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Original Research

A study on the Safety and Efficacy of Using Topical Cyclosporine A in Moderate to Severe Dry Eye Disease Treatment

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ABSTRACT:

Objective: To study the safety and Efficacy of Topical Cyclosporine A in treatment of moderate to severe Dry Eye Disease. **Materials and Methods:** It's a prospective study of patients with moderate to severe dry eye syndrome. All patients were selected from cases attending the OPD of our institute. 21 years was the minimum age of all eligible patients with confirmed diagnosis of Keratoconjunctivitis Sicca with or without Sjogrens syndrome refractory to conventional management. Unit dose vials of unpreserved Cyclosporin A 0.05% were used twice daily in this study. A 2week washout phase, and a 4week post treatment phase was the protocol followed. The evaluation of patients was done at 4, 8, 12 weeks of the treatment phase. The patients were evaluated for changes from baseline Schirmer test, Rose Bengal staining, Superficial Punctate erosions, BUT, Impression Cytology symptoms of Ocular discomfort and visual acuity during their visits. **Results:** In current study, 30 cases in mean age 45 years (12.7 %) range (20- 65) years, 4(13%) male and 26(85%) female were recruited. Out of them 10(36%) cases had Sjogrens syndrome. There was significant improvement in (P=0.012) in visual acuity, BUT (P<0.0001) for both eyes. Superficial punctate erosions (P < 0.0001) and P 0.0029 for OD and OS respectively. **Conclusions**: Use of Cyclosporine A 0.05% has been demonstrated to be effective and safe in human clinical trials. Signs and symptoms of Dry Eye disease are reduced. Its effect occurred during the treatment period and also improvement was noted even after the drug was stopped.

Keywords: Cyclosporine, Dry eye syndrome, Keratoconjunctivitis Sicca

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INTRODUCTION

As per recent studies, millions of people around the world are affected by Dry eye disease of Keratoconjunctivitis sicca . The frequency of patients visiting the eye care facilities with symptoms of dry eye disease has shown an increasing trend. Most common complaint is a foreign body sensation . Dry eye disease is under diagnosed though it is a common condition. Clinically it is classified into 2 categories. Evaporation loss and aqueous deficiency.

DES can also be caused by inflammatory mediated T cell lymphocytes and cytokines that affect lacrimal gland acini and ducts. This could lead to changes in tear film and homeostasis of ocular surface. tear substitutes or the tear presentations are most common treatment modalities of DES, though they cannot affect these processes. Decreased tear production and tear clearance leads to chronic inflammation on ocular surface. There is an increase in inflammatory cytokines in tear fluid and increased activity of matrix degrading enzymes such as metaloprominase -9 in tear fluid. Inflammation has been linked to aqueous deficiency dry eye disease and also to evaporative loss. Mebomian accumulation in Mebomian gland and bacterial colonization.

The lipases in the colonizing bacteria break the nonpolar wax and sterol esters into triglycerides and free fatty acids and so alter normal composition of meibum. The mucinous layer is made hydrophobic by the polar lipid. Topical cyclosporine A is a highly specific immunomodulator that affects T lymphocytes and decreases the inflammation of meibomian glands, treatment with topical cyclosporine A reduces the cell mediated inflammatory reactions associated with

ocular surface disease. It has been stated in previous studies that treatment with cyclosporine A improves symptoms and signs of od DES and also helps in DES due to aqueous deficiency.

All of this indicates that treatment with Cyclosporine A gives a curative treatment unlike others which gives only symptomatic treatment. Most appropriate concentrations of CsA ARE 0.05% and 0.1% as no additional benefits are observed with higher concentrations. In this study we evaluate the effiicacy and safety of topical CsA 0.05% for treatment of severe dry eye disease.

