

To Study Efficacy and Safety of Topical Cyclosporine 0.1% and Tacrolimus Ointment 0.1% Therapy in Comparison with Fluometholone 0.1% for Vernal Keratoconjunctivitis

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Abstract: To evaluate and compare the efficacy and safety of topical cyclosporine 0.1% , topical tacrolimus 0.1% and topical fluorometholone 0.1% in patients of vernal keratoconjunctivitis. Randomised controlled trial, patients divided into three groups and each group treated with one drug according to dose and duration decided. In our study it was observed that improvement in symptoms and signs was seen in all groups. Associated allergic diseases were noted in 80% of patients (allergic rhinitis most common followed by asthma and atopic dermatitis). All the three drugs cyclosporine, tacrolimus and fluometholone are effective in reliving symptoms and signs in patients of moderate to severe VKC. There is significant difference in onset of action , efficacy and adverse effects of three drugs.

Keywords: vernal keratoconjunctivitis, cyclosporine, tacrolimus, fluometholone, immunomodulators

1. Introduction

Allergic conjunctivitis disease (ACD) is a conjunctival inflammatory disorder caused by an immediate hypersensitivity response. ACD is divided into several clinical types such as allergic conjunctivitis (AC), atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC).

Vernal Keratoconjunctivitis (VKC) is one severe chronic form of seasonally exacerbated allergic conjunctivitis. Although many cases of VKC spontaneously enter a remission phase, in some the disease continues into adulthood. This disorder is usually triggered by allergens in the air, especially plant pollen, leading to seasonal exacerbations during the spring and summer months². Mild cases of VKC tend to remit with nonspecific and supportive therapy. In contrast, severe cases are usually more protracted with remission/relapse occurring for a prolonged period of time. 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 (accumulation of gelatinous inflammatory infiltrates) around the limbus.

Treatment of VKC includes non pharmacological and pharmacological management. In current study we will compare 0.1% tacrolimus ointment , 0.1% cyclosporine eye drops and topical fluorometholone 0.1% in terms of safety and efficacy in patients of moderate to severe VKC by means of serial clinical examinations. In this study we have analysed subjective symptoms and objective signs before and after treatment in patients with VKC in three different groups using three different medications. To best of our knowledge there is no documented comprehensive study in Indian subcontinent comparing cyclosporine ,tacrolimus and fluometholone in treatment of moderate to severe VKC.

The results of current study would help ophthalmic surgeons in providing alternatives to topical steroids in treatment of Vernal Keratoconjunctivitis (VKC).

2. Literature Survey

The first description of vernal keratoconjunctivitis (VKC) was by Arlt in 1846 when he reported 3 cases of perilimbal swelling in young patients³.

In 1871, von Graefe added "pavement-like granulations of the conjunctiva" to the clinical picture. The association with springtime (vernal means spring) reflects the seasonal increase in signs and symptoms of the condition, particularly the high prevalence in hot, arid environments; affected individuals have disease flares frequently during spring months, but can have signs and symptoms year round³.

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis (VKC) is a member of a group of diseases classified as allergic conjunctivitis including perennial and seasonal rhinoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis.^{4,5,6}

For many years, all allergic conjunctivites were considered (as suggested by Coombs and Gell⁷) the expression of a classical type I IgE-mediated hypersensitivity reaction at the conjunctival level. More recent clinical observations, however, suggest that other tissues of the eye are also involved in the ocular allergic reaction: the lids, with their high content of mast cells, the tear film, with its immunoglobulins, and the cornea, so important for visual function.

3. Methods/Approach

Place of Study- The study was conducted in department of Ophthalmology, Dr. Baba Saheb Ambedkar medical college

Volume 7 Issue 10, October 2018

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and Hospital, Rohini, New Delhi, It is a tertiary care hospital catering to both urban and rural population.

Study Population - Hospital OPD attending patients

Study Design:- Prospective and Interventional Randomised Comparative double Blinded Study.

- Group A : This comprises of 20 diagnosed cases of moderate to severe VKC treated with cyclosporine 0.1% eye drops
- Group B: This comprises of 20 diagnosed cases of moderate to severe VKC treated with tacrolimus 0.1% ointment.
- Group C: Comprises of 20 diagnosed cases of moderate to severe VKC treated with fluometholone 0.1% eye drops.

Inclusion criteria

- 1) Patients aged more than 5 years and less than 20 years.
- 2) Active moderate to severe vk

Exclusion criteria

- 1) Age < 5 years and > 20 years
- 2) Contact lenses users
- 3) Patients who cannot comply with the medical appointments or with all the protocol requirements.
- 4) Patients who disagree to participate in this clinical trial.
- 5) Patients with coexisting ocular disease like glaucoma, uveitis, corneal disease, ocular infection.
- 6) Reported hypersensitivity to tacrolimus, cyclosporine or fluometholone.

Method

Randomisation Technique: Block Randomisation with Sealed envelope system.

Block Randomisation- In this, I prepared 15 randomly generated treatment allocations within sealed opaque envelopes assigning A, B and C in 5 envelopes each, where A represents Group A receiving cyclosporine 0.1% eye drops, B represents Group B receiving tacrolimus 0.1% ointment and Group C receiving fluometholone 0.1% eye drops.

Once a patient gave consent to enter a trial an envelope was opened and the patient was then offered the allocated group. In this technique, patients were randomised in a series of blocks of 15—that is, for every 15 patients randomised 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.

Pre-treatment assessments included corrected distance visual acuity (CDVA) using Snellen standards, Intraocular pressure, Fundoscopic evaluation after pupil dilatation and slit lamp biomicroscopic examination.

