

Ocular surface disease among glaucoma patients in Ibadan, South-West Nigeria

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ABSTRACT

Objective: To study the frequency and severity of ocular surface disease among glaucoma patients attending the Eye Clinic of the University College Hospital, Ibadan, Nigeria.

Methods: A hospital-based, cross sectional study was carried out at the Eye Clinic of the University College Hospital, Ibadan. After a detailed ocular examination, each respondent completed an Ocular Surface Disease Index (OSDI) questionnaire and performed central visual field assessment. Participants were analyzed for the effect of anti-glaucoma topical medications (all BAK-preserved) and glaucoma severity on ocular surface disease.

Results: A total of 122 consecutive glaucoma patients were studied. Males accounted for 45.1%. Increasing daily drops of anti-glaucoma medication was significantly associated with increasing side effects such as redness, stinging and peppery sensations ($p < 0.01$). Eighty four patients representing 68.9% had some form of OSD using the OSDI score. The OSDI scores and the number of patients with OSD significantly increased with increasing glaucoma severity ($p < 0.01$).

Conclusion: Ocular surface disease was found to be associated with glaucoma severity and use of BAK-preserved topical anti-glaucoma medications.

Key words: Benzalkonium chloride, Glaucoma, Ibadan, Ocular surface disease

INTRODUCTION

Ocular Surface Disease (OSD) is a multi-factorial disease of the tear film and ocular surface resulting in symptoms of discomfort, visual disturbance and tear-film instability with potential damage to the ocular surface¹. The International Dry Eye Workshop of 2007¹ also defined it as a multi-factorial ocular condition that results from inadequate tear film production and/or increased tear evaporation, and may involve tear film degradation as well as damage to the ocular surface. It is accompanied with increased osmolarity of the tear film and inflammation of the ocular surface and affects a significant percentage of the population, especially those older than 40 years^{1,2}. It can affect any race, is more common in women, and is one of the most frequent reasons for seeking eye care²⁻⁴. Several factors influence the prevalence of OSD, such as age and race. In addition, OSD is associated often with other ocular diseases, such as meibomian gland dysfunction and blepharitis^{1,5}.

Glaucoma patients are presumably at a higher risk for developing OSD, as both glaucoma and OSD occur more commonly in older people⁶⁻¹⁰. Ocular surface disease occurring in glaucoma patients is however, thought to be multi-factorial and presence of additional anterior segment ocular disorders such as allergy, blepharitis, dry eye, or eyelid anatomical abnormalities may

further contribute to the onset of OSD¹¹. Furthermore, glaucoma patients are usually treated with preservative-containing Intraocular Pressure (IOP) lowering eye drops that may contribute to OSD⁸⁻¹³. A deleterious effect of Benzalkonium Chloride (BAK) on the ocular surface has been demonstrated both *in vitro* and *in vivo* in both animals and humans¹³⁻¹⁶. Benzalkonium chloride, also known as alkyl dimethyl benzyl ammonium chloride is a cationic surface acting agent and has three main categories of use (a biocide, a cationic surfactant and, a phase transfer agent in chemical industry). Its application is wide and includes its use as preservatives in pharmaceuticals and personal care products such as eye, ear and nasal drops. Preservatives have detergent effect on the lipid layer of the tear film and can decrease the density of goblet cells in the conjunctival epithelium¹³⁻¹⁵. These actions results in reduction of the stability of the pre-corneal tear film, compromising its ability to provide protection and trophic factors to the cornea^{13,15,16}.

MATERIALS AND METHODS

This was a hospital-based cross sectional study among glaucoma patients. Consecutive patients aged 40 years and above seen at the Eye Clinic of the University College Hospital Ibadan, south-west Nigeria between October 2012 and December 2012 were recruited into the study.

Informed written consent was taken from all participants. The protocol was approved by the Institute for Medical Research and Training (IMRAT) of the University of Ibadan.

