Original Article

Evaluation of Ocular Surface Disease in Patients on Topical Antiglaucoma Drugs

Authors

Dr Rakshan Reyaz MBBS¹, Dr Asif Amin Vakil MS², Dr Syed Sadaf Altaf MS³, Dr Sabia Rashid MS⁴, Dr Ifrah Davood MBBS⁵

¹²³⁵Postgraduate, Department of Ophthalmology, Government Medical College, Srinagar, J&K, India
2Associate Professor, Postgraduate Department of Ophthalmology, Government Medical College, Srinagar, J&K, India
³Senior Resident, Postgraduate Department of Ophthalmology, Government Medical College, Srinagar, J&K, India
⁴Professor, Postgraduate Department of Ophthalmology, Government Medical College, Srinagar, J&K, India

Corresponding Author

Dr Rakshan Reyaz

Abstract

Purpose: To evaluate Ocular Surface Disease in glaucoma patients using topical medications.

Material and Methods: A total of 108 eyes of 60 glaucoma patients who used topical antiglaucoma medications for a minimum period of 6 months were enrolled and followed up for a period of 1 year. Duration of therapy and drops/day were noted. Patients underwent complete ocular examination including Schirmer test, slit-lamp examination for tear film break-up time, and OSDI questionnaire.

Results: The mean age of the patients was 55 ± 11.84 yrs. Schirmer’s Test 1 at baseline had a mean value of 18.12 ± 6.98mm which decreased to a mean value of 13.40 ± 4.84mm at 1 year follow up. Schirmer’s Test 1 values worsened with increasing the number of daily drug instillations. Tearfilm Break Up Time (TBUT) had a baseline mean value of 16.01 ± 3.95 secs which decreased to a mean value of 13.06 ± 3.12 secs at 1 year follow up. TBUT values decreased with increasing the number of daily drops instilled. OSDI values increased with increasing the number of daily drops instilled.

Conclusion: OSD is common in treated glaucoma patients causing symptoms and signs that may hamper the patient’s quality of life. The symptoms worsen with increasing the number and frequency of drug instillation. The usage of preservative-free products, combination drug products, and concurrent use of lubricating eye drops may be helpful in alleviating the symptoms.

Keywords: Glaucoma, Ocular surface disease, OSDI, TBUT, Schirmer’s test.

Introduction

Glaucoma is a chronic, progressive optic neuropathy caused by a group of ocular conditions, which lead to damage of the optic nerve with loss of visual function.¹ The most common risk factor known is raised intraocular pressure. Other risk factors include age, African ethnic background, family history of glaucoma, low central corneal thickness, trauma, long-standing ocular inflammation, prolonged steroid...
use, oral contraceptive intake, systemic conditions like diabetes, hypertension, asthma, heart failure, peripheral vascular disease, migraine, and coronary artery disease.\(^{[2,3]}\)

Glaucoma is the 2nd leading cause of visual impairment and blindness in the world. According to Quigley and Broman, there will be 60.5 million people with OAG and ACG in 2010, increasing to 79.6 million by 2020.\(^{[4,5]}\)

The aim of glaucoma therapy is to preserve visual function with minimal complications. Treatment of glaucoma which revolves around reducing the intraocular pressure should be instituted as soon as a definite diagnosis of glaucoma is reached.\(^{[6]}\)

Medical treatment of glaucoma is conventionally the first modality of treatment and includes the use of drugs like Cholinergic agonists, Adrenergic agonists, β Blockers, Carbonic Anhydrase inhibitors, Prostaglandin analogs, and Hyperosmotic agents. These drugs are invaluable in the management of glaucoma but are associated with certain adverse effects.\(^{[7]}\)

Prolonged use of topical antiglaucomatous medications can lead to the development of Ocular Surface Disease (OSD), which affects the quality of life and disrupts treatment compliance. The prevalence of OSD in glaucoma patients is reported to be as high as 60%.\(^{[8,9]}\)

The clinical presentation of OSD varies in severity and includes symptoms of dryness, redness, tearing, irritation, burning, foreign body sensation, photophobia, and distorted vision.\(^{[10,11]}\) OSD primarily manifests in the cornea and conjunctiva as superficial punctate keratitis (SPK), tear-film instability, and allergic manifestations. Keratoepithelial chemical toxicity leading to SPK is most commonly associated with topical prostaglandin analogs, beta-blockers, and cholinergics.\(^{[12,13]}\)

The disruptive effects of topical glaucoma medications on tear film integrity are well known. It is reported that TBUT and Schirmer’s values are abnormal in over 60% of glaucoma patients with significant tearfilm hyperosmolarity and meibomian gland loss.\(^{[14,15,16]}\)