Diagnosis of VKC was made on basis of symptoms and signs of VKC which included itching, tearing, mucous secretions and photophobia. Signs included hyperemia, papillary hypertrophy, giant papillae, discharge, and Horner-Trantas dots (accumulation of gelatinous inflammatory infiltrates around the limbus) and corneal lesions.

At the time of inclusion in the study, all the patients were disease positive in an active stage. The eligibility approval for all the subjects was determined after concluding the clinical evaluation in the basal visit. A complete washout period was then initiated for all study participants, which consist in the use of only physical measures (preservative free lubricating eye drops and cold compress) during 1 week. After the washout each subject was randomly assigned to one of the three groups where they received one of the three treatments exclusively.

The patients were organized randomly in three groups: Group A received the cyclosporine 0.1% drops in a dosage of one drop every 12 hours in both eyes during the 90 days of the study.

Patients of group B received the tacrolimus 0.1% ointment twice a day, during the 90 days of the study.

Group C would receive the fluorometholone 0.1% eye drops four times a day, during the 90 days of the study.

All patients were evaluated by the same investigator in the screening period, as well as in the subsequent programmed followup visits (days 7, 14, 30, 60, 90)

The brand labels of these vials were removed and new similar labels for all medications were affixed. At each consecutive visit, patients were instructed to bring their medications. In all the visits, compliance to therapy was checked by questioning the patient and inspection of the vials given to the patients. During their follow up, the patients were supplied with fresh drugs according to their treatment status.

4. Results

In our study it was observed that improvement in symptoms (itching, tearing, fb sensation, photophobia, red eye) and signs (conjunctival hyperemia, conjunctival discharge, papillary hypertrophy, chemosis, corneal infiltrate) was seen in all groups.

Associated allergic diseases were noted in 80% of patients (allergic rhinitis, asthma and atopic dermatitis)

In cyclosporine group out of 20 patients one patient lost follow up after 60 days and 19 patients completed study.

In cyclosporine group (group A) improvement in all symptoms except foreign body sensation and red eye was seen earliest at 7 days after treatment and maximum effect was seen one month after treatment and this improvement was progressive till the end of study duration. Foreign body sensation started improving after two weeks of treatment and was progressive till the end of study duration. Red eye was

increased in few patients after 7 days of study but improved after 14 days of study and improvement persisted till end of study.

Improvement in all signs except papillary hypertrophy was seen earliest at 7 days after treatment and improvement was progressive till end of study duration. Papillary hypertrophy started improving after 30 days of treatment and was improving till 3 months of study .

There were no changes in fundus and IOP after treatment in cyclosporine group.

Mild redness and burning sensation was complained by patients after using cyclosporine drops but it relived after some time.

Our findings are consistent with study conducted by Leopodo et al⁸.

In tacrolimus group out of 20 patients two patient lost follow up after 30 and 60 days of study respectively and 18 patients completed study.

In tacrolimus group (group B) improvement in all symptoms was seen from 7 days of treatment and maximum effect was seen after 14 days to 1 month of treatment .signs in tacrolimus group also showed similar pattern of improvement as symptoms except papillary hypertrophy which showed maximum improvement after 60 days of treatment .improvement in signs and symptoms continued till end of study duration .

There were no changes in fundus and IOP after treatment in tacrolimus group.

Our findings are consistent with study conducted by panadda et al⁹ and yuchi et al¹⁰.

In fluometholone group (group C) out of 20 patients two patient lost follow up after 30 days and 18 patients completed study.

In fluometholone group significant improvement in all symptoms was observed earliest after 7 days of study and peak effect was seen after 14 days of treatment .This improvement in symptoms was progressive till end of study duration.

Signs in fluometholone group except papillary hypertrophy also significantly improved after 7 days of treatment and peak effect was seen after 14 days of treatment. Papillary hypertrophy started improving after 14 days of study and peak effect was seen after 60 days of study.

There were no changes in fundus after treatment in fluometholone group.

Significant rise in intraocular pressure was seen in three patients in fluometholone group.

Our findings are consistent with study conducted by Sanjiv Kumar et al¹¹.

On inter group comparison among three groups improvement in all symptoms and signs was earliest and maximum in fluometholone group followed by tacrolimus group . In tacrolimus group improvement in all symptoms and signs except papillary hypertrophy and conjunctivalchemosis was almost equivalent to fluometholonegroup .improvement in cyclosporine group was of delayed onset and peak effect was seen later compare to TCL and FML group.

Comparing adverse events mild burning and redness was observed , in both CsA and TCL group.

In fluometholone group significant rise in IOP was seen Our findings are consistent with study conducted by sanjivkumar et al¹¹, there was no significant change in IOP in CSA and TCL group.

Limitations of our study are short study duration and small sample size hence we need large sample size and long duration of study to authenticate results obtained in our study.

5. Conclusion

In present study, based on the data collected and statistical analysis we conclude

- All the three drugs cyclosporine , tacrolimus and fluometholone are effective in reliving symptoms and signs in patients of moderate to severe VKC.
- There is difference in time for maximum effect among three drugs ,earliest effect seen with fluometholone followed by tacrolimus and cyclosporine .
- Tacrolimus was more effective than cyclosporine in reliving signs and symptoms .
- Fluometholone caused rise in IOP but neither cyclosporine nor tacrolimus showed any significant effect on IOP.

To conclude fluometholone has early and maximum effect on patients with moderate to severe VKC as compared with tacrolimus and cyclosporine, but considering IOP rise seen in fluometholone group ,tacrolimus and cyclosporine can be safely used as an alternative to topical fluometholone in patients of moderate to severe VKC.

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