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A study of ocular surface disease in patients using topical antiglaucoma medication at a tertiary care centre

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Abstract
Aim: To study the ocular surface disease in patients being treated with topical antiglaucoma medication. And also study the relationship between the OSD and topical antiglaucoma medication.
Methodology: It was a A prospective study, carried out during the year from November 2019 to October 2020 Patients of age group 30 - 50 years who are diagnosed with glaucoma and started on topical antiglaucoma medication at glaucoma unit in Sarojini Devi eye Hospital, Hyderabad. Before starting topical antiglaucoma medication Patient is evaluated by measuring tear film break-up time, fluorescein staining of cornea, schirmer test and impression cytology. After starting topical antiglaucoma medication, the patient is evaluated again at 1 month, 3 months, 6 months and 1 year for any ocular surface changes or at any time if the patient develops symptoms of OSD.
Results: A total of 100 patients with glaucoma were included in the study, among them 56% were males and 44% were females. Mean age of the patients is 43.8 years, ranging from 37 to 50 years. Of the 100 patients, 21patients had primary open angle glaucoma, 60 patients had primary angle closure glaucoma, 19 patients had combined mechanism glaucoma. TBUT was significantly reduced in 60% patients, Schirmer's test showed that 84% patients had reduced tear production and 28% patients showed positive fluorescein staining. The prevalence of OSD among users of preserved topical antiglaucoma medications was significantly higher than among nonusers as assessed by FTBUT (83.5% vs. 57.3%; P<0.001), Schirmer I (30.1% vs. 17.5%; P = 0.033), and ocular surface staining (62.1% vs. 31.1%; P<0.001).
Conclusion: In this study we observed a serious impact on the tear function tests and low grade metaplasia in majority of the patients almost 84% at the end of 12 months of treatment and the impact was directly related to the number of medications used. Finally, OSD can influence treatment adherence and prognosis, thus greatly influencing the quality of the life of glaucoma patients. Further studies are needed to validate the effects of BAK and BAK- free agents on OSD. The quality of these glaucoma patients can be improved by switching over to medications with a smaller percentage of BAK or BAK - free.

Keywords: OSD, glucoma, TBUT, fluorescein, schirmer's test

Introduction
Ocular surface disease (OSD) is a major cause of ophthalmological consultation [1]. Within this group, glaucoma patients constitute an important percentage due to the nature of their chronic topical treatment. Glaucoma is the second leading cause of blindness in the world.
The first line of treatment typically constitutes topical medical treatment that either decreases aqueous humor production and/or facilitates its outflow. Just as with many eye drops, these medications generally contain preservatives to warranty their safety. Recent evidence has shown that some of the ingredients used as preservatives in many ophthalmic medications are at least partially responsible for the problem [1, 2].
In particular, glaucoma patients, who are exposed to a chronic use of preservatives in their treatment, constitute a significant percentage. It involves all sorts of pathological alterations of conjunctiva and cornea from the minor such as punctate keratitis, to the extreme such as symblepharon, or loss of limbal stem cells with corneal conjunctivalisation [1]. Within this group, dry eye syndrome (DES) constitutes a well-defined, multifactorial aetiology but clearly defined symptoms. Redness, itching, foreign-body sensation, tearing and pain are some of the frequent complaints ophthalmologists face on a daily basis from this group of patients. This ocular surface disease (OSD) can affect quality of patient's life and also treatment compliance thereby affecting the overall prognosis of glaucoma [2].

Ocular lubricants constitute the main treatment. Ophthalmological examination of DES patients for assessing diagnosis and progression of the disease needs specific approach. The clinical diagnosis of objective tests for DES includes the following: 1) the Schirmer test (ST), with or without anaesthesia, to measure tear production; 2) tear break-up time (TBUT) that reflects tear film stability; and 3) dye staining tests to evaluate the tissue integrity, by using the conjunctival lissamine green or the corneal fluorescein staining.

Aim and objectives of the study

Aim: To study the ocular surface disease in patients being treated with topical antiglaucoma medication.

Objectives: To study the relationship between the OSD and topical antiglaucoma medication.

Study design: A prospective study

Study period: November 2019 to October 2020

Materials and Methods

Patients of age group 30 - 50 years who are diagnosed with glaucoma and started on topical antiglaucoma medication at glaucoma unit in sarojini devi eye hospital, hyderabad.

