ORIGINAL RESEARCH

Prevalence of Ocular Surface Diseases in Patients on Long Term Antiglaucoma Medication

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ABSTRACT

Introduction: Glaucoma is a chronic progressive ocular disorder characterized by optic nerve damage associated with visual field loss, ultimately culminating to blindness. Topical anti-glaucoma medications are used commonly for the management of glaucoma. But the long term use of same may lead to various ocular surface disorders (OSD). Usually the preservatives added in these medications are responsible for OSDs. **Aim:** To evaluate the prevalence of OSD in patients treated with topical anti-glaucoma medications and to analyse the relationship of benzalkonium chloride (BAK) concentration with duration of topical medication and number of drug used as topical medication in glaucoma patients. **Materials and Methods:** The present prospective study was conducted on 38 patients (76 eyes) of glaucoma attending glaucoma clinic of a tertiary care health centre after taking informed consent from patients and approval from Institutional Ethics Committee. All patients with primary open angle glaucoma, primary angle closure glaucoma and ocular hypertension aged 18 years or above were included in the study. All the enrolled patients were asked to complete the Ocular surface disease index (OSDI) questionnaire; after that they all undergone Schirmer's 1 test and Tear Breakup Time (TBUT) for detection of OSDs. **Results:** Mild to moderate prevalence of OSD was reported in 10 (26.3%) patients by OSDI questionnaire. 13 (34.2%) patients showed mild to moderate symptoms of OSD by Schirmer's 1 test while 9 (23.7%) patients showed severe symptoms. Results by TBUT test showed mild to moderate symptoms of dry eye in 19 (50%) patients while 5 (13.2%) patients showed severe symptoms. Longer duration of treatment (more than one year) was associated with more symptoms of OSDs. **Conclusion:** Longer duration and increased number of anti-glaucoma medication lead to more subjective symptoms of OSD as calculated by OSDI questionnaire, Schirmer's test and TBUT test. Increased concentration of BAK in different anti-glaucoma medication was responsible for more symptoms of OSD.

Keywords: Anti-glaucoma medication, BAK, OSD, Schirmer's 1 test, TBUT tests.

INTRODUCTION

Glaucoma is a chronic neurodegenerative ocular disorder characterized by optic nerve damage and progressive visual field loss.[1] It is the second leading cause of irreversible blindness worldwide.[2] Around 76 million people are affected currently by primary open angle glaucoma (POAG) and it is estimated to reach around 111.8 million by 2040.[2] The pathology behind development of glaucoma are age, gender, genetics, myopia, family history, increased use of systemic or topical steroids and the most significant and only proven treatable cause i.e. increased intraocular pressure(IOP).[2-5]

Traditionally, the drugs lowering increased IOP are used for the management of primary open angle glaucoma. The available options are topical β-adrenergic blockers, α-adrenergic agonists, prostaglandin analogues, carbonic anhydrase inhibitors, cholinergic agonists and rho kinase inhibitors. Although the topical anti-glaucoma eye drops have many beneficial effects, the long term use of same may lead to various ocular discomforts like

corneal and conjunctival inflammation, tear film instability, corneal surface impairment, subconjunctival fibrosis and risk of failure of glaucoma surgery leading to possible vision loss.[6-8]

Studies suggest that preservatives and additives present in topical eye drops are responsible for these ocular cellular toxicities.[9] The preservatives are added to eye drops to prevent microbial contamination and to increase the shelf life of formulation by reducing its rate of biodegradation.[9-11] The most commonly added preservative in most of the preparations is benzalkonium chloride (BAK), quantity of which ranges from 0.005% to 0.02%.[12]

This BAK is a quaternary ammonium compound which acts as detergent and causes disruption of cell membrane lipid layer leading to evaporation of its aqueous component.[11] It also causes damage to cornea and conjunctiva leading to symptoms like burning, redness, dryness, grittiness, periorbital eyelid skin pigmentation, foreign body sensation, photophobia, fatigue, fluctuating visual acuity and superficial punctal keratitis etc, collectively called as ocular surface disorders (OSD).[13] OSD is a disorder affecting meibomian and lacrimal gland along with conjunctival and corneal epithelium, a well known complication of long term topical anti-glaucoma preparations.[13] The overall prevalence of OSD ranges from 20-59% in glaucoma.[14] These symptoms of OSD leads to frequent blinking of eyes thus cause rapid wash out of the topical medication further adding to the problem. All these factors together causes decreased drug compliance leading to poor IOP control and progression of glaucoma.

