Effect of topical cyclosporine A (0.05%) in dry eye disorders

Mahua Mazumder¹, Pinaki Sengupta²

Abstract

Introduction: To report effects of topical cyclosporine A (0.05%) on dry eye. Material methods: 63 consecutive dry eye patients underwent Mc Monnies questionnaire review, Fluorescein tear break-up time, Fluorescein staining of the cornea and conjunctiva, Schirmer I test (without anesthetic), Rose Bengal staining of the cornea and conjunctiva and Conjunctival impression cytology. Subsequently they were prescribed Cyclosporine eye drop 0.05% was instilled in the right eye (A) and artificial tears was instilled in the left eye (B) twice daily for nine months. Results were compared and presented. Results: In eyes with Cyclosporine treatment, the percentage improvement of all the above parameters of examination was greater than the eyes treated with artificial tears. This was of statistical significance. Visual acuity improvement was much better than those treated with artificial tears. The percentage of eyes showing normal cytology was higher in the Cyclosporine treated eyes than those treated with artificial tears. This was also of statistical significance. Conclusion: Topical cyclosporine (0.05%) causes significant betterment in dry eye cases.

Keywords: Dry eye; Medical management; Immunomodulators; Cyclosporine A.

Dry eye is a generic term for a group of conditions characterized by irritated, gritty, burning eyes and clinically by alteration in the tear film and the anterior surface of the eye. Lemp (1995) described it as “a disorder of the tear film due to tear deficiency or excess tear evaporation which causes damage to the interpalpebral ocular surface, and is associated with symptoms of ocular discomfort”. Dry eye is a common condition seen with increased prevalence in patients with autoimmune disease, post-menopausal women, and the elderly. Epidemiological studies have reported that more than 6% of the population over the age of 40 suffers from dry eye, with the prevalence increasing to 15% of the population over the age of 65.

There is increasing evidence that decreased tear secretion, decreased tear turn over, and desiccation promote inflammation on the ocular surface. An increase in soluble mediators (cytokines and proteases) in the tear fluid, adhesion molecules expression by the conjunctival epithelium and T-cell infiltration of the conjunctiva have been noticed in dry eye patients. Interestingly, a novel therapy for dry eye disease holds promise for treating both arms of the dry eye classification; aqueous deficiency and evaporative loss. This is accomplished by immunomodulation therapy. Clinical improvement of Keratoconjunctivitis Sicca (KCS) has been noted after therapy with anti-inflammatory agents including corticosteroids, Cyclosporine and doxycycline. Cyclosporine An emulsion was approved by food and drug administration (FDA) of USA as therapy for dry eye. This study is undertaken to report effects of topical cyclosporine A (0.05%) in dry eye disorders.

Materials and Methods:

The study was conducted with consecutive 63 patients with dry eye who attended the out patient department of a teaching institution in Kolkata, during the period from August 2005 to July 2008 and was analyzed at three months, six months and nine months intervals.

To each of these patients Cyclosporine eye drop 0.05% was instilled in the right eye (A) and artificial tears was instilled in the left eye (B) twice daily for nine months. The patients were selected by screening procedures at the OPD after the following examinations- Subjective interview of symptoms (Mc Monnies questionnaire), Medical and contact lens history, Slit lamp examination

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including lids, lashes and Meibomian glands, Fluorescein tear break – up time, Fluorescein staining of the cornea and conjunctiva, Schirmer I test (without anesthetic), Rose Bengal staining of the cornea and conjunctiva and Conjunctival impression cytology. All the symptomatic dry eye cases having Schirmer I test <5mm, Corneal and interpalpebral staining, Normal lid anatomy/blinking function and Visual acuity-Snellen >=6/24; were included in this study. Patients having Severe dryness: Schirmer test (nasal stimulation) <3 mm, permanent goblet cell loss/scarring, acute ocular infection, ocular rosacea, contact lens wear during study, severe blepharitis and history of punctal occlusion within 3 months were excluded from the study. These were followed up monthly for a period of nine months for improvements of all the criteria mentioned above. The improvements were compared with previous results.

Mc Monnies questionnaire (Mc Monnies 1986) is a well balanced focused simple test that allows the patient to think about when the symptoms occur. If symptoms occur occasionally, the questionnaire allows us to pinpoint the source of provoked symptoms. The questionnaire has been designed to determine if the symptoms are constant or occasional; and if the symptoms are related to external environmental factors or genuine intrinsic systemic factors. Mc Monnies questionnaire has a simple scoring system based on the patient’s answers, the higher the score the worse the condition. If a treatment is effective, at a later date the symptom scores should reduce and this indicates numerically the subjective value of the treatment regimen. The index score can range from 0 to 45, where higher scores are considered more indicative of dry eye syndrome. A cut point of greater than 14.5 is recommended for a dry eye diagnosis.

