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To Evaluate Dry Eye Parameters in Patients of Primary Open Angle Glaucoma

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Abstract:
Background: *Open angle glaucoma and dry eye are two different pathologies exhibiting diverse ocular signs and symptoms but both have chronic progressive course requiring lifelong management. Some factors involved in pathogenesis of glaucoma such as change in level of proinflammatory cytokines in tear fluid and serum of patients with glaucoma and role of IL1 and IL6, oxidative processes and immunological mechanisms are being implicated in dry eye also. Hence this study was initiated to further explore similarities in pathogenesis of POAG and Dry Eye Disease.*
Aim : *To evaluate dry eye parameters in cases of primary open angle glaucoma and compare the incidence of dry eye in newly diagnosed cases of POAG and already diagnosed cases of POAG instilling ocular hypotensives.*
Material and Methods : 150 patients were divided in 3 groups. 1st group included 50 newly diagnosed patients not instilling any antiglaucoma medication. 2nd group included 50 patients of POAG instilling ocular hypotensives. 3rd group included 50 non glaucomatous control patients.
Results: *Dry eye disease was found in 37 (74%) patients of newly diagnosed POAG who were not on antiglaucoma medication and 41 (81%) cases of POAG on antiglaucoma medication.*
Conclusion: *Dry eye is pre existent in patients of glaucoma which gets exacerbated on using antiglaucoma medication. Therefore one should be careful while prescribing ocular hypotensives in cases of glaucoma as they already suffer from dry eyes.*
Keywords: *primary open angle glaucoma, dry eye, ocular surface disease, antiglaucoma medications.*

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I. Introduction

Dry eye disease (DED) and glaucoma though are two fundamentally different diseases, their similarities are more numerous than one might expect. Both the diseases are chronic, progressive, age-related and require diligent medication compliance from patients. Complete cure of either disease is unlikely, thus subjecting patients to a lifelong treatment and compromised quality of life.

Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of tear film and accompanied by ocular symptoms in which tear film instability, hyperosmolarity and ocular surface inflammation along with neurosensory abnormalities play etiological roles. The common consequence of ocular surface disease is dysfunction of the ocular tear film and/or the integrity of the ocular surface. These changes may result in a wide range of ophthalmic symptoms and signs including discomfort, burning, fatigue, fluctuating visual acuity, ulceration, and scarring of the ocular surface.

Studies have shown that approximately 15% of the general elderly population experiences some level of OSD(ocular surface disease).1 In many other studies it has been reported that patients with glaucoma and ocular hypertension suffer OSD at a higher prevalence rate than the patients without these ocular conditions.2 It has been reported to occur in 48% to 59% of patients with medically treated glaucoma3

whereas the incidence of dry eye disease in general indian population is 18.4%.4

Glaucoma is a group of chronic degenerative diseases of optic nerve head characterized by the loss of retinal nerve fiber tissues, presenting clinically as visual field defect and loss of the neuroretinal rim of the optic nerve head, termed glaucomatous optic neuropathy (GON) with raised Intra Ocular Pressure (IOP) as the most common modifiable factor. It is the second leading cause of global blindness, and the leading cause of irreversible visual loss in the adult population worldwide, estimated to have affected 60.5 million people in 2010 and projected to affect 79.6 million by 2020.(5,6)

The medical management includes intraocular pressure lowering drugs which contains preservatives meant to prevent contamination. Repeated administration of intraocular hypotensive eye drops containg preservatives can cause adverse effects to ocular surface thus triggering OSD.

However , the raised IOP alone cannot explain the disease since 30% of glaucoma patients never develop raised IOP(normal pressure glaucoma) and in any case almost 10% of indivituals over 40 have raised IOP (ocular hypertension) , of whom, only a small proportion develop glaucoma. For this reason , other factors are also suggested as being involved in pathogenesis of glaucoma such as increased nitric oxide concentrations , oxidative processes and immunological mechanisms.7 Similar pathological processes are being implicated in dry eye also where tear defects initiate inflammation and activation of innate and adaptive immune responses.8. Therefore it remains unclear whether the development of dry eye disease in glaucoma patients is related to prolonged use of antihypertensive drops or pathological changes associated with glaucoma itself.