So, the present study aimed to evaluate the prevalence of OSD in patients treated with topical anti-glaucoma medications and to analyse the relationship of BAK concentration with duration of topical medication and number of drug used as topical medication in glaucoma patients.

METHODS

After taking approval from Institutional Ethics Committee (No.MCR/EC/13/259) and informed consent from patients, this prospective hospital based study was conducted on 38 patients (76 eyes) of glaucoma attending glaucoma clinic of a tertiary care hospital from November 2011 to October 2013 (24 months).

INCLUSION CRITERIA

All patients with POAG, primary angle closure glaucoma and ocular hypertension aged 18 years or above were included in the study.

EXCLUSION CRITERIA

a. Patients undergone YAG Laser, any anterior segment pathology or ocular surgery.

b. Any other ocular disease that can cause OSD in themselves like nutritional deficiency such as vitamin A deficiency, eyelid disease such as trichiasis, entropion and conditions leading to exposure keratitis, any congenital or systemic disease leading to dry eye or any pathology to corneal epithelium.

Demographic profile, brief medical history and information about concomitant medication were asked from the enrolled patients. All the enrolled patients were asked to complete Ocular Surface Disease Index (OSDI) questionnaire. After completing the OSDI questionnaire, the patients underwent standard clinical tests for detection of OSDs, Schirmer's 1 test and Tear Breakup Time (TBUT).

OCULAR SURFACE DISORDER INDEX (OSDI)

The OSDI is designed as a screening survey to assess symptoms and their impact on vision related functions. The 12 questions of OSDI questionnaire were graded on the scale of 0 to 4. The total OSDI score was calculated using the formula:

$$\text{OSDI} = \frac{\text{Sum of scores of all questions asked X 25}}{\text{Number of questions answered}}$$

Using OSDI score patients were categorized as:

Grades	OSDI Score
Normal	Score 0-12
Mild	Score 13-22
Moderate	Score 23- 32
Severe	Score 33-100

SCHIRMER'S 1 TEST

Schirmer's 1 test was performed using a special (no. 41 Whatman) filter paper about 5 mm wide and 35 mm long. Schirmer 1 test evaluates baseline secretion plus reflex secretion. The test was performed as follows:

i. The filter paper was folded 5 mm from one end (a notch is present in the filter paper 5 mm from one end) which indicates the point at which paper need to be folded.

ii. The folded tip was inserted in to the lower lid (at the junction of the middle and outer third of the lower eye lid) taking care not to touch the cornea or lashes.

iii. The patient was asked to keep their eyes closed for the duration of the test.

iv. After 5 minutes, the filter paper was removed and the amount of wetting from the fold was measured.

Schirmer's 1 test results were graded as:

Grade	Reading on Schirmer's strip
Normal	$\geq$ 15 mm wetting of the paper after 5 minutes
Mild	14 -9 mm wetting of the paper after 5 minutes

Moderate	8 – 4 mm wetting of the paper after 5 minutes
Severe	< 4 mm wetting of the paper after 5 minutes

TEAR BREAKUP TIME (TBUT) TEST

The test was performed as followed:

i. 2 % sodium fluorescent dye was administered into inferior culde sac. Patient was asked to blink his/her eyes several times so that fluorescent dye distributes uniformly.

ii. Examination of the eyes was performed under slit lamp using cobalt blue illumination.

iii. Patient was asked to blink and keep open without further blinking the eyes. TBUT was measured over the cornea as the time from last blink until the appearance of first black spot in the green yellow fluorescent.

iv. Care should be taken that the examination room does not have any draft or forced air unit that might prematurely dry out the tear film.

