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Study of changes in tear film in patients Using topical anti glaucoma medication in rural teaching hospital of Bihar

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Abstract:
Background*: Topical agents when used over a long period are likely to cause ocular surface changes like decrease in tear secretion, tear break up time changes and epithelial changes of conjunctiva and cornea. The aim of this study is to assess the integrity of tear film by simple tests to quantify the function, in patients using topical anti glaucoma medication and to compare them with normal subjects.*
Materials and Methods*: A total of 60 patients (120 eyes) were evaluated in our cross sectional analytical study. 30 healthy patients of 20-55 years age group acted as controls and 30 patients on topical glaucoma medication for more than six months were the glaucoma group. Apart from the routine examination, the specific tests done were Schirmers test, TBUT, and Rose Bengal staining quantified by Oxford scheme.*
Results: *Abnormal Schirmers test without anesthesia was noted in 63% of the glaucoma group and 6% of the normal ($p<0.05$). Abnormal Schirmers test with anesthesia was seen in 62% of glaucoma group and 3.3% of normal ($p<0.05$). Rose Bengal test was normal in 47% of the glaucoma group, whereas 97% of the normal subjects. The frequency of dry eye was 70% as per left eye tear breakup time test in glaucoma group. Corrected visual acuity was higher in glaucoma group as compared to normal study population. There was no significant correlation of number of drops instilled with the tear film tests.*
Conclusion: *Our study concluded that chronic use of topical medication for glaucoma impairs the ocular surface and the tear film functions to a varying extent. It depends on multiple factors as the cause could be the medication itself or the preservative or both.*
Key Word*: tear film, ocular surface, topical agents, glaucoma therapy*

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I. Introduction

The tear film is a complex and dynamic unit, well balanced by different components, and is important for maintaining the health of the ocular surface. The quality of optical image is also affected by changes in the tear film and this can be altered by many conditions that disturb the homeostasis provided by the neuroimmunoendocrine network (1). An inadequate tear volume or function can cause an unstable tear film and ocular surface disease. 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 (2). Glaucoma affects 2–3% of people over the age of 40 years, but up to 50% may be undiagnosed. It is the second leading cause of blindness in the world. Worldwide, glaucoma is the second most common cause of blindness (3). Patients with glaucoma require long term treatment with topical agents to lower the intraocular pressure. The topical medication include alpha agonists, beta blockers, prostaglandin analogues, carbonic anhydrase inhibitors. These agents when used over a long period are likely to cause ocular surface changes like decrease in tear secretion, tear break up time changes and epithelial changes in the cornea and conjunctiva (4). The aim of this study was to assess the integrity of tear film by Schirmer's test without and with anaesthesia, Tear Breakup Time and Rose Bengal staining in patients using topical anti glaucoma medication and to compare them with normal subjects.

II. Material And Methods

This prospective observational cross sectional study was carried out on patients of Department of Ophthalmology at Katihar Medical College, Katihar, Bihar for 1.5 year after the approval from ethical committee. A total 60 adult subjects (both male and females) of aged between 20 and 55, years were for in this study.
Study Design: Prospective observational cross sectional study.

Study Location: This was a tertiary care teaching hospital based study done in Department of Ophthalmology at Katihar Medical College, Katihar, Bihar.

Study Duration: 18 Months, August 2022- February 2023.
Sample size: 60 patients.
Sample size calculation: Sample size was calculated on the basis of study of Yalvaç IS (5) . In this study the proportion of dry in normal eyes was 33% and in glaucoma patients undergoing medical treatment was 70% with alpha values of 5 and beta values of 20 . Sample size was calculated to be 30 in each group.
n=Z2 (1-a/2) Z(1-B)x z[p1(1-p)+p2(1-p2)]\(p1-p2)2

Subjects & selection method: The study population was drawn from patients who presented to Ophthalmology department at Katihar Medical College, Katihar, Bihar between from August 2022- February 2023. Patients were divided into two groups (each group had 30 patients).
Group A (n=30) Known case of glaucoma
Group B (n=30) Controls without glaucoma excluded by IOP and CCT.

Inclusion criteria:
1. Patients whose age is <20 and> 55 years.
2. Patient who give informed consent.
3. Patients with primary angle-closure glaucoma, ocular hypertension and primary open-angle glaucoma.
4. Patients using one or more topical anti-glaucoma drug as single or combination treatment with one or more an*-glaucoma topical preservatives (timolol 0.5%, brimonidine 0.1%, latanoprost 0.005%).
5. Patients using topical drugs for > 6 months.