Benzalkonium chloride (BAK) was one of the first preservatives introduced in the 1950s and remains the most common ophthalmic preservative today. BAK’s cationic quaternary ammonium preservative allows it to act as a surfactant by which it has been proposed to promote drug transmission into the anterior chamber. BAK destabilizes the tear film lipid layer through its detergent-like tensioactive effects, which may promote excessive evaporation of the aqueous tear film. Polyquaternium-1 (Polyquad) is another quaternary ammonium preservative considered to be less toxic to the ocular surface.\(^{[17]}\)

Noninvasive OSD indicators such as Ocular Surface Disease Index (OSDI), Tear Film Breakup Time (TBUT), and Schirmer’s Test can be used to evaluate for OSD in glaucoma patients. Among treated patients, worsening OSDI and decrease in TBUT and Schirmer test values are indicators of poor ocular surface health.\(^{[18,19]}\) This is directly related to the presence of preservative substances and the number of daily drug instillations.\(^{[20,21]}\)

The purpose of the study was to evaluate OSD in patients with glaucoma who used topical hypotensive medication using subjective (OSDI questionnaire) and objective (Schirmer’s test 1 and TBUT) parameters. We also evaluated number of drugs and number of drops/day that may affect the ocular surface.

**Materials and Methods**

**Study Design**

This was a hospital-based, prospective, observational study which was conducted over a period of one year. The study was undertaken after obtaining clearance from the Institutional Ethical Committee.

**Patients**

Diagnosed cases of POAG belonging to the age group 18 years and older, using one or more antiglaucomatous medication for at least 6 months were included in the study. Patients who were excluded from the study were patients with secondary forms of glaucoma such as uveitic, neovascular or steroid induced glaucoma,
systemic diseases affecting the ocular surface (e.g. collagen vascular diseases, Wilson disease, Mucopolysaccharidoses, Fabry’s disease), any acute disease affecting the cornea (e.g. ulcer, keratitis), any previous ocular surgery or trauma, use of contact lenses, patients with a history of Ocular Surface Disease (OSD), patients with blinking abnormality (e.g. Parkinson Disease, Facial Nerve Palsy), patients using drugs e.g. Antidepressants, Antihistaminics, Corticosteroids, Birth control pills.

After explaining the purpose and procedure of the study an informed consent of the patient was taken. Demographic information, medical and surgical history, medication usage, occupational history, personal history was taken. For ophthalmic history, the following parameters were recorded regarding topical medication use: number of IOP lowering medication, total duration of treatment, and the total number of drug instillations per day.

Patients underwent a complete ophthalmological examination including best-corrected visual acuity (BCVA), Slit Lamp examination, IOP determination, Gonioscopy, and Fundus examination.

**Study procedures and outcome measures**

Subjective assessment for Ocular Surface Disease was performed using Ocular Surface Disease Index questionnaire. The OSDI questionnaire has 12 questions which are subdivided into three groups: ocular discomfort, function, and environmental triggers. The OSDI questionnaire is graded on a scale from 0 to 4, where 0 indicates none of the time; 1, some of the time; 2, half of the time; 3, most of the time and 4 indicates all of the time. Scores range from 0 to 100; with a score of 0-12 as normal, 13-22 as mild dry eye, 23-32 as moderate dry eye, and 33-100 as severe dry eye. Patients further underwent objective assessment for OSD by measurement of Tear Film Breakup Time and Schirmer’s Test 1. TBUT measurement was done using a slit lamp and sodium fluorescein. A fluorescein strip was moistened with saline and applied to the inferior cul-de-sac. After several blinks, tear film was examined using a broad-beam of slit lamp with a cobalt blue filter for the appearance of the first random dry spot on the cornea. Three consecutive measurements were taken, and the time was averaged to obtain the TBUT. Normal values of TBUT are between 15-35 seconds. A TBUT of less than 10 seconds is considered abnormal, indicative of tear film instability.

Schirmer’s test was performed using Whatman filter paper strip (measuring 5mm x 35mm) to measure the quantity of tears produced over a period of 5 min. The strip was placed in the lower fornix at the junction of medial 2/3 and lateral 1/3 of the lower lid margin. The patients were directed to look forward and to blink normally during the course of the test. The extent of wetting of the strip was measured after 5 minutes. Values of less than 10mm are considered abnormal.

**Statistical Analysis**

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Statistical software SPSS (version 20.0) and Microsoft Excel were used to carry out the statistical analysis of data. Continuous variables were expressed as Mean±SD and categorical variables were summarized as percentages. Paired t-test was employed to compare various parameters between baseline and one year follow-up. Graphically the data was presented by bar and pie diagrams. A P-value of less than 0.05 was considered statistically significant.