Before starting topical antiglaucoma medication Patient is evaluated by measuring tear film break-up time, fluorescein staining of cornea, schirmer test and impression cytology.

After starting topical antiglaucoma medication, the patient is evaluated again at 1 month, 3 months, 6 months and 1 year for any ocular surface changes or at any time if the patient develops symptoms of OSD.

Inclusion criteria

Patients diagnosed with glaucoma and started on topical antiglaucoma medication and without any preexisting dry eye disease.

Exclusion criteria

- Patients with pre-existing dry eye disease, ocular infection, inflammation, previous ocular trauma, corneal surgeries, contact lens users.
- Patients already on topical antiglaucoma medication.

Sample size and duration of the study: 100 patients and 18 months.

The patients who are diagnosed with glaucoma and started on topical antiglaucoma medication, are taken into study after fulfilling inclusion and exclusion criteria.

200 eyes of 100 patients were studied who are treated with one or more topical antiglaucoma medications with preservatives (dorzolamide 2% + timolol 0.5%, brimonidine 0.1%, bimatoprost 0.01%, travoprost 0.04%, latanoprost 0.05%). Patients with primary open angle glaucoma, primary angle closure glaucoma, combined mechanism glaucoma and pigment dispersion glaucoma were included.

For all the patients comprehensive ocular examination, aided snellen's visual acuity, Intraocular pressure by Goldmann applanation tonometry, ocular surface evaluation tests (tear film break-up time, Schirmer's test, fluorescein staining, conjunctival impression cytology) were done at starting of the study and then during follow ups at 3 months, 6 months and 1 year.

Patients were evaluated by

1. Recording of visual acuity on snellen's acuity chart.
2. Slit-lamp biomicroscopy using 90D / 78D lens.
3. Measurement of Intraocular pressure by Goldmann applanation tonometer.
4. Gonioscopy.
5. Syringing of the eye.
6. Random blood sugar.
7. Blood Pressure.
8. Fluorescein staining of cornea.
9. Tear film break-up time.
10. Schirmer's test.
11. Conjunctival impression cytology.

Fluorescein staining of the cornea

Normally, the corneal surface is regular, smooth and shiny and the tear film covering the epithelium is not directly seen. The intact corneal epithelium because of its high lipid content resists penetration of water soluble fluorescein and is not stained by it. Any break in the epithelial barrier permits rapid fluorescein penetration and staining of areas denuded of epithelium.

Tear film break-up time (TBUT)

It is defined as the interval between a complete blink and the appearance of the appearance of the first randomly distributed dry spot on the cornea. It is noted after instilling a drop of fluorescein and examining in the cobalt blue light of Slit-lamp. Values > 10 seconds: Normal, The values 5-9 sec: mild to moderate, values < 5sec: severe dry eye due to mucin deficiency.

Schirmer's test

A 5×35 mm blotting paper strip after folding 5mm from one end and placing it in the lower fornix, at the junction of outer one-third and inner two-thirds for 5 minutes. Whatman filter paper number 41 was standardised for this test. Wetting of less than 10mm/5 min would indicate a diminished lacrimal secretion. Values are classified as >10 mm: Normal, 6-10 mm: mild to moderate, <5mm: severe deficiency of tears.

Conjunctival impression cytology

Ocular surface cells are obtained by using cellulose acetate filter material to make an impression and stained with periodic acid schiff stain and examined for squamous metaplasia which is a feature of dry eye.

Squamous metaplasia involves three major steps, namely loss of Goblet cells, increase in cellular stratification and keratinization. On the basis of cellular changes occurring in the course of squamous metaplasia, the findings on conjunctival impression cytology have been graded according to the severity of dry eye state from 0 to 5 as follows.

Stage 0: Normal cellular structure.

Stage 1: Early loss of goblet cells without keratinization.

Stage 2: Total loss of goblet cells with slight enlargement of epithelial cells.

Stage 3: Early and mild keratinization.

Stage 4: Moderate keratinization.

Stage 5: Advanced keratinization.

Results

A total of 100 patients with glaucoma were included in the study, among them 56% were males and 44% were females. Mean age of the patients is 43.8 years, ranging from 37 to 50 years. Of the 100 patients, 21 patients had primary open angle glaucoma, 60 patients had primary angle closure glaucoma, 19 patients had combined mechanism glaucoma.

