A Study on the Effect of Topical Cyclosporin-A in Dry Eye Patients.

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Abstract:
Dry eye is a multifactorial disease, with two major recognized forms: one is characterized by a reduction of tear production, and the other is characterized by tear hyperosmolarity, mainly due to excessive evaporative water loss. The study was conducted on 63 patients of Dry Eye Patients. The right eye was treated with topical Cyclosporin A 0.05% twice daily and the left eye was treated with an artificial lubricating eye drop twice daily. McMonnies score, Schirmer's test, Conjunctival impression Cytology (CIC) grading, Tear break up time (TBUT), Staining scores and visual acuity were recorded before the instillation of the topical drugs and at 6 months follow up. Chi Square Test was applied for statistical analysis.

23 eyes (36.5%) which were treated with Cyclosporin A showed a normal Schirmer’s Test with reading greater than 15mm while 0 eyes in the arm treated with Lubricating eye drop showed any improvement greater than 15mm in the schirmer’s strip at 6 months follow up (P<.001). 61(96.82%) showed a normal TBUT in the Eyes treated with Cyclosporin A while only 10 eyes (15.87%) in the group treated with lubricating eye drops showed a normal TBUT (P <.001). Similarly all other parameters such as McMonnies score, CIC grading, Staining Score and Visual Acuity were found to be favourable in the eyes treated with Topical Cyclosporin A eye drops compared to the eyes treated with lubricating eye drops and all of them attained a statistical significance with P < .001. Cyclosporin A (0.05%) is a safe and effective alternative therapy for dry eye patients and yields improvement in both objective and subjective measures.

Key Words: Cyclosporin A, Dry eye, Schirmer’s Test, Tear Break up Time.

Introduction:
Dry eye is a multi factorial disease, with two major recognized forms: one is characterized by a reduction of tear production, and the other is characterized by tear hyperosmolarity, mainly due to excessive evaporative water loss [1,2]. These two components of dry eye engender inflammation and ocular surface irritation. Thus, the goals for the treatment of this disease are to improve the patient’s ocular comfort and to return the ocular surface and tear composition to their basal and healthy states.

Although the reported prevalence of Dry eye varies among populations, it affects millions of individuals worldwide. In American men, Schaumberg et al found prevalence rates ranging from 3.9% in men aged 50–54 years to 7.7% in those 80 years or older [2]. In American women, the prevalence also increased with age, from 5.7% among women younger than 50 years to 9.8% among women aged 75 years or older [3]. Other studies have found DES in 14% of individuals aged 65–85 years [4]. Prevalence rates in Asian populations appear to be even higher [4.5].

There is no population-based study in relation to dry eye disease in India. However, there are only three published reports on prevalence of dry eye among hospital-based population from North and Eastern India and the prevalence varies between 18.4% and 40.8% [6-9]. One small study from high altitude showed a higher prevalence of 54% [10].
Many etiological factors for dry eye have been proposed. Older age and female gender have been identified as risk factors for dry eye [11-13]. Other risk factors implicated are arthritides, smoking, multivitamin use. Hormone replacement therapy, and especially when estrogen is used alone, was associated with an increased risk of clinically diagnosed dry eye syndrome or severe symptoms [14].

The goals for the treatment of this disease, thus, are to improve the patient's ocular comfort and to return the ocular surface and tear composition to their basal and healthy states. Two main therapeutic approaches are used in the clinic: instillation of artificial tears for tear supplementation and stimulation and instillation of anti-inflammatory drugs to reduce ocular surface inflammation. Inflammation can be reduced by the use of corticosteroids, tetracyclines or cyclosporine A. For Cyclosporin A, the mechanism of action of how tear production is increased is not totally clear, but it seems to be related to its immuno-modulatory activity, which decreases the local inflammation [15]. Cyclosporine A is a neutral, cyclic undecapeptide with many pharmacological activities: suppression of T-cell-mediated responses, inhibition of chronic inflammatory reactions, fungicidal activity, and anti-hepatitis C virus activity.

While artificial lubricating eye drops form the mainstay for treating dry eye, Cyclosparin (0.05%) ophthalmic emulsion which has been FDA approved December 2002 has since been used to treat dry eye disease [16]. It prevents activation and nuclear translation of cytoplasmic transcription, factors that are required for T-cell activation and inflammatory cytokine production. It also inhibits mitochondrial pathways of apoptosis of lacrimal gland and goblet cells. While the drop is typically well tolerated, ocular burning was reported in 17% of the patients. It typically takes 3 months for the medication to prove to be effective [17].

A recent study evaluated the efficacy of topical cyclosporine 0.05% in patients with mild, moderate, and severe dry eyes. They demonstrated success in 74%, 72%, and 67% of patients, respectively. With time the dose of topical cyclosporine was reduced to once daily with equal effect [19].

