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TOPICAL CYCLOSPORIN A 0.05% IN DRY EYE DISORDERS AND OCULAR INFLAMMATORY DISORDERS-AN OBSERVATIONAL STUDY STUDY

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KEYWORDS :

INTRODUCTION:

Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort (DEWS 2007)[1]

Dysfunctional tear syndrome (DTS) is the new term proposed for dry eye disease and sub classified into DTS with clinically apparent inflammation and DTS without clinically evident inflammation[2] with a prevalence of 10.8% to 57.1%[3,4] dry eye is one of the commonest and frustrating ocular morbidity

Hyperosmolarity of the tear fluid acts as a proinflammatory stimulus, triggering the increased activation of T lymphocytes resulting in the increased production and activation of pro inflammatory cytokines ex: IL-α, IL-β, IL6, IL8, TNF- α and also matrix metalloproteinases (MMPs) by the stressed ocular surface and glandular epithelial cells[5]

Neural signals to the lacrimal gland inhibited depriving the gland of the trophic stimulation resulting in its progressive destruction[6]

Inflammation is the key mechanism of ocular surface injury, as both the cause and consequence of cell damage Rational to treat dry eye syndrome with therapeutic anti-inflammatory agents instead of with the traditional palliative tear substitutes Topical corticosteroids not recommended for long term usage because of the adverse effectsOral tetracycline usage is off label Topical CsA represents a new pharmacologically based treatment for dry eye disease that may provide significant patient benefits Cyclosporin A (CsA) discovered by BOREL in 1969, isolated from the fungus Tolypocladium inflatum

CsA

- inhibits T-cell activation and consequently inhibits the Inflammatory cytokine production (selective inhibition of IL-I)
- inhibits apoptosis by blocking the opening of the mitochondrial permeability transition pore (MPTP)
- increases the density of conjunctival goblet cells

The infiltration of T-cells in the Conjunctival tissue and the presence of cytokines and proteases in the tear fluid were the main reason introducing the use of immunomodulator agents such as corticosteroids, cyclosporine A (CsA), and doxycycline in order to treat dry eye syndrome[1]. CsA emulsion is approved by the FDA, in U.S.A., for the treatment of dry eye, and subsequent clinical trials have demonstrated efficacy and safety of CsA in many countries. CsA seems to be a promising treatment against dry eye disease.

Dry eye is diagnosed clinically with symptoms associated with such as ocular burning, stinging, scratchiness, soreness, photophobia, blurred vision and foreign body sensation.

To supplement clinical proof, the three main pathways leading to dry eye, namely aqueous, meibomian secretions and conjunctival goblet cells dydfunction could be established by clinical tests. Tear film stability can be assessed with the fluorescein tear break-up time test (TBUT), aqueous tear production measured with Shirmer test. Meibonian gland disease is diagnosed by biomicroscopic recognition of pathological signs such as ductal orifice metaplasia, reduced expressibility of meibonian gland secretions, increased viscosity of the expressed secretion and dropout of glandular acini. Conjunctival goblet cell density and epithelial morphology can be directly evaluated by cytology.

Among all the above methods, the most practical clinical method for assessing the severity of dry eye is the ocular surface dye staining. Fluorescein, rose Bengal and lissamine green are use as diagnostic dyes for evaluating the staining. Fluorescein staining occurs when the epithelial barrier is disrupted, due to the loss of the epithelial cells, is well tolerated by patients and evaluates better corneal staining. Rose Bengal and lissamine green stain the conjunctiva more brightly than the cornea. Rose Bengal stains devitalized epithelial cells or cells without protective mucus layer, but cause transient irritation after installation. Lissamine green dyes degenerated or dead cells and produces less irritation than rose Bengal[2].

The Dry Eye Workshop (DEW 2007) committee recommended classification of dry eye disease based on etiopathogenic, mechanistic severity of the disease. and illustrating the multiple causes of dry eye[3]. As per the DEW classification, dry eye was divided in two principal categories based on etiopathogenesis: aqueous deficient (Sjogren or non-Sjogren related) and evaporative (intrinsic or extrinsic causes). According to mechanistic severity, the common pathway, tear hyperosmolarity and tear film instability are the causes for dryness and classification based on the multiple causes and severity of the disease (four groups correlated to visual symptoms, conjuctival injection, conjunctival staining, corneal staining, corneal/tears signs, lid/meibonian glands, tear break-up time, and Shirmer test), providing a rational basis for therapy.