TBUT test results were graded as:

Grade	Time in seconds
Normal	≥10 seconds
Mild to moderate	5 -9 seconds
Severe	<5 seconds

STATISTICAL ANALYSIS

Data has been collected in Microsoft Excel sheet and results have been presented in counts and percentage using descriptive statistics.

RESULTS

A total of 38 patients (76 eyes) were enrolled in the study. Of which 28 (74%) were male and rest 10 (26%) were female. The age ranged from 28-81 years with mean age of 56.4 years. Out of 38 patients, 23 (60.5%) were diagnosed having POAG, 14 (36.8%) were having angle closure glaucoma and 1 (2.6%) patient was suffering from ocular hypertension. The distribution (%) of dry eye by OSDI, Schirmer's 1 test and TBUT have been presented in Table I.

Table I: Distribution (%) of dry eye by OSDI, Schirmer's 1 test and TBUT (n=38)

OSDI Grades	No. (%) of dry eye in patients	Schirmer's 1 test Grades	No. (%) of dry eye in patients	TBUT Grades	No. (%) of dry eye in patients
Normal	28 (73.7%)	**Normal**	16 (42.1%)	**Normal**	14 (36.8%)
Mild	8 (21.1%)	**Mild**	4 (10.5%)	**Mild-moderate**	19 (50%)
Moderate	2 (5.2%)	**Moderate**	9 (23.7%)	**Severe**	5 (13.2%)
Severe	0	**Severe**	9 (23.7%)		

Longer the duration of anti-glaucoma medication, more and more patients develop subjective symptoms of OSD as calculated by OSDI questionnaire. Duration of TBUT was also decreased by longer treatment duration by anti-glaucoma medication and more patients showed positive Schirmer's test by longer duration of treatment as presented in Table II.

Table II: Duration of treatment by anti-glaucoma medication and OSDI, Schirmer's 1 and TBUT grades (n=76)

OSDI Grades	Duration of treatment (years)			
	<1	**1-5**	**6-10**	**>10**
Normal	2 (2.6%)	30 (39.5%)	10 (13.2%)	2 (2.6%)
Mild-Moderate	0	14 (18.4%)	12 (15.8%)	6 (7.9%)
Severe	0	0	0	0
Schirmer's test grades				
Normal	2 (2.6%)	26 (34.2%)	5 (6.6%)	0
Mild	0	2 (2.6%)	6 (7.9%)	0
Moderate	0	9 (11.8%)	5 (6.6%)	3 (3.9%)
Severe	0	6 (7.9%)	6 (7.9%)	6 (7.9%)
TBUT test grades				
Normal	2 (2.6%)	17 (22.4%)	8 (10.5%)	1 (1.3%)
Mild-Moderate	0	21 (27.6%)	10 (13.2%)	6 (7.9%)
Severe	0	6 (7.9%)	4 (5.3%)	1 (1.3%)

Instilling multiple drugs resulted in increased frequency of subjective symptoms in patients as calculated by OSDI questionnaire. The same has been reported by Schirmer's test and TBUT test also as shown in Table III.

Table III: Relation between number of anti-glaucoma medications and OSDI, Schirmer's 1 and TBUT grades (n=76)

OSDI Grades	Number of anti glaucoma drugs		
	1 drug	2 drugs	3 drugs
Normal	22 (28.9%)	18 (23.7%)	0
Mild-Moderate	6 (7.9%)	18 (23.7%)	0
Severe	0	0	0
Schirmer's test grades			
Normal	16 (21.1%)	11 (14.4%)	4 (5.3%)
Mild	8 (10.5%)	11 (14.4%)	2 (2.6%)
Moderate	1 (1.3%)	9 (11.8%)	2 (2.6%)
Severe	3 (3.9%)	5 (6.6%)	4 (5.3%)
TBUT test grades			
Normal	14 (18.4%)	12 (15.8%)	2 (2.6%)
Mild-Moderate	11 (14.4%)	19 (25%)	7 (9.2%)
Severe	3 (3.9%)	5 (6.6%)	3 (3.9%)

It has been seen that concentration of BAK available in different anti glaucoma medication is responsible for symptoms of OSD. The same has been presented in Table IV.