A Literature search on the effects of Cyclosporin A on the spectrum of Dry Eye disorders revealed similar results [19-23].

Taking a cue from these published studies we decided to do a similar study in the Indian subpopulation to assess if a similar response was observed in this group of patients as most of these studies have been carried out in the Caucasian race.

Material and Methods:

The study was conducted in patients who attended the Outpatient Department (OPD) of RIO (Regional Institute of Ophthalmology), Kolkata West Bengal, India during the period of April 2005 - February 2006 and was analyzed at one months, three months and 6 Months. It involved 63 pair of eyes. To each of these eyes Cyclosporineye drops (0.05%) were instilled in the right eye and artificial tears were instilled in the left eye daily for six months. The patients were selected by a screening procedure at the OPD after subjecting them to the a procedure that involved a subjective interview of Questions (McMonnies Questionnaire), a Medical and Contact Lens history, detailed slit lamp evaluation, estimation of the Flourescein break up time, Flourescein staining of the conjunctiva and the cornea, Schirmer 1 test without Anaesthesia, Rose Bengal staining of the cornea and conjunctiva and Conjunctival Impression Cytology (CIC).

Inclusion Criteria:
- Symptomatic Dry eye
- Schirmers 1 test <5mm.
- Corneal and inter palprebral staining.
- Normal lid anatomy and blinking function.

Exclusion Criteria:
- Severe dryness: Schirmers Test (Nasal stimulation) <3mm.
- Permanent goblet cell loss and scarring
- Acute ocular infection
- Ocular Rosacea
- Contact lens wear during the study period.
- Severe Blepharitis and lid margin infection.
- Punctal occlusion within 3 Months.

These were followed up monthly for a period of 6 months to see for improvement of all parameters mentioned above. The improvements were compared with the previous results.

McMonnies Questionnaire (Mc Monnies1986) 24 is a well balanced focused simple test that allows the patient to think about when the symptoms occur. If symptoms occur occasionally, the questionaire 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 the external environment factors or genuine intrinsic systemic factors. The Questionnaire has a simple scoring system based on the patients answer. 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 0-45 where higher scores are generally considered more indicative of dry syndrome 0.25. A cut point of greater than 14.5 is recommended for a dry eye diagnosis.

Ocular Examination involved measuring the Visual acuity on a Snellens Chart with the patient standing at a distance of 6 metres from the chart. The anterior segment and ocular adnexae was examined in detail with special emphasis on lid margin, puncta, canthi, blinking response and patency of lacrimal passage.

The extent of ocular surface damage was assessed by instilling a small amount of Rose Bengal or Fluorescein onto the ocular surface. It is usually the area within the lid aperture that is most likely to stain in dry eye.

Schimer's test was conducted in a temperate room comfortably and the electric fan was switched off. No 41 Whatman Filter Paper 35mm x 5mm was inserted from one end at the lower fornix at the junction of the middle third and outer third of lower eyelid taking care not to touch the cornea. The paper irritates the ocular surface initiating a reflex action whereby the volume of tears secreted by the lacrimal gland increases. The paper absorbs tears on contact with the ocular surface. The length of the paper wetted over a set time of 5 minutes is an indication of tear volume. The patient was asked to keep the eyes open and blink normally. After 5 minutes the filter paper was removed and the amount of wetting measured in mm. The test was performed without anaesthesia (Schimers Test 1) and is thus a measure of both basal and reflex tearing.

The Tear Break up Time (TBUT) was estimated 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. In dry eyes break up time is usually less than 10 seconds.

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 fluorescein 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 devitalised epithelial cells and mucus. The typical staining pattern in Keratoconjunctivitis sicca consisted of two triangles with their bases at the limbus.

Van Bijsterveld's scoring system (1969) was used to quantify the level of staining observed (with scores ranging from 0-9) [26]. The visible area of the eye was divided into three zones formed by imaginary vertical lines at either side of the limbus. Each zone is given a score depending upon the degree of staining contained, through 1 for mild staining and 2 for moderate staining to 3 for severe staining. A total score is calculated by adding the scores for the 3 zones of the ocular surface.

Conjunctival Impression cytology (CIC) is a minimally invasive technique allowing for the investigation of the conjunctival changes at the cellular level. After instilling a drop of topical anesthesia to each eye, the filter paper is placed at the desired area (four quadrants at the limbus and two on the upper fornix and lower fornix) using a smooth and flat end forceps. The filter paper is then gently smoothed on the ocular surface by touching the forcep tip at each of the four corners of the paper against the ocular surface. The filter paper is then removed by picking up the tip of the filterpaper with the same forceps. It is then placed in a bottle containing a fixative solution, containing 5 ml glacial acetic acid, 5ml of 37% Formaldehyde, and 100mlml of 70% ethyl alcohol and the bottle is sealed within a screw.