Purpose of the study:

The present study has been undertaken to test the use of cyclosporine A in dryness of eyes due to different etiopathogenesis in a clinical setting with limited resources. Use of simple but indicative tests like OSI, Schirmer I, TBUT provide sufficient clinical evidence to deduce severity and extent of inflammatory nature of the disease process of dry eye. This is a retrospective, observational study. The purpose is to analyze the safety and efficacy of topical cyclosporin A 0.05% in the treatment of moderate to severe dry eye, not alleviated with conventional therapy.

In 2006 in a Delphi panel approach to treatment recommendations by international specialists on dry eye syndrome, the common clinical tests are fluorescein staining (100%), tear break up time (94%), Shirmer test (71%), and rose Bengal staining (65%)[4]. Based on this observation, the present study chose to the first three tests for the evaluation of CsA in the treatment of dry eye and safety and efficacy.

MATERIALS AND METHODS:

Retrospective review of medical records of 15 patients, diagnosed to have moderate to severe dry eye, based on clinical symptoms, who were prescribed topical cyclosporin A 0.05% (CsA) at "Cornea clinic" of the Department of Ophthalmology, Andhra medical college,

Visakhapatnam between March 2018 and August 2018. The results analyzed are, Demographic data, etiology for dry eye, previous treatment history, Ocular surface parameters -Ocular Surface Staining (OSS), Schirmer's I Test, Ocular Surface Disease Index (OSDI), frequency of instillation of tear substitutes, adverse reactions , if any on instillation of topical CsA , at baseline and at review visits at 2 weeks, 1month, 3 months and 6 months after the prescription of CsA 0.05% drops, two times a day.

Inclusion criteria: All the patients above 18 years of age, moderately severe dry eye with clinically evident inflammatory signs, Patients on tear substitutes for more than one year, Affordability of the patient ,and patients who are residing locally

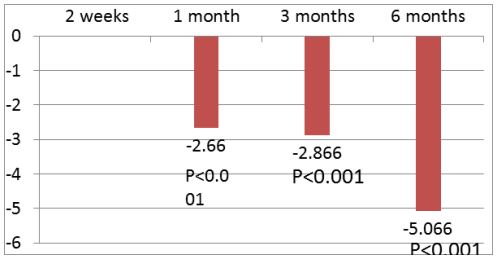
Exclusion criteria: Pregnancy and lactation

Outcome measures analyzed :Ocular surface staining(OSSS), Schimers' test(SCh 1),Tear break up time(TBUT),Ocular surface Disease index(OSDi),Frequency of instillation of tear substitutes, Drug related adverse affects on instillation of cyclosporine the effects were studied eye drops 0.5 % BiD the effect was studied for 2 weeks one month 3 months and 6 months

RESULTS:

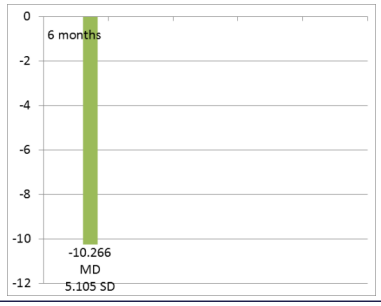
Out of 15 patients, males 3 (20 %), females 12 (80%), Mean age 51.93 yrs (range 27-80 yrs, SD 14.71), Mean follow up period (217.4 days, range 184-264 days). The diagnoses of the cases are Sjogren syndrome (4), MGD (2), steven-Johnson syndrome (2), drug induced dry eye (beta blocker) (1), VKC (1), AIDS (1) and age relared dry eye (4). At baseline, the mean value for ocular surface staining 6.06. No improvement has been noticed at 2 weeks. However improvement in subsequent visits, greater at 6 months with Mean -5.06, SD - 1.66 has been noticed. Improvement in Sjogren' syndrome and Age related dry eye group is more. Schirmer's I test, at baseline, the mean value for 3 mm, at 6 months with Mean -5.06, SD 2.54. TBUT measured at baseline is 3.67 and at 6 months improvement Mean - 4.13, SD - 3.16. At baseline, the mean value for OSDI score 26.67and at 6 months Mean – 12.64, SD 4.72. Change from baseline in concomitant usage of tear substitutes, the average daily usage of concomitant tear substitutes was 8.93 and at 6 months Mean - 4.93, SD - 2.86. Treatment-related adverse events were reported in 46.67% of patients at 2weeks, 26.67% at 1month, 26.67% at 3months and 20.0% at 6months. Most of these events were mild to moderate and transient. Most commonly reported treatment related adverse event was mild ocular burning None of the patients experienced ocular infection during treatment. All patients were compliant with using the drug.As this parameter was not quantified, it was not analyzed statistically. Gradual improvement in BCVA from baseline at all review visits, notable at 6 months. Other confounding factors affecting visual acuity not noted elaborately at baseline, hence improvement in BCVA not taken as an efficacy measure.