Exclusion criteria:
1. Patients who have undergone any Lasik or intraocular surgery.
2. Patients with any conditions known to affect the tear film.
3. Patients with any systemic conditions known to affect the tear film and cornea.
4. Patients with secondary glaucoma.
5. Patients with any other ocular pathology.
6. Patient using any artificial tear therapy.
The individuals was assessed by consultant Ophthalmologist for Dry eyes by enquiring about symptoms of stinging and burning sensations, itching, watering, irritation, due to regular use of topical anti-glaucoma drugs. A written consent was taken from every patient before the test.
Two tests were performed by the ophthalmologist to assess Dry eye syndrome. 1) Basal schirmer's test
2) Tear film breakup time test (TBUT).

Procedure methodology

After assessing the inclusion criteria and obtaining relevant history and tests, the participants were subjected to following tests.
Tear break up time (TBUT): The tear film break-up time assessment was recorded in seconds. First, the tear film was stained by using sterile fluorescein strips. Under a slit lamp with blue filter, the time interval between the appearance of a dark (dry) spot on the cornea after a complete blink was noted. An average of three readings were taken.
Schirmer's test without anaesthesia: Whatman no. 41 filter paper with dimensions 5mm x 35mm was folded and kept in the junction of the lateral one third and the medial two third of the lower fornix of the eye and kept for 5 minutes. The wetting of the strip at the end of 5 minutes was noted by using the scale (in millimetres) on the strip.
Schirmer's test with anaesthesia: It was done similarly, after application of a single drop of topical anaesthetic (prochlorparacaine) and gently removing any excess fluid from the fornix and then readings were noted after 5 minutes.
Rose Bengal staining: Rose Bengal impregnated strip was used to stain the lower fornix, the patient was then asked to blink and the ocular surface was viewed with the cobalt-filtered illumination in slit lamp. The temporal conjunctiva was graded with patient looking nasally, and nasal conjunctiva when patient looks temporally. The grading was noted as per Oxford scheme (36) ranging from grade 0 to 5.

Statistical analysis
Data was analyzed using SPSS version 20 (SPSS Inc., Chicago, IL). Independent *t*-test was used to ascertain the significance of differences between mean values of two continuous variables and confirmed by

nonparametric Mann-Whitney test. Chi-square and Fisher exact tests were performed to test for differences in proportions of categorical variables between two or more groups. The level $P < 0.05$ was considered as the cutoff value or significance.