**Results**

A total of 108 eyes of 60 patients (35 males and 25 females) with a mean age of 55.7±11.84 yrs who met the inclusion criteria participated in the study. The patients had the disease for a mean duration of 39.5±22.02 months. Schirmer’s Test 1 at baseline had a mean value of 18.12 ± 6.98mm which decreased to a mean value of 13.40 ± 4.84mm at 1 year follow up (Table 1). The comparison between Schirmer’s Test 1 values
and the number of daily drops instilled by patients revealed that patients using 1-2 drops had a difference of 4.56mm between the baseline and 1-year follow-up values. The difference was 4.78mm and 6.82mm in patients using 3-4 and 5-6 daily drug drops respectively (Table 2).

Tearfilm Break Up Time (TBUT) had a baseline mean value of 16.01 ± 3.95 secs which decreased to a mean value of 13.06 ± 3.12 secs at 1 year follow up (Table 3). The comparison between TBUT values and the number of daily drops used by patients revealed that patients using 1-2 drops had a difference of 3.12 secs between the baseline and 1-year follow-up values. The difference was 3.15 secs and 4.64 secs in patients using 3-4 and 5-6 daily drug drops respectively (Table 4).

The Ocular Surface Disease Index (OSDI) had a baseline mean value of 30.30 ± 14.89 which increased to a mean value of 40.90 ± 14.32 at 1 year follow up (Table 5). The comparison between OSDI and the number of daily drops used by patients revealed that patients using 1-2 drops had a difference of 10.33 between the baseline and 1-year follow-up values. The difference was 11.35 and 13.98 in patients using 3-4 and 5-6 daily drug drops respectively (Table 6).

### Table 1: Schirmer’s Test 1 at baseline and one-year follow-up in study eyes

<table>
<thead>
<tr>
<th>Schirmer’s Test 1 (mm)</th>
<th>Mean</th>
<th>SD</th>
<th>Difference</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>18.12</td>
<td>6.98</td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>At 1 year follow-up</td>
<td>13.40</td>
<td>4.84</td>
<td>4.72</td>
<td>13.89</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Statistically significant difference with respect to baseline (P-value<0.05); P-value by paired t-test

### Table 2: Schimer test as per number of drops at baseline and one year follow-up

<table>
<thead>
<tr>
<th>Number of drops</th>
<th>Baseline</th>
<th>At 1 year follow-up</th>
<th>Difference</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>1-2 Drops</td>
<td>19.36</td>
<td>6.91</td>
<td>14.80</td>
<td>5.35</td>
<td>4.56</td>
</tr>
<tr>
<td>3-4 Drops</td>
<td>17.66</td>
<td>7.41</td>
<td>12.88</td>
<td>4.59</td>
<td>4.78</td>
</tr>
<tr>
<td>5-6 Drops</td>
<td>18.32</td>
<td>6.00</td>
<td>11.50</td>
<td>3.25</td>
<td>6.82</td>
</tr>
</tbody>
</table>

*Statistically significant difference with respect to baseline (P-value<0.05); P-value by paired t-test

### Table 3: Tear film breakup time at baseline and one-year follow-up in study eyes

<table>
<thead>
<tr>
<th>Tear film breakup time (secs)</th>
<th>Mean</th>
<th>SD</th>
<th>Difference</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>16.01</td>
<td>3.95</td>
<td></td>
<td>2.95</td>
<td>14.05</td>
</tr>
<tr>
<td>At 1 year follow-up</td>
<td>13.06</td>
<td>3.12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant difference with respect to baseline (P-value<0.05); P-value by paired t-test

### Table 4: Tear film breakup time as per number of drops at baseline and one year follow-up

<table>
<thead>
<tr>
<th>Number of drops</th>
<th>Baseline</th>
<th>At 1 year follow-up</th>
<th>Difference</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>1-2 Drops</td>
<td>16.47</td>
<td>4.04</td>
<td>13.34</td>
<td>3.43</td>
<td>3.12</td>
</tr>
<tr>
<td>3-4 Drops</td>
<td>15.76</td>
<td>3.79</td>
<td>12.61</td>
<td>2.88</td>
<td>3.15</td>
</tr>
<tr>
<td>5-6 Drops</td>
<td>17.36</td>
<td>3.54</td>
<td>12.73</td>
<td>2.85</td>
<td>4.64</td>
</tr>
</tbody>
</table>

*Statistically significant difference with respect to baseline (P-value<0.05); P-value by paired t-test

### Table 5: Ocular Surface Disease Index (OSDI) at baseline and one-year follow-up in study patients

<table>
<thead>
<tr>
<th>OSDI</th>
<th>Mean</th>
<th>SD</th>
<th>Difference</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30.30</td>
<td>14.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 year follow-up</td>
<td>40.90</td>
<td>14.32</td>
<td>10.60</td>
<td>10.35</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>
Discussions
This prospective, observational, hospital-based study evaluated 60 patients of Primary Open Angle Glaucoma (POAG) using topical antiglaucoma drugs for a minimum period of 6 months before entering the study. The patients were in the age group of 30-80 yrs with the mean age of 55 ± 11.84 yrs. Our study group consisted of 35 (58.3%) males and 25 (41.7%) females. Schirmer Test at baseline had a mean value of 18.12 ± 6.98mm which decreased to a mean value of 13.40 ± 4.84mm at 1 year follow up. The difference was 4.72mm with a t-value of 13.89 and a P-value of <0.001 which was statistically significant. Wong et al[22] reported that the Schirmer test value was decreased in treated eyes as compared to controls. However, similar to our study the values were above 10mm and within physiological limits, therefore, likely to be of limited clinical significance.