The purpose of this study was to evaluate dry eye parameters in patients of primary open angle glaucoma and to compare the incidence of dry eye in newly diagnosed cases of primary open angle glaucoma not yet instilling antiglaucoma medication with already diagnosed cases of POAG on treatment.

II. Materials and Methods

Study Design

This was a Prospective Observational Comparative Study to evaluate dry eye parameters in primary open angle glaucoma cases and compare incidence of dry eye in newly diagnosed cases of primary open angle glaucoma not yet instilling antiglaucoma medication and in already diagnosed cases of POAG instilling ocular hyoptensive eye drops.

The study was conducted in department of Ophthalmology, Dr. Baba Saheb Ambedkar Hospital, Rohini, New Delhi, India. It is a tertiary care hospital catering both urban and rural population.

Subjects

150 cases were studied among which 50 patients were newly diagnosed cases of POAG who were not instilling topical hypotensive drugs , 50 diagnosed cases of POAG instilling topical hypotensive drugs and 50 non glaucomatous patients as control.

Group A : Newly diagnosed cases of POAG who were not instilling topical hypotensives.

Group B : Diagnosed cases of POAG were are instilling topical hypotensives.

Group C : Non glaucomatous patients.

Patients were excluded if they had conditions that could adversely affect tear film stability, such as connective tissue disorder, thyroid eye disease, history of chemotherapy or radiotherapy, history of ocular surgery, history of chronic contact lens wear or allergy to any of the components and the agents used in this study, for example, sodium fluorescein.

Clinical Examination

A. Evaluation of newly diagnosed cases of POAG was done in following order :

Schiotz Tonometery

Intra ocular pressure was measured in both eyes using schiotz tonometer after instilling topical anaesthetic with patient in supine position. Diurnal variation of IOP was done in all patients. Diurnal variation of 8 mmHg or more and IOP> 21mmHg was taken as significant.

Direct Ophthalmoscopy

Fundus examination was done with direct ophthalmoscope. Glaucomatous changes in optic disc were looked for which included :

1. Increased Cup-disc ratio (Difference of 0.2 in both eyes)
2. Nasal displacement of the vessels
3. Baring of the circumlinear vessels
4. Disc pallor
5. Thinning of neuro retinal rim
6. Bayonetting of vessels
7. Disc hemorrhages
8. Laminar dot sign

Gonioscopy

Gonioscopy was done so as to take up only open angle cases in the study. It was done using 2 mirror gonioscopic lens.

Visual field testing

It was done using Humphreyfield analyser. The patient is instructed to maintain fixation on the central target and is given a buzzer to press only on seeing a light stimulus.The eye not being tested is patched and the room lights are dimmed prior to commencement of the test. The Analyser projects a series of white light stimuli of varying intensities (brightness), throughout a uniformly illuminated bowl.This test assesses the retinal ability to detect a stimulus at specific points within the visual field. This is called retinal sensitivity and is recorded in 'decibels' (dB).

The Analyser utilised the Swedish Interactive Thresholding Algorithm (SITA. Results were then compared against an age-matched database which highlights unusual and suspicious vision loss, potentially caused by pathology.

B. Ocular surface assessment was done in following order :

Tear film break up time measurement (TBUT)

TBUT test was performed by applying fluorescein solution onto the inferior palpebral conjunctiva. After intial blinking,the tear film was examined using a slit lamp with cobalt blue light. The interval between the last blink and the appearance of a first hypofluorescent spot or streak was recorded as the TBUT.

Values <10 seconds were taken as abnormal.9

Schirmer's 1 test

The Schirmer test was performed using precalibrated filter strip which was placed between the lower fornix and lower eyelid margin and left in place for 5 min. The strip was removed after 5 min and the amount of wetting was recorded. Wetting of ≤10 mm was taken as abnormal.9

Subjective symptoms of Dry Eye were assessed in terms of ocular discomfort, foreign body sensation, painful or sore eyes, photophobia, blurred or poor vision and were recorded as normal, mild, moderate and severe symptoms.