METHODS

In this prospective study, patients with moderate to severe DES were recruited. All the cases recruited were from patients attending our out patient department. 21 yrs was the minimum age of our patients with a confirmed diagnosis of Keratoconjunctivitis Sicca with or without Sjogrens syndrome resistant to conventional treatment. The inclusion criteria was Schirmer test (without Anesthesia) of 5mm/5mn in at least one eye, mild superficial punctate erosions defined as corneal punctate fluorescein staining score of >1 in either eye and one or more moderate dry eye related symptoms, including itching, burning, blurring foreign body sensation, dryness, photophobia/pain. Our exclusion criteria were any ocular surface disease or surgery or trauma within 6 months. Patients with uncontrolled systemic disease, pregnant or lactating mothers were excluded. The eye drops used in the study were preservative free vials of cyclosporine A 0.05 %.

There were 3 phases to treatment protocol

First phase: 2week washout phase, during this phase patients were asked to stop all eye drops except preservative free tear substitutes.

Second phase: 12week treatment phase, patients who finished the washout phase were given Cyclosporine A 0.05% eye drops to both eyes twice a day in morning and evening for 12 weeks. Use of preservative free tear substitutes was allowed during this phase.

Regular evaluation at 4,8 and 12 weeks was done on all patients. The patients were revaluated for changes from baseline in Schirmer test, rose Bengal staining, superficial punctate erosions, impression cytology, ocular discomfort, bio microscopy and vision.

Third phase: 4 week post treatment phase. After end of treatment phase, patients were again evaluated for Schirmer test, rose Bengal staining, superficial punctate erosions, impression cytology, ocular discomfort, bio microscopy and vision.

The efficacy was measured using rose Bengal staining (graded on scale 0 = none to 3 = severe) punctate erosions (graded on scale 0 = none to 3 = severe) Tear breakup time. Treatment safety was proven using systemic BP, Kidney function test, ocular tension by Goldman applanation tonometry and vision as indicators. Clinical examination included clinical and ocular medical history taking, detailed slit lamp exam with BUT rose Bengal staining and Schirmer test. Cellulose acetate filter paper (Millipore type G) was taken for impression cytology. It was placed on temporal part of bulbar conjunctiva just below horizontal midline of cornea and conjunctival sac. Strips were left in place for 3-4 seconds and removed with peeling motion. Then the detached conjunctival cells in the filter paper were fixed and stained for microscopic examination.

Microscopic Examination

Slides were examined using an ordinary microscope under magnifications of 40x, 100x and 250x.

The morphologic appearance of conjunctival epithelium, goblet cells and nucleus to cytoplasm ratio was used for grading.

Samples were examined for following cytological features

1. Morphological features of nucleus
2. Metachromatic changes of cytoplasmic colour and Emergence of Keratinization.
3. Nucleus – Cytoplasm ratio.

Conjunctival impressions were graded on scale from 0 – 3.

Grade 0 – epithelial cells are small and round with eosinophilic staining cytoplasm. Nuclei are large with nuclear/ Cytoplasmic ratio of 1:2

Grade 2; epithelial cells are larger with eosinophilic staining. Nuclei are smaller.

N/C ratio of 1:3 goblet cells are markedly decreased in number.

Grade B; Epithelial cells are large and polygonal. Nuclei are small pyknotic and many cells completely absent. N/C ratio is < 1:6.

Statistical section pre and post investigative data was collected using specific data collection sheet, the data was cleaned, managed and coded using Microsoft excel. The analysis was done using SPSS version. Categorical variables were presented in the form of frequencies and percentages, while continuous variables in the form of mean (ISD) were used for descriptive analysis. To test the potential change between pre and post intervention, inferential analysis was done. To evaluate the significance of change in wilcosol signal ranks test was done. Potential association of categorical variables was assisted by doing Chi square test.

Confidence interval was set to 95% where a corresponding P value threshold was identified as 0.05. Where any output of P below 0.05 is interpreted as an indicator of statistical significance.

