis. Most of its effects on signs and symptoms were achieved after 2 weeks of treatment. The only side effect was mild burning sensation and tearing soon after the instillation of the eye drops.

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