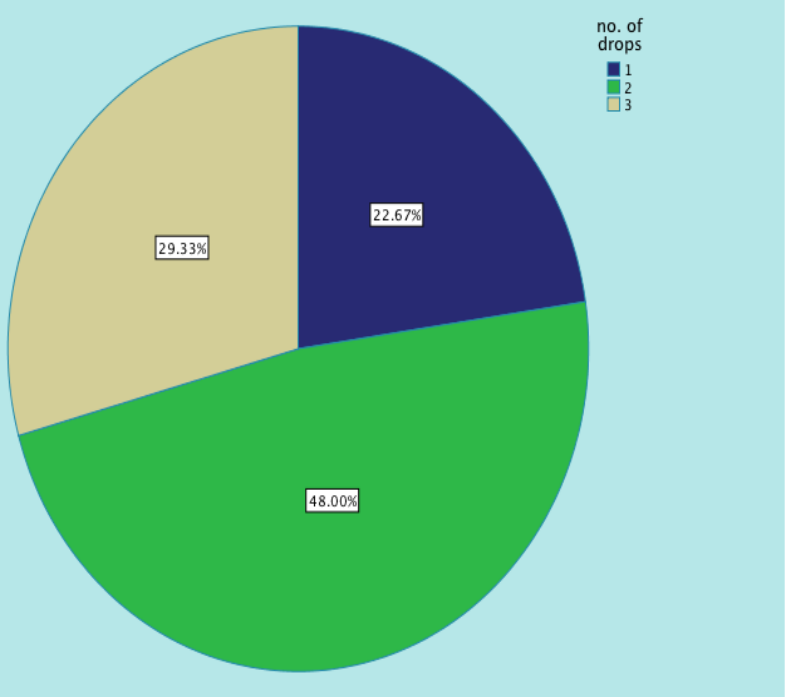
III. Result

The mean age of all the participants in the study was 55.7(±7.69) years. In this study, the mean age of subjects not using any topical medication was 53.7 (±7.05) years and among the glaucoma patients was 55.79 (± 7.32) years. Of the 30 normal subjects the gender distribution was almost equal with 16 males and 14 females (Table 1). Among the glaucoma patients 50% were male and 50% female. Independent T test for comparison between the two groups showed poorer vision among the glaucoma subjects but it was statistically not significant (p value =0.151). The mean value of Schirmers without anaesthesia of right eye in the control group was 22 and 15.8 in the glaucoma group; the mean in the left eye was 22.04 in controls and 15.23 in glaucoma group of patients. There existed a significant correlation between abnormal Schirmer's test (without anaesthesia) in the glaucoma group, with a p value <0.001 as per the independent t test for comparison of means. 93% of the control group showed a normal Schirmers test for right eye as compared to 47% in the glaucoma group. For the left eye, 93% were normal in control group and 40% in the glaucoma group. The Pearson Chi- square test showed a significant correlation for the abnormal Schirmers test in the glaucoma group with a p-value of <0.001. The mean Schirmers of the right eye for the glaucoma patients was 15.3. The mean Schirmers of the left eye for the glaucoma patients was 15.23. The mean value of Schirmers with anaesthesia of right eye in the control group was 18.57 and 11.38 in the glaucoma group; the mean in the left eye was 18.77 in controls and 11.38 in glaucoma group of patients 96% of the control group showed a normal Schirmers test for right eye as compared to 58% in the glaucoma group. For the left eye, 96% were normal in control group and 57% in the glaucoma group. The Pearson Chi-square test showed a significant correlation for the abnormal Schirmers test in the glaucoma group with a p value of <0.001. The mean tear film breakup time of right eyes in the control group of the study was 12.19 and 11.27 in the glaucoma group. The mean TBUT in left eye of control group was 12.2 and that of the glaucoma group being 11.25. The difference between the control and glaucoma was significant at p value <0.05. The right eye breakup time was abnormal in 22% of the controls and 42% of the glaucoma patients. The left eye breakup time was abnormal in 16% of controls and 43% of glaucoma group. The Pearson chi- square test was done and showed significant correlation of abnormal values in glaucoma group (p value <0.001) The mean tear breakup time of the right eye for the glaucoma patients was 11.27 The mean tear breakup time of the left eye for the glaucoma patients was 11.25, The Rose Bengal staining of conjunctiva and cornea graded as per Oxford schema showed grade 1 staining in 17% of glaucoma patients and in 2% of the control group. None of the patients in the study had a grade of 2 or higher. The Pearson Chi-square test showed a significant correlation of higher score in the glaucoma group.

Table no 1 (10 Bold)**:** Distribution of Gender in both study groups

		Group		Total	p-value	95% CI
		Glaucoma	Control			
Sex	F	15	14	29	0.79	0.41-2.34
		50.0%	46.7%	48.3%		
	M	15	16	31		
		50.0%	53.3%	51.7%		
Total		30	30	60		
		100.0%	100.0%	100.0%		

Figure 1: Pie Chart showing the Distribution of number of drugs taken by Glaucoma study group



Most of the patients in our study took 2 drugs for glaucoma control (Figure 1)

Table no2 : Comparison of findings of both side Red Bengal Gram stain in both study groups

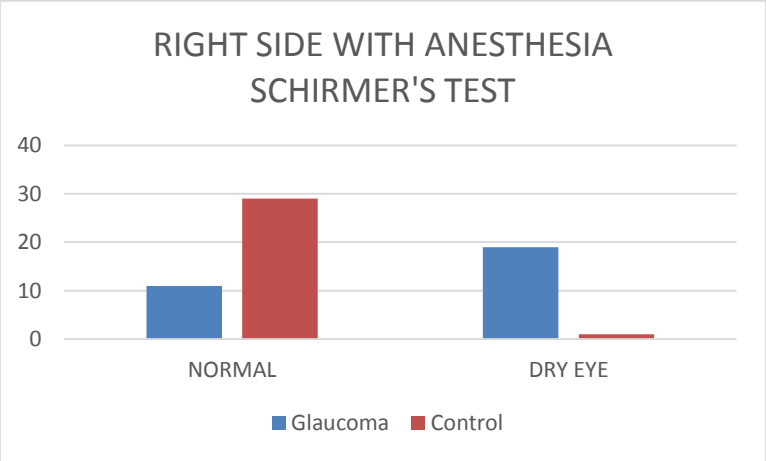
Red Bengal Gram stain		Group		Total	p-value	95% CI
		Glaucoma	Control			
Right eye	Normal	14	29	43	0.00	0.00-0.25
		46.7%	96.7%	71.7%		
	Dry Eye	16	1	17		
		53.3%	3%	28.3%		
Left eye	Normal	13	28	41	0.00	0.01-.27
		43.3%	93.30%	68.3%		
	Dry Eye	17	2	19		
		56.2%	6.7%	31.7%		

53% of the patients in glaucoma group as per Right side Red Bengal Gram stain were found to have dry eye and 43% in left side had normal eye (Table 2).