CHANGE FROM BASELINE in OSS Score

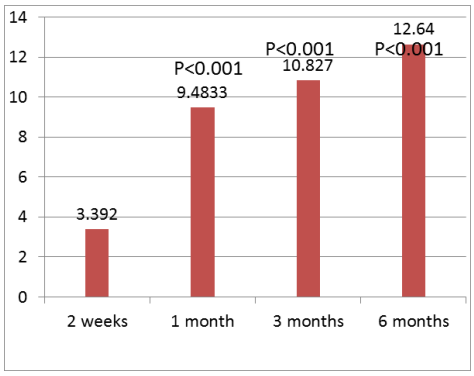


CHANGE FROM BASELINE IN SCHIRMER'S 1 TEST

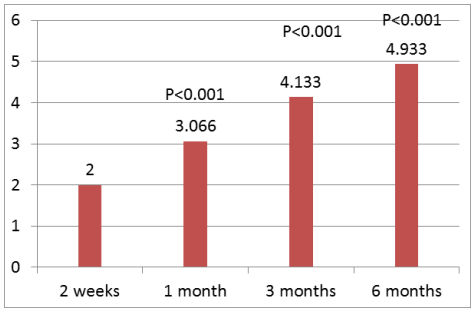
Change from baseline in TBUT



Change from baseline in OSDI score



Change from baseline in concomitant usage of tear substitutes



DISCUSSION:

Dry eye is associated with ocular surface inflammation that may further compromise tear secretion and cause ocular surface disease and irritation symptoms. Ocular surface inflammation should be assumed in patients with an unstable tear film and ocular surface epithelial disease as proved with diagnostic staining agents. Though symptomatic treatment with lubricants, still remains the method of choice, considering the inflammatory mechanism of dry eye, it is rational to use imunomodulators like CsA in treating patients who already use artificial tears and who continue to have detectable ocular surface disease associated with inflammatory signs.

The study has shown that changes in corneal staining and Shirmer scores were not statistically significant. The most common adverse events with CsA, were burning eye, stinging eye, and Conjunctival hyperaemia. Previous studies have reported treatment-related adverse effects in 22% of patients whereas in the preset study only 2 patients reported these symptoms as severe.

The use of CsA as anti-inflammatory treatment for dry eye has advantages over corticosteroids as it has not demonstrated serious adverse effects and its action is reversible after the treatment. At as low strength as 0.05%. it has a very low rate of systemic absorption. These pharmacokinetic characteristics make it suitable for long-term therapy in a chronic disease such as dry eye.

Cost is a major limiting factor in the use of CsA[5]. However, dry eye syndrome is associated with a measurable adverse impact on several common and important tasks of daily living, further implicating this condition as an important public health problem deserving increased attention and resources[6]. Considering the impact on quality of life, the cost should not be a limiting factor.

The cost versus benefit can be assessed through subjective measures using standardized questionnaire and effect in addition objective tests. However the process of designing and validating custom made questionnaire in local languages is an arduous task. Modified and adopted measuring instruments to gauze everyday activities, driving, working at the computer, professional activities, and watching television are some of the variables that could be included in measuring limitation of activities of affected persons in future studies. Choice of concomitant therapy had significant effects on outcome measures[7]. The study has shown that use of concomitant low cost artificial tears has been reduced considerably over long term, unlike Sal et al study whic has shown significant reduction of symptoms with costly combination of CsA and hydroxypropylguar gellable lubricant eye drop.

In disease with an inflammatory base, such as vernal kerato-conjunctivitis, atopic kerato-conjunctivitis, ligneous conjunctivitis, and superior limbic kerato-conjunctivitis associated with dry eye also could benefit from CsA. The study subjects have been selected to include all types of etiological causes as proved by Akpek[8] Pucci[9].

Notwithstanding the limitations of this study, further clinical studies will provide more definitive recommendations about the timing, efficacy, safety, and relative costs/benefits of anti-inflammatory therapy with CsA for dry eye in a socio-economic milieu as diverse as ours.

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