Eligibility criteria for participants: Patients with Primary Open-angle Glaucoma (POAG) already on medical treatment who were at least 40 years of age were eligible for the study. The following patients were excluded: patients with history of ocular surgery or trauma; any ocular laser surgery within the last six months; patients with punctal occlusion or cautery; history of blepharitis in the previous one year; use of topical ocular lubricating agents, tears substitute, or medications for other ocular conditions in the last two months; history of other ocular inflammatory conditions (e.g., herpes simplex viral keratitis). The presence of the following ocular findings were excluded: non-glaucomatous ocular conditions affecting visual function (e.g. cataract, retinal pathology, non-glaucomatous optic neuropathy); and patients with conditions that could be responsible for glaucomatous visual field defects such as pigmentary glaucoma, pseudoexfoliation syndrome (secondary glaucoma) and angle closure glaucoma. All patients with severe visual loss (from glaucoma) preventing them from performing the central visual field with their best correction on were excluded. Symptomatic or uncontrolled systemic diseases affecting visual function such as diabetes mellitus; suspected or diagnosed systemic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus or scleroderma, Sjogren's syndrome; patients with cognitive and hearing impairment, mobility impairment such as Parkinson disease were all excluded.

Primary open angle glaucoma was defined as the presence of glaucomatous optic neuropathy in at least one eye, corresponding visual field changes and gonioscopically open anterior chamber angle and no identifiable secondary cause for the glaucoma. Intraocular pressure was not considered in the criteria for diagnosis in this study, as could be high-tension or normal tension glaucoma¹⁷. The glaucoma severity was classified into mild ($MD \leq 6dB$), moderate $MD -6$ to $\leq 12dB$) and severe ($MD \geq 12dB$) glaucoma using the 'Hodapp, Parrish and Anderson's Classification.

All participants were screened using the Ocular Surface Disease Index (OSDI) questionnaire. This is a self-administered, validated instrument for assessing the presence and severity of OSD symptoms¹⁸. The OSDI questionnaire includes 12 questions about the participant's past week experience with ocular symptoms, vision-related functioning and environmental triggers. Response options for each question were "all of the time" (score=4), "most of the time" (score=3), "half of the time" (score=2), "some of the time" (score=1), and "none of the time" (score=0). Questions about vision-related functioning or environmental triggers could also be answered with "not applicable" aside the listed options of scores of zero to four. In such situations, that

question was not factored into the final score calculation. The following vision related questions of the OSDI questionnaire were modified to sooth local relevance; 'driving at night': questions asked were disturbances in vision noticed while walking at night or sitting in the front seat of the tricycle and the effect of the headlamp of an oncoming vehicle. 'Computer/ATM': alternative question was effect of the phone screen on their eyes.

The total OSDI score was then calculated for each patient as illustrated below.

$$\text{OSDI score} = \frac{(\text{sum of scores for all questions answered}) \times 25}{\text{Total number of questions answered}}$$

The final total score ranges from 0 to 100. The OSDI scores classified as ≤ 12 = normal, 13 – 22 = mild OSD, 23 – 32 = moderate OSD, and ≥ 33 = severe OSD.

The current anti-glaucoma medication for each patient was recorded including the number, types and frequency of instillation. Combination medications were treated as one product when analyzing the total number of topical medications applied per day. Also each patient was asked for the presence or absence of side effects noticed with drug use and to list such symptoms.

Statistical analysis: Statistical analyses were conducted using Statistical Package for Social Sciences (SPSS, Inc, Chicago, Illinois, USA) for Windows (Version 17.0; Microsoft Corporation, Redmond, Washington, USA). Categorical variables such as visual acuity in the better eye, number of topical medications used, number of daily ocular drops of medication applied, demographic characteristics were assessed by Chi-square test with $\alpha = 0.05$ and continuous variables such as visual field severity (MD), OSDI score were assessed using a two-sample *t*-test with two-sided $\alpha = 0.05$.

