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EFFICACY OF 2% TOPICAL CYCLOSPORINE AS COMPARED TO 1.4% TOPICAL POLYVINYL ALCOHOL FOR TREATING DRY EYES OF NON-IMMUNE ORIGIN: A RANDOMISED CONTROL TRIAL

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Abstract. Background: The purpose of this study was to compare the efficacy of 2% topical cyclosporine (Cs) with 1.4% topical polyvinyl alcohol (PVA) for treatment of idiopathic dry eye syndrome.

Methods: Forty two patients (including 28 males and 24 females) in the age range of 18-85 years of dry eye were enrolled in the study. Appropriate history for ocular complaints, underlying systemic disease, predisposing environmental conditions and occupation of the patients was recorded. The baseline Schirmer's test and tear film break up time was also recorded. The patients were randomly allocated into one of the two groups. Twenty six patients received 2 % topical Cs four times a day and twenty six patients received topical PVA four times a day. Follow up examination was done at two weeks for any side effects and at six months to assess the outcome of treatment.

Results: The mean age of the patients in Cs group was 52.6±18.1 years. The mean age of the subjects in PVA group was 46.9±11.3 years. With the use of topical Cs, there was a statistically significant relief in ocular complaints of foreign body sensation (p= 0.0067), itching (p= 0.03), conjunctival hyperemia (p= 0.02) and lacrimation (p= 0.001) while there was no statistically significant subjective relief in any of the ocular complaint with topical PVA. In the Cs group, the post treatment Schirmer's test (8 mm; range 1-30mm) reading showed a statistically significant increase from its pre-treatment value (3mm; range 0-5mm) (p=0.004). In PVA group, the post treatment Schirmer's test (3.6±1.07mm; range2-5 mm) reading did not show a statistically significant increase from its pre-treatment value (3.5±1.1mm; range2-5 mm) (p=0.59). In the Cs group, the post treatment tear film break up time (10.8 ±6.2 seconds) did not show a statistically significant increase from its pre-treatment value (10.2 ±5.4 seconds) (p= 0.78). Also, in the PVA group, the post treatment tear film break up time (10.3± 1.7 seconds) did not show a statistically significant increase from its pre-treatment value (10.1±1.9 seconds) (p=0.16). Similar to PVA group, the patients in topical Cs group did not have any local or systemic side effect except for burning sensation in one patient and mild pain in another.

Interpretation: The efficacy of topical Cs (2%) is significantly more than topical PVA in treatment of dry eyes of non-immune origin.

Key words: Topical cyclosporine, dry eyes, Topical cyclosporine and adverse events.

INTRODUCTION

Dry eye disease is one of the most frequently encountered categories of ocular morbidity in Ophthalmic practice. Dryness of eyes can be of autoimmune or non-immune origin. The ocular abnormalities like presence of inflammatory cell infiltrate in lacrimal gland and conjunctiva, and upregulation of immune related antigens and inflammatory cytokines at the level of conjunctival epithelium are seen in keratoconjunctivitis sicca both of autoimmune and non-immune origin.

Because of a possible immune-based inflammatory patho-mechanism of dry eye disease, the previous workers experimented with immunomodulatory agents in its treatment. Cyclosporine (Cs), a cyclic undecapeptide produced by the fungal species Tolypocladium inflatum. It was used for treatment of dry eye in human clinical trial for the first time in 1993.[1] Cs acts by preventing synthesis and/or secretion of several proinflammatory cytokines.[2] It is also known to stimulate lacrimation through sensory neurotransmitter release.[3] The use of PVA in topical ocular solutions was introduced in 1964 in order to enhance ocular contacts.[4] It is a long chain synthetic polymer.[5] PVA enhances viscosity,[6] promotes tear film stability[6] and increases thickness of precorneal tear film.[7]

We aimed to compare the efficacy of 2% topical Cs with 1.4% topical PVA in treatment of dry eyes of the Indian patients.

MATERIALS AND METHODS

Forty two patients (including 28 males and 24 females) in the age range of 18-85 years of dry eye were enrolled in the study. These patients presented with complaints like foreign body sensation, diminution of vision, burning sensation, photophobia, itching, conjunctival redness, discharge and lacrimation. Inclusion criteria included anaesthetized Schirmer's test < 5.0mm/5minutes and tear break up time (tear BUT) < 15 seconds. Exclusion criteria were - use of topical or systemic Cs 90 days prior to initiation of treatment; use of any topical ophthalmic drug in the prior 3 weeks; contact lens wear; active ocular infections, lid pathology; other anterior segment diseases, or surgery or trauma within the prior 12 months; and endocrine disease like diabetes.

Twenty six patients received 2 % topical Cs four times a day and in second group twenty six patients received topical PVA (Allergan: Liquifilm tears. 1.4% polyvinyl alchohol, 0.5% chlorobutanol) four times a day. In a two-week run in phase, the included patients did not use any topical eye medication. No periocular cosmetics were permitted during the entire study period. Topical Cs (2%) was prepared under sterile conditions using commercially available Cs diluted in olive oil solution. 2% Cs was used topically 4 times a day in these patients. Patients were asked to press the medial canalicular system to minimize absorption of drug from naso-lacrimal system. Systemic side effect of Cs therapy by periodic estimation of kidney function tests, liver function test, blood pressure and complete blood count. Follow up examination was done at two weeks to look for side effects and at six months to assess the outcome of treatment.