Statistical Analysis

Statistical analysis was performed as :

1. Quantitative variables were compared using ANOVA/Kruskal Wallis test between three groups and Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed.) between the two groups.
2. Qualitative variables were compared using Chi-Square test /Fisher's exact test.

A p value of <0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

III. Results

A total 150 patients participated in the study. There were no statistically significant differences between the glaucoma and control groups in terms of

age, sex, or ethnicity. The results of the TBUT test are shown in table 1and Figure 1.

The percentage with abnormal TBUT was larger in the group B (86%),that is, patients who have been already using ocular hypotensives as compared to newly diagnosed cases of POAG in group A (82%) who were not instilling ocular hypotensives, however it was not statistically significant (p1= 0.785)

In the control group (group C) 62% patients had TBUT less than 10 sec as compared to group B (86% p2= 0.045) and group A(82% p3 = 0.012) which was significant statistically.

Table 1. Results of TBUT in groups A,B and C.

TBUT	**GROUP A (n=50)**		**GROUP B (n=50)**		**GROUP C (n=50)**				
	n	%	N	%	N	%	p1	p2	p3
<10sec	41	82	43	86	31	62	0.785	0.045	0.012
>10sec	09	18	7	14	19	38			

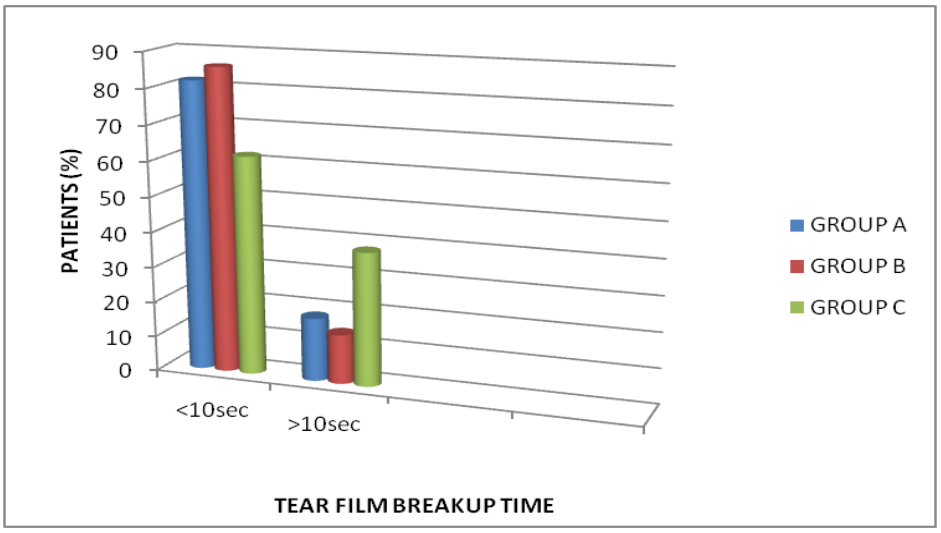

Figure 1. Percentage distribution in Group A, B and C for TBUT.

The results of shirmer's 1 test are shown in table 2 and Figure 2.In shirmer 1 test a decrease in total tear production was detected in 88% of patients in group B and in 80% of patients in group A. Differences in the results of patients of group A and group B were statistically unreliable (p> 0.05). In the control group C, the decrease in total tear production was recorded in 42% patients which was significantly less by 38% when compared with group A (p2= 0.0002)and by 46% less when compared with group B which was also significant (p3= <.0001).

Table 2. Results of Shirmer's 1 test in Group A,B and C.