Sheets of Impression cytology specimen information was labelled accordingly, by entering the date of sample collection, Patients name, Medical record number, the corresponding eye, the area of the conjunctiva, or cornea where the sample was removed using abbreviation such as OD (Right eye), OS (Left eye), IB (Inferior bulbar Conjunctiva), TB (Temporal Bulbar Conjunctiva), IT (Inferior Tarsal).

While examining the slides the following features were taken into account. Findings were plotted according to the following parameters such as Stained characteristics and Nucleus/cytoplasm ratio, goblet cell density, Squamous metaplasia and mucin aggregates. Squamous metaplasia was said to occur in those cells, where there was marked elongation and enlargement of cells, with pyknotic changes in the nuclei, giving NC ratio greater than 1:4. Squamous metaplasia of the conjunctival epithelium referred to the pathological transiton involving increased stratification and keratinization of the epithelial cells, together with loss of goblet cells. Changes in the epithelial surface were enlargement, flattening and pyknotic changes in the nuclei within decreased nucleus-cytoplasmic ratios. Squamous metaplasia of the conjunctiva has been divided into 6 sages by Tseng, based on the presence of...
goblet cells, goblet cell density, morphological changes in the nucleus, nucleus cytoplasmic (N/C) ratio, metachromatic changes of cytoplasmic colour and emergence of keratinisation [27]. Another method of Staging of CIC Findings on the basis of Epithelial cells morphology, Goblet Cell density, presence of Mucin granules has been done by Nelson, Wittpen, Norn [28]. In the present study, the CIC specimens were examined and staged according to the degree of squamous metaplasia as described by Wittpen [29] as Normal, Borderline Normal, Borderline Abnormal. 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 could be seen and in Borderline Normal, the picture was similar to Normal, with the exception of the epithelial cells, which were abnormal.

Table 1: Categories of Interpretation of Specimen:

<table>
<thead>
<tr>
<th>Interpretation Of Specimens</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>Diffusely covering &lt;25% of sample</td>
</tr>
<tr>
<td>Borderline Abnormal</td>
<td>Diffusely covering &lt;25% of Sample</td>
</tr>
<tr>
<td>Borderline Normal</td>
<td>Covering &gt;25% of sample</td>
</tr>
<tr>
<td>Unreadable</td>
<td>Too few mucin spots or epithelial cells to read with confidence</td>
</tr>
</tbody>
</table>

Table 2: Observation & Results:

<table>
<thead>
<tr>
<th>Age-Group</th>
<th>No. of percentage</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>12</td>
<td>19.04%</td>
</tr>
<tr>
<td>40-60 years</td>
<td>18</td>
<td>28.57%</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>33</td>
<td>52.38%</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>100%</td>
</tr>
</tbody>
</table>

Out of 63 patients, 12 (19.04%) patients from age group <40 years, 18 (28.57%) patients from age-group 40-60 years & 33 (52.38%) patients from more than 60 years of age.

Table 3: Outcome of Schirmer’s test in Cyclosporine A and those treated with artificial tears:

<table>
<thead>
<tr>
<th>Schirmer Reading</th>
<th>After Treatment with Cyclosporin (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 (10-15)</td>
<td>35 (55.55%)</td>
<td>4 (6.39%)</td>
</tr>
<tr>
<td>Borderline (5-9)</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

In the study group among 63 patients treated with cyclosporin in the right eye, 23 (36.5%) showed more than 15 mm of Schirmer’s strip wetting, 35 (55.55%) patients had a low normal value of 10-15 mm wetting, 3 (4.76%) showed borderline 5-9 mm wetting and no improvement was found in 2 (3.17%) patients. On treatment with artificial tears no patient showed > 15 mm 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 4: TBUT in Cyclosporin A and eyes treated with Artificial Tears.

<table>
<thead>
<tr>
<th>TBUT</th>
<th>After Treatment with Cyclosporin (N=63)</th>
<th>After Treatment with Cyclosporin (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&gt;10 seconds)</td>
<td>61 (96.82%)</td>
<td>10 (15.87%)</td>
</tr>
<tr>
<td>Abnormal (&lt;10 seconds)</td>
<td>2 (3.17%)</td>
<td>53 (84.12%)</td>
</tr>
</tbody>
</table>

Chi Square 83.92  P value < 0.001

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

Table 5: Improvements in staining score in Cyclosporine A treated and artificial tears treated eyes

<table>
<thead>
<tr>
<th>Staining Score</th>
<th>Treated with Cyclosporin A (N=63)</th>
<th>Treated with Artificial Tears (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>56 (88.88%)</td>
<td>40 (63.49%)</td>
</tr>
<tr>
<td>Not Improved</td>
<td>7 (11.11%)</td>
<td>23 (36.50%)</td>
</tr>
</tbody>
</table>