RESULTS

The mean (± SD) age of the subjects in Cs group was 52.6±18.1 years. The mean (± SD) age of the subjects in PVA was 46.9±11.3 years. The patients in the two groups had dry eye due to trachoma, mebomitis, computer work, dusty environmental condition or idiopathic. Burning sensation and foreign body sensation were the most commonly reported symptoms of dry eyes in the patients of these two groups.

There was no change in visual acuity of the subjects following treatment with either 2% topical Cs or topical PVA. With the use of topical Cs, there was a statistically significant relief in ocular complaints of foreign body sensation (p= 0.0067), itching (p= 0.03), conjunctival hyperemia (p= 0.02) and lacrimation (p= 0.001) while there was no statistically significant subjective relief in any of the ocular complaint with topical PVA. In the Cs group, the pre-treatment Schirmer's test had median value of 3 mm and a range from 0-5mm. The post-treatment Schirmer's test had mean value of 8 mm and a range from 1-30mm. There was a statistically significant difference between the pre-treatment and post treatment values of Schirmer's test (z=2.85, p=0.004; Wilcoxon signed-rank test). In the topical PVA group, the post treatment Schirmer's test (3 mm; range2-5 mm) reading did not show a statistically significant increase from its pre-treatment value (4 mm; range2-5 mm) (t=0.55;p=0.59, NS; paired t test). In Cs group, the pre-treatment mean tear film break up time was 10.2 ±5.4 seconds. The post-treatment mean tear film break up time was 10.8 ±6.2 seconds. The difference between the pre-treatment value and post-treatment value was statistically not significant (p=0.78; NS). In topical PVA group, the post treatment tear film break up time (10.3± 1.7 seconds) did not show a statistically significant increase from its pre-treatment value (10.1±1.9 seconds) (p=0.16, NS).

All the patients in the topical Cs group desired to continue the treatment with this drug. One patient had burning sensation from topical Cs, one patient experienced pain and twenty four patients did not have any side effect. No patient had any side effect from treatment with topical PVA.

DISCUSSION

A few studies have found dry eye to be more common in females,[1,8] while others have not reported any sex predilection.[2,9,10] We also did not notice any male or female preponderance in our patients of dry eyes.

When used for treating ocular surface diseases like cicatricial pemphigoid,[11] vernal keratoconjunctivitis[12] or ulcerative keratitis,[13] topical Cs failed to show an obvious ocular surface wetting effect. Hence, some workers opined that the little benefit observed during treatment with Cs is in fact due to lubricating properties of corn oil vehicle.[1] The previous studies utilised impression cytology,[14] conjunctival biopsy,[2] analysis of tear antibodies[22] and human colon adenocarcinoma cell line[11] to find its therapeutic benefits in ocular diseases. Topical Cs was found to cause a decrease in epithelial turn over[2] and a clinical improvement in ocular surface rose Bengal staining,[1,14] Schirmer's test value[9] and goblet cell number.[2] Surprisingly, even when there was an improvement in the objective signs, the subjects did not essentially experience a symptomatic improvement of clinical features with topical Cs.[1,16] In this study we found the therapeutic benefit produced by these in terms of relief in clinical features and this relief was measured both by subjective and objective means.

Similar to the previous observation, the subjects in the either group did not experience any alteration in visual acuity following the use of either topical Cs[9,10] or topical PVA.[5]

Topical Cs is safe and of significant benefit in relieving the signs[9,10,14] and symptoms[9,10] of dry eye. With use of topical Cs, our patients experienced a symptomatic relief in all the ocular complaints. However, there was a statistically significant relief in ocular complaints of foreign body sensation (p= 0.0067), itching (p= 0.03), conjunctival hyperemia (p= 0.02) and lacrimation (p= 0.001) while there was no statistically significant subjective relief in any of the ocular complaint with topical PVA. In this study we found that after treatment with topical Cs, the subjects experienced a statistically significant increase in Schirmer's test value while similar increase in tear film break up time was not seen. It is stated that PVA can bring about an increase in tear film break up time by a factor as much as 1.89.[17] However, in our study, the PVA group did not have a statistically significant change in either Schirmer's test value or tear film break up time.

Previous studies have shown that Cs is safe both locally and systemically[1,11,12] and causes mild side effects like discomfort,[1,14,11] redness,[1] itching,[1] blurring of vision,[1] transient epitheliopathy (attributed to olive oil)[18] and the most commonly seen one i.e. ocular burning.[1] The patients invariably develop tolerance to these adverse events and do not require discontinuation of medication.[1] Our patients also did not need to discontinue treatment with topical Cs on account of any local or systemic side effect. Similar to the previous observation our patients did not experience any side effect from PVA.[5]

We postulate that a lower success rate in terms of relief of clinical features with use of topical Cs, which is an immuno-modulatory agent, was that the subjects enrolled in this study trial had dry eyes exclusively of a non-immune origin. More studies in different population groups are needed to find out the role of topical Cs in treatment of dry eyes especially of non-immune origin as this type of dry eye disease is the commonest in clinical practice.

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