SHIRMER 1	**GROUP A (n=50)**		**GROUP B (n=50)**		**GROUP C (n=50)**				
	N	%	N	%	n	%	p1	p2	p3
<10mm	40	80	44	88	21	42	0.41	.0002	<.0001
>10mm	10	20	6	12	29	58			

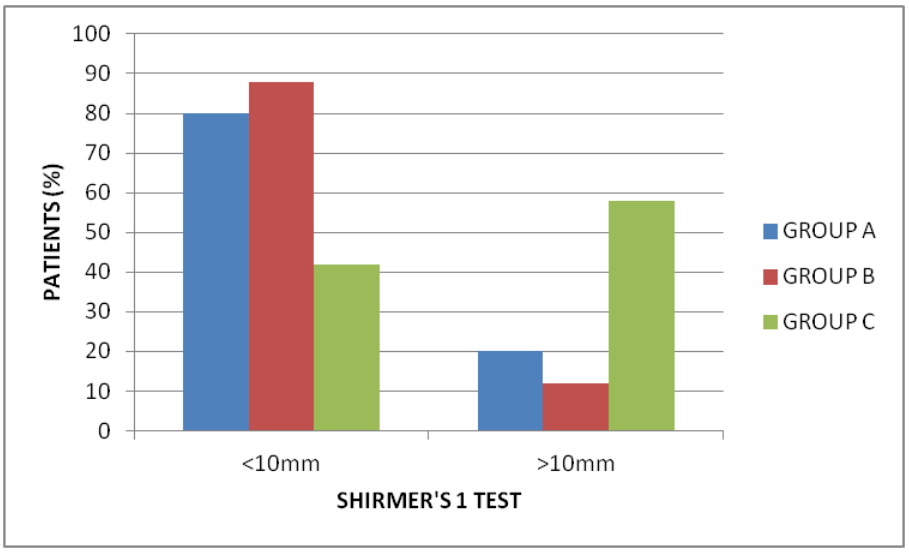

Figure 2. Percentage distribution in Group A,B and C for Shirmer's 1 test.

The Dry Eye symptoms (Table 3.) as recorded in group B showed clear cut increase when compared with group A and controls. Similar but milder forms of OSD symptoms were recorded even in group A as compared with controls. The percentage of patients in each category are shown in Figure 3.

Table 3. Comparison of Dry Eye symptoms in Group A,B and C.

SYMPTOMS	GROUP A (N=50)	GROUP B (N=50)	GROUP C(N=50)	P 1	p2	p3
NORMAL	15	6	18	0.049	0.671	0.010
MILD	13	11	13	0.815	0.820	0.815
MODERATE	12	14	10	0.820	0.809	0.482
SEVERE	10	19	9	0.078	0.100	0.045

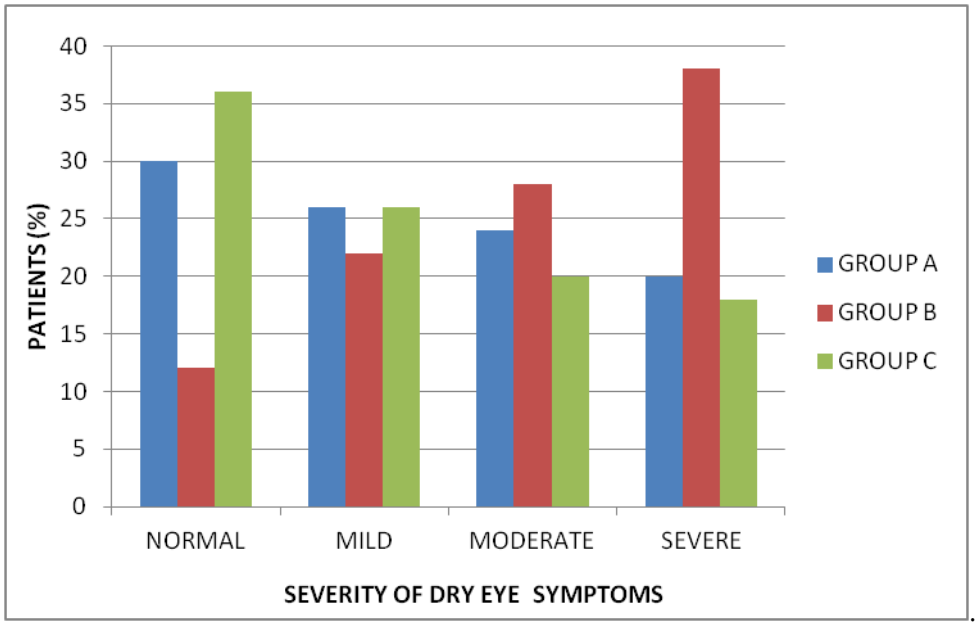

Figure 3. Percentage patient distribution for severity of Dry Eye symptoms.