RESULTS

A total of 122 consecutive patients with POAG who met the inclusion criteria were recruited over an eight weeks period. The mean age of the patients was 59.02 (± 10.08) years and 51.6% were below 60 years of age, with a range of 40 to 85 years. Fifty five (45.1%) of the patients were males and Table 1 shows the sociodemographic spread of the patients. The average follow-up clinic visit of the patients in a year was 3.7, ranging from 2 – 6 visits per year. Twenty seven (22.1%) of the patients were hypertensive. Table 1 shows the sociodemographic spread of the patients.

Presenting Visual Acuity (VA) better than 20/40 in the better eye was seen in 99 (81.1%) of the patients while 8 (6.6%) patients presented with VA less than 20/200 in the better eye but with correction all had vision greater than 20/100. The mean IOP was 19.84 (± 6.72) mmHg. The mean central visual field Mean Deviation (MD) was 9.04 (± 6.94). The mean mild, moderate and severe glaucoma MD were 3.98 (± 1.07), 7.04 (± 2.62) and 20.66 (± 6.43) respectively and the difference was statistically significant ($p < 0.01$).

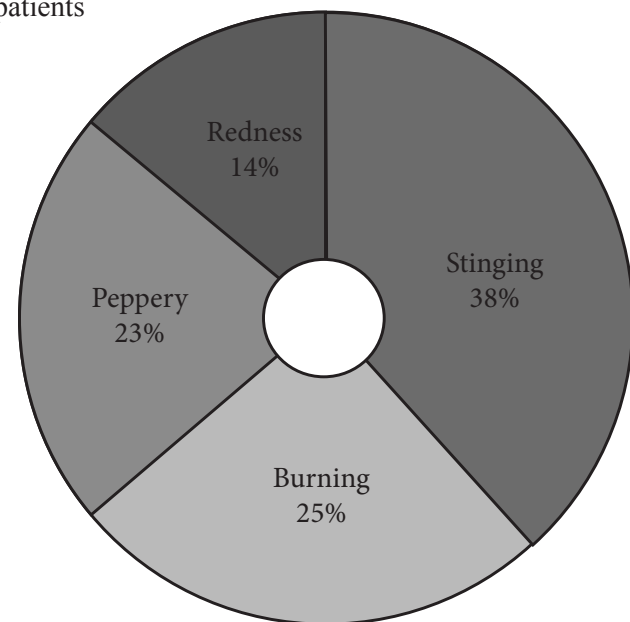
Eighty four (68.9%) patients had Ocular Surface Disease (OSD) in at least one eye using the Ocular Surface Disease index (OSDI) score.

Table 1: Sociodemographic characteristics of the participants

Variable	Frequency	(%)
Age groups (years)		
<60	63	51.6
≥60	59	48.4
Total	122	100
Gender		
Male	55	45.1
Female	67	54.9
Total	122	100
Marital status		
Single/Widowed	15	12.3
Married	107	87.7
Total	122	100
Occupational status		
Unemployed	2	1.6
Unskilled/Semiskilled	40	32.8
Skilled/Professional	55	45.1
Retired	25	20.5
Total	122	100

Forty four patients (36.1%) reported side effects from applied eye drops. These side effects were stinging, burning, peppery sensations and redness of the eyes as shown in Figure 1.

Figure 1: Side effects of medications as reported by the patients



There was a statistically significant association between increasing number of topical daily medication and the presence of side effects. However, there was no significant association between duration on medications and side effects. This is depicted in Table 2.