64 patients were on more than 1 topical glaucoma medication by the end of study period. 12 patients were on timolol 0.5% (one drop twice daily), 24 patients were on the combination of dorzolamide 2% + timolol 0.5% (one drop twice daily), 64 patients were on combination of dorzox 2% + timolol 0.5% (one drop twice daily) and Latanoprost 0.05% or bimatoprost 0.01% or brimonidine 0.1% or travoprost 0.04%.

Tear functions: At the end of the 12 months study period, Schirmer's test was normal in 16 patients, significantly reduced in 84 patients. Contributing to Mild - Moderate dry eye in 46% (P value 0.001) and severe dry eye in 38% (P value 0.001) patients. While TBUT was significantly reduced in 60% patients at the end of 12 months with mild to moderate dry eye in 55% (P value 0.01) and severe dry eye in 5% P value (0.0005) of patients. It was normal in 40% of patients.

Fluorescein staining: Staining was not seen in 72% of the patients, whereas mild to moderate staining was seen in 26% of patients and severe staining seen in 2% patients at the end of 12 months study period.

Impression cytology: Almost all patients showed mild to moderate squamous metaplasia with reduced goblet cell density at the end of 12 months of treatment.

Table 1: Tear function by various Staining Methods.

Results	Schirmer's test (%)	TBUT (%)	Fluorescein staining (%)	Conjunctival impression cytology (%)
Normal	16	40	72	0
Mild- Moderate	46	55	26	100
Severe	38	5	2	0

Gender distribution

Males were 54% and 46% were females among the study group. Among males Schirmer's test was normal in 11 (20.3%) patients, Mild to moderate dry eye in 26(48.1%) patients, severe dry eye in 19(35.1%) patients. Whereas in females Schirmer's test showed normal in 5(10.8%), mild to moderate in 20(43.4%) and severe dry eye in 19(41.3%) patients.

Table 2: Distribution of Schirmer's test in males vs females

	Total	Normal	Mild moderate	Severe
Males	54	11(20.3%)	26(48.1%)	19(35.1%)
Females	46	5(10.8%)	20(43.4%)	19(41.3%)

Among male patients, TBUT was normal in 24(44.4%), mild to moderate in 27(50%) patients and severe in 3(5.5%). In females, TBUT was normal in 46(32.6%) patients, mild to moderate in 29(63%) and severe in 2(4.3%) patients.

Table 3. Distribution of TBUT in males vs females

	Total	Normal	Mild-moderate	Severe
Males	54	24(44.4%)	27(50%)	3(5.5%)
Females	46	15(32.6%)	29(63%)	2(4.3%)

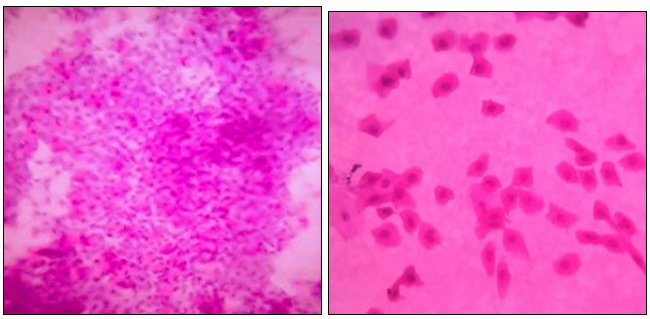

Fig 1: Conjunctival impression cytology [A, B]

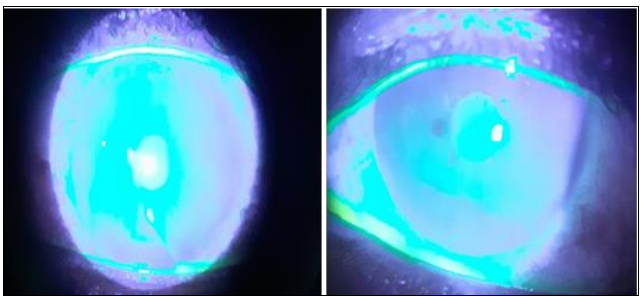

Fig 2: Positive fluorescein staining of cornea in both eyes in a patient after 12 months of treatment with topical antiglaucoma medication. [A, B]

Discussion

The ocular surface provides protection and refractive surface that allows for good quality vision. The tear film plays an important role in the maintenance of the ocular surface. Any condition affecting the stability and function of the tear film may result in unstable tear film and OSD onset [3].