The comparison between Schirmer’s Test 1 values and the number of daily drops used by patients revealed that patients using 1-2 drops had a difference of 4.56mm between the baseline and 1-year follow-up values. The difference was 4.78mm and 6.82mm in patients using 3-4 and 5-6 daily drug drops respectively. The P-value was <0.001 which was statistically significant. This is consistent with a study done by Dogan et al[23] where the mean Schirmer test was found to be statistically lower in patients who used 3 drops daily in comparison to those using 1 daily drop.

Tearfilm Break Up Time (TBUT) had a baseline mean value of 16.01 ± 3.95 secs which decreased to a mean value of 13.06 ± 3.12 secs at 1 year follow up. The difference was 2.95 secs with a t-value of 14.05 and a P-value of <0.001 which was statistically significant. This was consistent with Baffa et al[24] who reported TBUT of 6.4 ± 5.9 seconds for glaucomatous and 14.1 ± 2.4 seconds for controls (p<0.05). Wroblewska[25] reported a statistically significant decrease in break-up time in glaucoma patients. However, similar to other studies the decrease in our study was not found to be clinically significant.

The comparison between TBUT values and the number of daily drops used by patients revealed that patients using 1-2 drops had a difference of 3.12 secs between the baseline and 1-year follow-up values. The difference was 3.15 secs and 4.64 secs in patients using 3-4 and 5-6 daily drug drops respectively. The P-value was <0.001 which was statistically significant. Ghosh et al[26] showed that each additional eye drop was associated with about two times higher rates of impaired TBUT and attributed this to the preservatives in the eye drops.

The comparison between OSDI and the number of daily drops used by patients revealed that patients using 1-2 drops had a difference of 10.33 between the baseline and 1-year follow-up values. The difference was 11.35 and 13.98 in patients using more than one drop/drug and/or preserved antiglaucomatous agents had higher levels of inflammatory markers leading to progressively worsening OSDI scores. This was consistent with a study done by Fechtner et al[27] which reported patients on a single medication had a mean OSDI score of 12.9 ± 13.1, which was significantly lower than those of patients on 2 (16.7 ± 17.0; P = 0.007) or 3 medications (19.4 ± 18.1; P = 0.0001). Rossi et al[28] evaluated the presence of dry eye in glaucoma patients and the impact on Quality of Life (QoL). They found that the presence of dry eye negatively influenced the
patients’ QoL. They also noted that a greater number of prescribed glaucoma medications was associated with a higher prevalence of dry eye: 40% in patients taking two or three drugs, 11% with one drug, and 5% with none. Pisella et al\textsuperscript{[29]} demonstrated the correlation between increased signs and symptoms of OSD with the number of antiglaucoma medications used. Kumar et al\textsuperscript{[30]} reported that BAC-preserved travoprost leads to higher OSDI scores, which correlate strongly with poor QoL scores as compared to BAC-free travoprost (r values: BAC: 0.63, BAC-free: 0.23, controls: 0.29).

This study had many limitations. Environmental factors such as time, temperature, and ventilation which may affect the results could not be controlled. Our study group consisted of a wide variety of patients using topical antiglaucomatous agents, and the number of patients in these groups was relatively unequal. More accurate results can be obtained with a long-term prospective study in a newly diagnosed group of patients using only the same antiglaucomatous medications. Therefore, detailed prospective studies with larger sample sizes and longer follow-up periods are required.

**Conclusion**

Glaucoma is a chronic disease for which medical management is the cornerstone therapy. Prolonged use of topical antiglaucoma drugs has adverse effects on the ocular surface leading to the development of Ocular Surface Disease. Schirmer’s Test I and TBUT values decreased over the one-year study period. Further, the values were found to be worsened with increasing the number of drugs used and daily drops instilled. OSDI values increased with increasing the number of drugs used and daily drops instilled. Concurrent use of lubricating eye drops and using preservative-free eyedrops is helpful in alleviating the symptoms. Using combination drug products instead of multiple individual drug units reduces the frequency of drug instillation and thereby decreases the burden of ocular surface disease.

**Conflicts of Interest:** None

**Bibliography**