**Schirmer Test**

The patient was seated in a temperate room comfortably and the electric fan was switched off. No-41 Whatman filter paper 35 mm × 5mm was folded 5 mm from one end and inserted at the lower fornix at the junction of middle third and outer third of lower eyelid taking care not to touch the cornea. The patient was asked to keep the eyes open and to blink normally. After 5 minutes the filter paper was removed and the amount of wetting measured in mm. This test was performed without anaesthesia (Schirmer test I), and was thus a measure of both basal and reflex tearing.

**Measurement of Tear Stability and Break-up Time**

This test was done by observing the cornea using a slit lamp biomicroscope, with a broad beam cobalt-blue light source. To view the tear film, fluorescein dye was instilled, by wetting a dry fluorescein impregnated paper strip with a drop of saline and placing on the bulbar conjunctiva for a brief moment. The patient was asked to refrain from blinking, and in most cases within 60 seconds dark spots or streaks were found within the tear film. The time elapsing between a complete blink, and the appearance of the first ‘dark spot or streak’ was measured, and taken to be the ‘break-up time’. Five successive measures were routinely taken, and the mean value was calculated.

**Ocular Surface Staining**

The extent of ocular surface damage was assessed by instilling a small amount of Rose-Bengal or Fluorescein onto the ocular surface. Fluorescein sodium in the form of sterile filter paper strips impregnated with fluorescien was applied to the lower conjunctival sac. It stained areas of epithelial cell loss when viewed by slit lamp, using a cobalt blue filter. Rose Bengal was also applied to the conjunctival sac by sterile filter paper strips. It stained dead and devitalized epithelial cells and mucus. Van Bijsterveld’s scoring system (1969) can be used to quantify the level of staining observed (with scores ranging from 0 to 9). The visible area of the eye was divided into three zones, formed by imaginary vertical lines at either side of the limbus. Each zone was given a score depending upon the degree of staining contained, from 0 for no staining, through 1 for mild staining and 2 for moderate staining to 3 for severe staining. A total score was calculated by adding the scores for the 3 zones of the ocular surface.

**Conjunctival Impression Cytology**

Specimen collection: After one drop of topical anaesthetic to each eye excessive tear fluids was wiped and the filter paper was applied to the desired area using a pair of smooth and flat ended forceps. Filter paper was placed on four quadrants at the limbus and two on the upper fornix and lower fornix. The filter paper was removed by picking up the tip of the filter paper with the forceps. The
filter paper was dropped into sample bottle, which contains the fixative solution, containing glacial acetic acid 5 ml, 37% formaldehyde 5 ml and 70% ethyl alcohol 100 ml in a sample holder. Sheets of impression cytology specimen information was labeled accordingly, by entering the date of sample collection, patient’s name, medical record number, which eye, which area of the conjunctiva or cornea where the sample.

Findings were plotted according to following parameters-staining characteristics and NC ratio, goblet cell density, squamous metaplasia and mucin aggregates. Staging of CIC findings on the basis of epithelial cell morphology goblet cell density, presence of mucin granules has been done by Nelson⁶.

In the present study, the CIC specimens were examined and staged according to the degree of squamous metaplasia as described by Wittpen – normal, borderline normal, borderline abnormal, abnormal⁹. The characteristic features of each of this group as described by Wittpen are as follows. In the normal group, the predominant cells were small epithelial cells found in sheets together with presence of goblet cells and mucin spots. The goblet cells showed a tendency to aggregate into groups. In those having abnormal cytology, the predominant cells were large discrete epithelial cells with rare or no goblet cells and mucin spots. The borderline abnormal showed cytology similar to abnormal, except that few goblet cells can be seen and in borderline normal, the picture was similar to normal, with the exception of the epithelial cells, which were abnormal.

**Results:**

In the study group of 63 patients who were treated with Cyclosporine eye drops in the right eye and artificial tears in the left eye, 61 (96.82%) patients treated with Cyclosporine in right eye showed normal TBUT as compared to only 10 (15.87%) patients treated with artificial tears in the left eye. This improvement on treatment with Cyclosporine in the right eye was found to be statistically significant (Table 1).

In the study groups among 63 patients treated with Cyclosporine in the right eye, 23 (36.5%) showed more than 15mm of Schirmer strip wetting, 35 (55.55%) patients had low normal value of 10 – 15 mm wetting, 3 (4.76%) patients showed borderline 5 - 9 mm wetting and no improvement was found in 2 (3.17%) patients. On treatment with artificial tears no patient showed >15mm or normal wetting, 4 (6.39%) patients showed low normal 10-15 mm wetting, 50 (79.36%) showed borderline 5-9 mm and 9 (14.28%) showed abnormal values (Table 2).

The staining score improved in 56 (88.88%) patients treated with Cyclosporine as compared to 40 (63.49%) patients treated with artificial tears in the left eye (Table 3).