Table 2: Topical medications and side effects in 122 patients

Number of drops/day	Patients with side effects No. (%)	Patients without side effect No. (%)	p value
1	3 (13.64)	19 (86.36)	<0.01
2	5 (26.32)	14 (73.68)	
3	28 (38.36)	45 (61.64)	
5	6 (100)	0 (100)	
6	2 (100)	0 (100)	
Duration on medication			0.10
6 months – 1 year	10 (31.25)	22 (68.75)	
>1 year – 2 years	4 (19.05)	17 (80.95)	
>2 years	30 (43.48)	39 (56.52)	
Total	44 (36.1)	78 (63.9)	

Table 3 shows the relative frequency of the various severity of the OSD among the patients using the OSDI score in the patients

Table 3: Frequency of ocular surface disease severity using the OSDI score

Ocular surface disease (OSD)	Frequency	(%)
Normal	38	31.1
Mild	38	31.1
Moderate	31	25.5
Severe	15	12.3
Total	122	100

OSDI=Ocular Surface Disease Index Score

The association between evaluated factors such as gender and age on the OSDI score is shown in Table 4. Age stratified into < 60 years and ≥ 60 years resulted in OSDI score mean of 19.08 and 20.07 respectively. This increase with age was not statistically significant ($p = 0.73$).

Table 4: Effect of evaluated factors on OSDI score

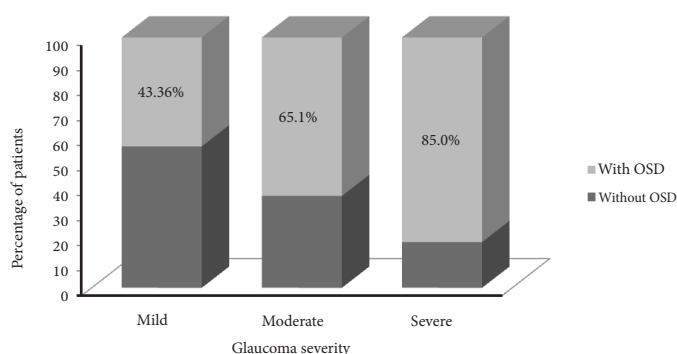
Evaluated factors	Gender		P value
	Male	Female	
No. of glaucoma patients	55	67	
No. of patients with OSD (%)	37 (67.27)	47 (70.15)	
OSDI Score, Mean (SD)	19.01 (15.23)	16.53 (16.41)	0.35
Age (years)	<60	≥60	
No of glaucoma patients	63	59	
No of patients with OSD (%)	43 (68.25)	41 (69.49)	
OSDI Score, Mean (SD)	16.98 (16.11)	18.91 (15.31)	0.73
Topical glaucoma medications*	On medications		
No. of glaucoma patients	122		
No. of patients with OSD (%)	84 (68.90)		
OSDI Score, Mean (SD)	18.30 (16.10)		

No. = number, OSDI score= ocular surface disease index score, *All containing Benzalkonium chloride

Seventeen patients out of 39 with mild glaucoma had OSD (mean OSDI score = 10.89), 28 patients out of the 43 with moderate glaucoma had OSD (mean OSDI score = 14.53) and 34 of the 40 patients with severe glaucoma had OSD (mean OSDI score = 27.16). The frequency of OSD with glaucoma severity is depicted in Figure 2. There was a significant association between glaucoma severity and OSD occurrence ($p < 0.01$).

On stratifying glaucoma severity into mild, moderate and severe groups, there was a statistically significant association between the stratified age groups and moderate glaucoma group ($p < 0.01$) as depicted in Figure 2.