IV. Discussion

On the basis of the results of the conducted tests in the study of tear production and subjective signs of dry eye, it was found that ocular surface disease was present in 37 (74%) cases in patients with POAG before the initiation of hypotensive drop treatment and in 41 (82%) cases in patients with POAG on treatment with hypotensive drops.(p= 0.469).

As evident from the results of this study, dry eye is more prevalent in glaucoma cases as compared to non glaucomatous patients. Between the two groups with glaucoma (Group A : newly diagnosed cases not on antiglaucoma drops and Group B: diagnosed cases of POAG on antiglaucoma drops) , there was no statistically significant difference in the number dry eye patients.

It is believed that dry eye in patients with POAG instilling ocular hypotensives develops because of the preservative benzalkonium hydrochloride, which, according to the literature, adversely affects the lipid layer and has a direct toxic effect on the secretory and non-secretory epitheliocytes of the conjunctiva (10-12)

that explains the worsening of dry eye symptoms on using antiglaucoma medication in these cases .

As seen in this study, dry eyes develop in patients of POAG not using ocular hypotensives also , therefore causes other than preservatives are also responsible for dry eyes in these cases. Some causes of dry eyes include atherosclerosis and arterial hypertension13, leading to a violation of the microcirculation of the bulbar conjunctiva (ischemic factor), hemodynamic disturbances in the orbital artery and its terminal branches , disruption of the trophic and regenerative processes of the eye,increased frequency of concomitant diseases of the ocular surface,leading to a disruption in the production of the lipid component, which is typical pathological change not only for dry eyes, but also in glaucoma.

Another possible cause is chronic infectious14 and inflammatory process 15, which also Occurs with POAG and is confirmed by reports of changes in the level of proinflammatory cytokines in tear fluid and serum in patients with glaucoma (16-18). The roles of IL6, IL1 and their soluble receptors sIL-6R and sIL-1R,TNF,TGFb1 and more recently IL-17 in dry eye disease pathogenesis are confirmed in some researches.19 Eye pain in dry eye disease is, also, correlated with IL-6 and IL-8 levels.20 Enhanced production of TNF-a and IL-6 in optic nerve head injury after enhancing intraocular pressure is a pathological condition which is responsible for nerve damage.

Autoantibodies to heat shock proteins (HSP27, HSP60)(21-22) have been found in the blood of glaucoma patients leading to the hypothesis of role played by autoimmunity in pathology of glaucoma and the dry eye thus creating a connecting link between the two diseases.

Thus, Primary Open Angle Glaucoma cases have an increased manifestation of dry eyes, even before the initiation of hypotensive eye drops and it may further make ocular surface disease more pronounced after local drops are started. These undesirable effects of OSD may lead to treatment discontinuation and reduced quality of life in patients with glaucoma. Animal studies and in vivo experiments have demonstrated various adverse effects of preservatives (like benalkonium chloride). Hence preservatives free therapies are becoming available, but are not always feasible alternative. So one needs to carefully pick up changes due to Dry Eye Disease at the earliest , in all cases of glaucoma so as to avoid ocular damage related to Dry Eye Disease**.**

V. Conclusion

The newly diagnosed cases of POAG already have dry eye to some extent which gets exacerbated by use of anti glaucoma medications containing preservatives. As both the diseases are age related and require regular use of medication and active compliance of patient, it is important to carefully prescribe antiglaucoma medication in cases of primary open angle glaucoma to avoid OSD symptoms. If OSD symptoms are present, topical glaucoma treatment should be adjusted by decreasing the amount of drops instilled daily or using preservative free medication and lubricants if necessary. Awareness of the presence and importance of OSD, will in turn improve patient's adherence and complications, ultimately improving long term preservation of vision.

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