In the present study of 63 patients Mc Monnies score improved in 52 (82.53%) patients treated with Cyclosporine in the right eye as compared to only 8 (12.69%) patients treated with artificial tears in the left eye. (Table 4)

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**Table 1: Table showing the results of TBUT in Cyclosporine treated and eyes treated with artificial tears.**

<table>
<thead>
<tr>
<th>TBUT</th>
<th>After treatment with cyclosporine (n=63)</th>
<th>After treatment with artificial tears (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&gt;10 sec)</td>
<td>61 (96.82%)</td>
<td>10 (15.87%)</td>
</tr>
<tr>
<td>Abnormal (&lt;10 sec)</td>
<td>2 (3.17%)</td>
<td>53 (84.12%)</td>
</tr>
</tbody>
</table>

Chi Square = 83.92, p Value = < 0.001, dF1

**Table 2: Table showing the results of Schirmer test in Cyclosporine treated and those treated with artificial tears.**

<table>
<thead>
<tr>
<th>Schirmer reading</th>
<th>After treatment with cyclosporine (n=63)</th>
<th>After treatment with artificial tears (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&gt;15mm)</td>
<td>23 (36.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Low Normal (10-15mm)</td>
<td>35 (55.55%)</td>
<td>4 (6.39%)</td>
</tr>
<tr>
<td>Borderline (5-9mm)</td>
<td>3 (4.76%)</td>
<td>50 (79.36%)</td>
</tr>
<tr>
<td>Abnormal (&lt;5mm)</td>
<td>2 (3.17%)</td>
<td>9 (14.28%)</td>
</tr>
</tbody>
</table>

Chi Square = 93.77, p Value = < 0.001, dF3
In the study group of 63 patients with right eyes treated with Cyclosporine and left eyes treated with artificial tears for 6 months it was found that in Cyclosporine treated eyes, 18 (28.57%) patients had normal CIC, 29 (46.03%) had borderline normal CIC, 16 (25.39%) had borderline abnormal CIC and no patient had abnormal CIC on treatment, while in artificial tears treated group no patient had normal CIC, 14 (22.22%) patients had borderline normal CIC, 41 (65.07%) had borderline abnormal CIC and 8 (12.69%) had abnormal CIC which showed that treatment with Cyclosporine in the right eye was statistically significant (Table 6).

Discussion:

Several recent publications have suggested that dry eye disease is the result of complex inflammatory processes and suggest that the immuno modulatory drug Cyclosporine may have potential as a novel therapeutic treatment for moderate to severe dry eye. The epidemiological studies have reported that more than 6% of the population over the age of 40 suffers from dry eye, with the prevalence increasing to 15% of the population over the age of 3, 4, 5.

Most dry eye symptoms result from an abnormal, non lubricating ocular surface that increases shear forces under the eye lids and diminishes the ability of the ocular surface to respond to environmental challenges. This ocular surface dysfunction may result from immuno compromise due to systemic auto immune disease or...
Components of the ocular surface (cornea, conjunctiva, accessory lacrimal glands), the main lacrimal gland, and interconnecting innervations act as a functional unit. When one portion is compromised, normal lacrimal support of the ocular surface is impaired. Resulting immune based inflammation can lead to lacrimal gland and neural dysfunction. Restoration of lacrimal function involves resolution of lymphocytic activation and inflammation. The efficacy of Cyclosporine may be due to its immuno modulatory and anti inflammatory functions on the ocular surface resulting in a normalization of nerve traffic. Evidence linking this disease to T-cell mediated inflammatory processes lays the foundation for understanding the clinical benefits of topical Cyclosporine, and immuno modulatory and anti inflammatory agent. After analysis of the results of Schirmer test in the present study it was found that statistically significant improvement with Cyclosporine treatment, as was intended for the study. In the present study there was statistically significant improvements of TBUT in Cyclosporine treated eyes as compared to artificial tears. After analysis of the results of TBUT, 61(96.82%) patients had normal values on treatment with Cyclosporine in the right eyes and 10(15.87%) patients treated with artificial tears in the right eye.

In the present study, conjunctival impression cytology was used to evaluate the ocular surface changes. Wittpenn grading system was used, as it simple and easy to work with. In the present study it was found that in Cyclosporine treated eyes, 18(28.57%) patients had normal CIC, 29(46.03%) patients had borderline normal, 16 (25.39%) patients had border line abnormal CIC & no patient had abnormal CIC. The improvements were found to be statistically significant when compared with eyes treated with artificial tears in which no patients had borderline normal CIC, 14(22.22%) patients had borderline normal CIC, 41(65.07%) had borderline abnormal CIC and 8 (12.69%) patients had abnormal CIC. In the study conducted by Kenneth Sall in 2000, density of conjunctival goblet cells was observed to be significantly greater after 6 month of treatment with Cyclosporine than had been seen at baseline10. Our study results were similar to those found by other workers11,12,13.

Major limitation of our study was short period of followup. Immunomodulatory effects of topical cyclosporine A usually appear slowly. Number of recruited eyes is second limitation of this study. Greater number of eyes being followed up for longer duration should definitely yield better results specially using a comparative model of different concentrations of topical cyclosporine A preparations.

References:


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