Chi Square 11.20  P value = 0.00081

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 6: Improvements in McMonnies score after treatment with Cyclosporine A and those treated with Artificial Tears

<table>
<thead>
<tr>
<th>McMonnies Score</th>
<th>Cyclosporin Treated</th>
<th>Treated with Artificial Tears</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;14.5</td>
<td>52 (82.53%)</td>
<td>8 (12.69%)</td>
</tr>
<tr>
<td>&gt;14.5</td>
<td>11 (17.46%)</td>
<td>55 (87.30%)</td>
</tr>
</tbody>
</table>

Chi Square 61.60  P value = 0.001

In the present study of 63 patients McMonnies score improved in 52 (82.53%) patients treated with Cyclosporine A in the right eye compared to only 8 (12.69%) patients treated with artificial tears in the left eye. The results showed statistically significant improvement in the right eye compared to treatment of left eyes with artificial eye drops.

Table 7: Improvement in Visual acuity in Cyclosporine treated eyes and in those treated with Artificial Tears

<table>
<thead>
<tr>
<th>Visual Acuity (&lt;6/24)</th>
<th>After treatment with Artificial Tears</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>57 (90.47%)</td>
</tr>
<tr>
<td>Not Improved</td>
<td>6 (9.52%)</td>
</tr>
</tbody>
</table>

Chi square 59.66  P value < 0.001

In the study group, visual acuity improved in 57 (90.47%) patients treated with Cyclosporine while only 14 (22.22%) patients improved with artificial tear eye drops in the left eye. The improvements with Cyclosporine treatment were significantly better than those treated with artificial eye drops.

Table 8: CIC grading in Cyclosporine treated eyes and those treated with Artificial Tears After Treatment;

<table>
<thead>
<tr>
<th>CIC Grading</th>
<th>After Treatment with Cyclosporine</th>
<th>After Treatment with Artificial Tears</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>18 (28.57%)</td>
<td>0</td>
</tr>
<tr>
<td>Borderline Normal</td>
<td>29 (46.03%)</td>
<td>14 (22.22%)</td>
</tr>
<tr>
<td>Borderline Abnormal</td>
<td>16 (25.39%)</td>
<td>41 (65.07%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>0</td>
<td>8 (12.69%)</td>
</tr>
</tbody>
</table>

Chi-square 42.20  P Value < 0.001
In the study group of 63 patients with right eyes treated with Cyclosporin and left eyes treated with artificial eye drops for 6 months it was found that Cyclosporin treated eyes, 18 (28.57%) patients had normal CIC, 16 (25.39%) had borderline treatment. While in the artificial eye treatment 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 within Cyclosporin in the right eye was statistically significant. No definite relation could be established between dry eye disease and gender of individuals but the present study showed that the incidence of dry eye disease increases with age. Females affected were mainly in the post menopausal group.

**Discussion:**
In the year 1995, Lemp described dry eye 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.” Severe recent publications have suggested that dry eye disease is the result of complex inflammatory processes and suggest that the immunomodulatory drug Cyclosporine may have potential as a novel therapeutic treatment for moderate to severe dry eyes [31-34]. It was also recently reported that DES can be progressive in patients treated with artificial tears alone, whereas topical anti-inflammatory therapy with Cyclosporin A 0.05% may slow or prevent the disease progression in patients with DES [35].

The present study was a prospective one, aimed to find out the effect of Topical cyclosporine in Dry Eye Patient. The parameters used in the present study were Mc Monnies Index, Schirrmers Test without anaesthesia, Tear breakup time, Flourescin and Rose Bengal staining, Visual acuity Measurement and finally CIC to find out the ocular surface morphology. Results obtained from the present study matched with the previous studies with few differences regarding some parameters.

As seen from the tables it was noted that all the parameters measured were favourable in the Cyclosporin Treated eyes compared to the eyes treated with artificial eye drops and the P reached a value of statistical significance for all the parameters compared. The significant decrease in the corneal staining was of particular clinical relevance because it indicates an improvement in the integrity of the ocular surface as a result of treatment. A direct effect of this change may be an improvement seen in visual acuity in the cyclosporin treatment group which was again statistically significant. It could also be concluded that the decrease in the corneal staining represents an improvement on

**Conclusion:**
Although lubricating eye drop forms the main stay of treatment in Dry eye patients, topical Cyclosporin A offers a novel, alternate, safe and effective therapy. More long term studies in the future will throw more light into this aspect.

**References:**


32. Wan KH, Chen LJ, Young AL. Efficacy and Safety of Topical 0.05% Cyclosporine Eye Drops in the Treatment of Dry Eye Syndrome: A Systematic Review and Meta-analysis.Ocul Surf. 2015 Jul;13(3):213-2


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