RESULTS

Thirty cases in the mean age of 45 (1.7) range (21-65) yrs, 4 (11%) and 26(85%) ere recruited in the current study. Out of them 10(36%) cases had Sjogren syndrome. As of dry eye clinical indices, comparing

base line pre intervention assessment to the 4 week (during treatment) showed that there was significant improvement in visual acuity. (P = 0.012) BUT (P >0,001) for both eyes. Schirmer measurements (P > 0.0001) and P = 0.029 for OD and OS.

Comparing pre intervention assessment to twelve months assessment yielded improvement in all of indices was highly significant. (P > 0.001 for visual aquity) BUT and Schirmer test for both eyes.

Comparing clinical indices at the second assessment visit to clinical indices at last assessment visit, demonstrated that statistically significant improvement in such indices continued to show up P = 0.012 for visual aquity and P > 0.001 for all other indices.

Comparing visit 4 and visit 5 showed that dry eye status continued further improvement with a significant P value of 0.012 for all assessed indices.

Comparing findings from rose Bengal and impression cytology, comparison of pre intervention to four week, there is statically significant difference between the two.

Comparing the pre intervention assessment with twelve week visit showed statistically significant difference in both rose Bengal and impression cytology. Finding P > 0.001 for both the eyes in rose Bengal and P > 0.001 and P = 0.013 for impression cytology in OD and OS.

For assessment of improvement in comparing visits 2 week to 12. Findings showed that improvement continued to show up in both rose Bengal. P>0.001 for both eyes and p< 0.0021 and p = 0.002 for PD and OS.

Finally in post intervention phase, comparing 12 week visit to post intervention visit assessment, the difference continued to be significant for rose Bengal in OD P = 0.014 while it was not significant in OS. P = 0.998. The difference was significant in the impression cytology reading. P = 0.014 for both eyes.

DISCUSSION

In ophthalmic practice keratoconjunctivitis sicca is a very common problem. KCS is classified in two new categories by National Eye Institute. The two are

- Aqueous production efficient
- Evaporative loss dry eyes

The aqueous production efficient category includes Sjogren associated KCS and Non Sjogren associated KCS.

In this study we tried to evaluate safety and efficacy of CSA 0.05% twice daily in treatment of moderate to severe dry eyes. Significant improvement in eye condition was noted in our study. The improvement occurred during the treatment period and also continued after the treatment was stopped. There was no systemic harm with regard to BP and renal function were noted. In 2000 Stevenson and his colleagues investigated the efficacy and safety of CSA for treatment of moderate to severe dry eye. So Stevenson ET AL observed that topical CSA 0.04- 0,4 % ophthalmic solution led to significant improvement in ocular manifestation of moderate to severe dry eye. These findings support our study that tropical CSA has positive effect on DES.

Though the mechanisms are still being investigated, evidence suggests that dry eye disease results from cytokines and receptor mediated inflammatory process. This inflammatory process affects lacrimal acini and glands. It is important to note that there were similar findings in our study. Though systemic changes in BP or kidney function.

In barber etal study decrease in visual equity was more frequent than increased visual equity. Our study findings show that impression cytology was improved in all stages. Another study by Wilson and Percy showed that tropical CSA appears to be associated with a cure of chronic DES. The efficacy of immunomodulatory agent tropical CSA in improving the manifestations of DES without Sjogrens syndrome gives further support to this hypothesis.

Finally, though the treatment was stopped the improvement continued. This stability showed that the drug has successful impact. Treatment modality after comparing a case of dry eyes through duplicating eye drop or mild case and use of 0.05% topical CSA for moderate to severe DSO.

CONCLUSIONS

The first definition of treatment of chronic DES is immunomediated CsA 0.05%. CsA ophthalmic emulsion is safe in human trials. Signs and symptoms of DES are decreased. It continued to decrease even after treatment was stopped and it was more towards stability.

There are no ocular side effects reported and it was well tolerated. No ocular infections and bacterial overgrowth were reported during clinical studies. Topical CsA is well tolerated and accepted by patients as they can expect results in 3-6 months of treatment this agent provides rational prioritized therapy where nine currently exists.

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