Table IV: Relation between BAK concentration in various ophthalmic anti glaucoma agents and OSDI, Schirmer's 1 and TBUT grades (n=76)

OSDI Grades	Concentration of BAK in various ophthalmic preparations		
	<0.007	**0.01**	**>0.01**
Normal	8 (10.5%)	13 (17.1%)	1 (1.3%)
Mild-Moderate	4 (5.3%)	8 (10.5%)	4 (5.3%)
Severe	0	0	0
Schirmer's test grades			
Normal	12 (15.8%)	8 (10.5%)	3 (3.9%)
Mild	2 (2.6%)	3 (3.9%)	3 (3.9%)
Moderate	5 (6.6%)	10 (13.2%)	2 (2.6%)
Severe	4 (5.3%)	11 (14.4%)	3 (3.9%)
TBUT test grades			
Normal	11 (14.4%)	15 (19.7%)	2 (2.6%)
Mild-Moderate	6 (7.9%)	23 (30.3%)	8 (10.5%)
Severe	7 (9.2%)	4 (5.3%)	0

DISCUSSION

This prospective hospital based study was conducted on 38 patients (76 eyes) attending glaucoma clinic at a tertiary care hospital to evaluate the prevalence of OSD in patients treated with topical anti-glaucoma eye drops and to analyse the relationship of BAK concentration with duration of topical medication. The overall prevalence of dry eye among glaucoma patients based on OSDI standard questionnaire was reported 26.3% in the present study while none of the enrolled patient showed severe subjective symptoms. Leung EW et al reported subjective symptoms by OSDI in 60% of the eyes and severe symptoms in 27%.[10] Awe et al also reported mild to moderate OSDI symptoms in 46.6% while severe OSDI score in 15.5% patients on anti-glaucoma medications.[15] Similar results were obtained by Schirmer's 1 and TBUT test also in the present study as well as in the study conducted by Awe et al.[15]

In the present study patients with glaucoma diagnosed less than 5 years had a lower mean OSDI score (18.4%) relative to patients with glaucoma diagnosed of 10 years or more (23.7%). Similar results has been obtained by study conducted by Garcia-Feijoo J et al who also reported significantly lower mean OSDI score in patients with glaucoma diagnoses of less than 6 years duration.[16]

Increasing the number of anti-glaucoma medication from 1 to 2 or 3 leaded to worsening of OSDI score, Schirmer's test score and TBUT score in the present study. The same has been concluded by Fechtner RD et al and Ruangvaravate N et al also.[7, 17] In contrast to the findings of present study, Awe et al reported that the prevalence of OSD using all three objective tests was not significantly affected by the number of medications.[15]

Increased BAK concentration in various ophthalmic preparations has been associated with poorer objective and subjective score of OSDI, Schirmer's and TBUT in the present study. The same has been reported by Leung et al who showed approximately 2 times higher odds of abnormal results with additional BAK containing eye drop.[10] The same has been concluded by Kahook MY et al and Jaenen N et al also.[18, 19]

LIMITATIONS TO THE STUDY

There are some limitations of the study like small sample size and relationship between class of drug and symptoms of OSD has not been studied.

CONCLUSION

The study concludes that prevalence of OSD is higher in patients using anti-glaucoma medications for long term. The prevalence is even much higher with increasing numbers of medications. Preservative (BAK) has dose dependent toxic effects, compromising tear film stability leading to conjunctival and corneal damage. OSD in glaucoma patients causes decreased drug compliance resulting in poor IOP control, thus leading to progression of disease. To prevent the above symptoms of OSD, use of preservative free drops or drops with less toxic preservatives like SOC, Purite, Sofzia must be sought for. The patient who presented early or those not controlled on single medication, in them Selective Laser Trabeculoplasty (SLT) may be tried, which may prevent the onset of ocular surface damage in patients and help in preserving their quality of life.

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