Figure 2: Glaucoma severity and ocular surface disease



DISCUSSION

In this study about 69% of the patients had OSD using the OSDI score. This high frequency is similar to studies by Leung *et al*⁶ and Garcia-Feijo *et al*¹⁹ who reported a frequency of 59% and Barisic *et al*²⁰ who had 75%. Skalicky *et al*¹⁷ however, reported a slightly lower frequency of 47.6% which is still quite high prevalence rate. Majority of the patients had mild to moderate OSD and only 12.3% of the total patients had severe OSD. This is in contrast to previous studies^{6,17,19} listed above where the occurrence of severe OSD among glaucoma patients ranged between 20.3%¹⁹ to 47%¹⁷. The reason for this difference is not clear, but race/geography may be a factor. Garcia-Feijo *et al*¹⁹ in their study reported a notable difference in the mean (SD) OSDI scores among the different race/ethnic groups. They reported that in the Latino or mixed race/ethnicity had the highest mean OSDI score of 29²¹ units, indicating moderate OSD. This score was significantly higher than the score for the Asian patients (mean [SD] = 17¹⁷ units; $P = 0.0001$) and the Caucasian patients (mean [SD] = 20¹⁷ units; $P = 0.009$), both indicating mild OSD. There was an increase in the mean score of OSD in the older age group in our study. Though this difference was not statistically significant, but after stratifying into glaucoma severity it was found to be significant among those with moderate glaucoma.

Preservative-containing topical medications (especially BAK) had been reported to hasten drying and thus the reduction in the stability of the pre-corneal tear film thereby reducing its ability to provide protection to the cornea^{12,14}. Preservatives act as detergent on the lipid layer of the tear film, compromising its protective ability and decrease the goblet cell density, mucus granules and reticular sheets in the conjunctiva epithelium¹⁵. These mechanisms possibly explain the high level of OSD reported in this study.

Increased frequency of side effects with increasing number of daily anti-glaucoma topical medication was seen in this study. This may further explain the higher frequency of OSD in our patients. This is because multiple medications are indicative of more preservatives (BAK) the eye is exposed to daily and this can destabilize the ocular surface^{14,15,21}. There was no significant association between the duration patients had been on medication and increased side effects in this study. The study by Barisic *et al*²⁰ where they had patients on topical medications of over ten years, however reported a statistically significant ($p=0.042$) increase in the mean OSDI score with duration in years on medications. It is thus possible that duration on topical medications in our study may not have been long enough.

Previous studies^{6,17} have shown a strong correlation between the use of BAK-containing topical medications and severe OSD. Skalicky *et al*¹⁷ reported a significant risk for OSD in glaucoma patients on ≥3 drops and also in those on ≥4 drops daily of BAK-containing anti-glaucoma medications on univariate analysis. This significance was maintained in those on ≥3 daily drops

following multivariate regression analysis. In their study they also noted that increasing number of glaucoma medication was associated with more advanced glaucoma and suggested that this association may explain the observation they noted of increasing daily drops and increase risk of OSD. Leung *et al*⁶ reported that after adjusting for age and sex on multivariate regression analysis, each additional BAK-containing eye drop was associated with approximately two times higher odds of showing abnormal results on the lissamine green staining test. Katz *et al*²¹ in a multicenter controlled trial reported that switching from BAK-preserved latanoprost 0.005% to BAK-free travoprost 0.004% yielded significant improvements in symptoms of OSD in patients with glaucoma or ocular hypertension. This further reveals the adverse effect of preservative containing topical anti-glaucoma on the ocular surface health. This is so important in developing countries where most of the available drops contain BAK, preservative-free drops being much more expensive, and problems of storage due to poor power supply, thus not readily available.

The mean OSDI score was seen to significantly increase with increasing severity of glaucoma. This may not be unconnected to the increasing frequency and number of anti-glaucoma medications used with increasing glaucoma severity. A similar finding was reported by Skalicky *et al*¹⁷, who noted a significant relationship in their patients after age stratification. This suggests that the more severe the glaucoma the more the OSD in patients and this may adversely affect their visual function, hence the need to identify and treat the OSD component in glaucoma patients in order to give them the best functional visual outcome that is possible.

A limitation in our study is that we did not evaluate the relationship between the type of topical medication used and the OSDI.

In conclusion, OSD is common in patients with glaucoma. The frequency increased with increasing glaucoma severity and worse with increasing total daily BAK- containing anti-glaucoma medications. The adverse effect from these agents can negatively impact on compliance, which may result in the reduction in the optimum benefit expected from their use.

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