OSD is known to occur in approximately 15% of the general elderly population and is reported in 48% to 59% patients on treatment with topical antiglaucoma medication [3]. The mechanisms of ocular damage as well as the respective role of the active compound and the preservatives in ophthalmic solutions are still being investigated.

In the present study, we measured tear quality with TBUT and tear production with Schirmer's test and evaluated the ocular surface by corneal staining and conjunctival impression cytology.

TBUT was significantly reduced in 60% patients,

Schirmer's test showed that 84% patients had reduced tear production and 28% patients showed positive fluorescein staining.

Vinutha *et al*. [4] observed TBUT (74%) (Mild to moderate 54% and severe: 20%) and lissamine green staining (47%) was more positive in their study. They also reported that with increased treatment duration and number of medication more patients became symptomatic and test results became abnormal. Schirmer's test showed more positive results in this study (total: 84%, mild - moderate: 46%, severe: 38%) in this study.

Leung *et al*. [5] examined the prevalence of OSD using the OSDI questionnaire, TBUT, Schirmer's test and lissamine green staining. They observed that the use of more BAK - containing drops was significantly associated with higher prevalence of abnormal results on lissamine green staining (22%), none of them had severe staining with lissamine green. Whereas in this study 28% patients had positive fluorescein staining and 2 patients (2%) had severe staining. Similar to the findings by Leung *et al*. This study showed that with increased number of medications test results became more positive.

The most significantly affected ocular sign of OSD was reported to be decreased TBUT, indicating tear film instability while corneal and conjunctival staining was a reliable indicator of severity in the literature [6, 7]. Rossi *et al*. showed abnormal TBUT and punctate keratitis, which was more frequent with increasing number of eye drops and number of instillations per day in the patients with topically treated glaucoma [7, 8]. This study also showed the same results with severe corneal staining in patients using more number of topical antiglaucoma medications.

The decrease in conjunctival goblet cell density is accepted as an important parameter in assessing the OSD. The conjunctival inflammation and reduced goblet cell density of dry eye are exacerbated by use of preserved topical agents [9, 10]. In our study, the mean count of goblet cells showed significant reduction by the end 12 month of study period, almost in all patients.

The prevalence of OSD among users of preserved topical antiglaucoma medications was significantly higher than among nonusers as assessed by FTBUT (83.5% vs. 57.3%; $P<0.001$), Schirmer I (30.1% vs. 17.5%; P = 0.033), and ocular surface staining (62.1% vs. 31.1%; $P<0.001$) [1].

In the present study TBUT was significantly reduced in 60% patients, Schirmer's test showed that 84% patients had reduced tear production and 28% patients showed positive fluorescein staining.

In the studies mentioned above only Leung *et al*. and Vinutha *et al*. [4] Used methods like OSDI questionnaire for subjective analysis, Schirmer's test for tears production, TBUT for meibomian gland function and Lissamine green staining to assess OSD. In present study conjunctival impression cytology was done to assess OSD, OSDI questionnaire was not used.

The differences among the prevalence of OSD in different studies could be due to differences in methodology, severity of disease, age, duration of therapy and the type and number of medications used. The severity of dry eye was more evident with TBUT and Schirmer's test as compared to fluorescein staining.

Limitations of the study

The main limitation of this study is, there is no control group to compare. The study period was only for 1 yr, which was less and with increased duration of therapy the results may change. Also the study did not compare specific drugs, as, majority of patients were on more than one drug, two or more drugs of different combinations. And at each follow up drugs are changed or added depending on the response of the patient to the treatment. The study also did not compare different preservatives used in different preparations as there was a wide range of medications used and brands were changed according to the availability and response to the treatment.

Conclusion

In this study we observed a serious impact on the tear function tests and low grade metaplasia in majority of the patients almost 84% at the end of 12 months of treatment and the impact was directly related to the number of medications used. Finally, OSD can influence treatment adherence and prognosis, thus greatly influencing the quality of the life of glaucoma patients. Educating patients about the adverse effects of the drugs and recommending them to avoid aggravating environmental factors such as dry air can play an important part in the management of glaucoma. Further studies are needed to validate the effects of BAK and BAK- free agents on OSD. The quality of these glaucoma patients can be improved by switching over to medications with a smaller percentage of BAK or BAK - free.

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