Table no 3: Comparison of findings of both eye Schirmer's test without anesthesia in both study groups

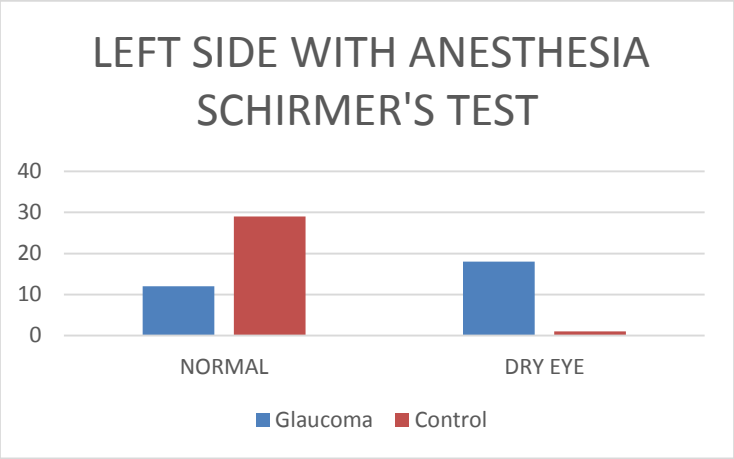
Schirmer's test without anesthesia		Group		Total	p-value	95% CI
		Glaucoma	Control			
Right eye	Normal	14	28	42	0.00	0.013-.311
		46.7%	93.3%	70%		
	Dry Eye	16	2	18		
		53.3%	6.7%	30%		
Left eye	Normal	12	28	40	0.00	0.01-.23
		40%	93.3%	66.7%		
	Dry Eye	18	2	20		
		60%	6.7%	33.3%		

Figure 2: Bar diagram showing Comparison of Right eye Schirmer's test with anesthesia in both study groups



The frequency of dry eye in glaucoma group as per Right eye Schirmer's test with anesthesia was found to be 63% as compared to 3.3% in normal population (Figure 2).

Figure 3: Bar diagram showing Comparison of Left eye Schirmer's test with anesthesia in both study groups



The frequency of dry eye in glaucoma group as per Left eye Schirmer's test with anesthesia was found to be 60% as compared to 3.3% in normal population (Figure 3).

Table no 4: Comparison of findings of both eye tear breakup time test in both study groups

Tear Breakup Time		Group		Total	p-value	95% CI
		Glaucoma	Control			
Right eye	Normal	10	22	32	0.00	0.00-0.23
		33.3%	73.3%	53.3%		
	Dry Eye	19	8	27		
		66.7%	26.7%	45.0%		
Left eye	Normal	9	23	32	0.00	0.00-.34
		30.0%	76.7%	53.3%		
	Dry Eye	21	7	25		
		70.0%	23.3%	41.7%		

IV. Discussion

Although topical antiglaucoma medications are commonly used as the primary treatment for glaucoma, they may result in ocular surface complications in the setting of prolonged and persistent ocular diseases such as glaucoma (6,7). The deleterious impact of preservatives on ocular solutions is a subject of ongoing medical investigation (8,9). Prolonged use of topical medications may result in ocular surface disease, including dry eye syndrome, subconjunctival fibrosis, epithelial apoptosis, and cellular loss. The study cohort comprised individuals aged 20 to 55 years, with a mean age of 55.68±12.43 years and a mean BMI of 25.15±6.32 kg/m2. The study population comprised of 60 cases, out of which 30 (50%)

were male and 30 (50%) were female. Our findings were consistent with the results reported in the study conducted by Kovaevi et al (11). The study comprised of a sample size of 60 patients, with 28 (46%) male and 32 (54%) female participants. The age range of the patients was between 45 to 70 years, with a median age of 54.5 years (11).

Within the scope of this investigation, 36 patients (49.32%) reported experiencing itching and sensations, while 12 patients (14.68%) reported experiencing incontinence and inflammation. Additionally, 11 patients (15.8%) reported experiencing symptoms of xerophthalmia. Pisella et al (12) reported the presence of ocular symptoms such as burning and stinging (36%), foreign body sensation (27%), dry eye sensation (23%), and tearing (20.1%). In the year 2001, a study found that 17% of participants reported experiencing symptoms of dry eyes and pruritus of the eyelids. The results of our inquiry corroborate the aforementioned statements. The efficacy of the drug and the patient's quality of life have been affected by the elevated incidence of dry eye syndrome symptoms and signs in individuals with glaucoma (13). As per the results obtained from the tear film break-up time test, it was observed that out of the total number of patients, 21 (26.76%) exhibited mild dry eyes, 25 (34.65%) exhibited moderate dry eyes, 13 (18.66%) exhibited severe dry eyes, and 16 (20.1%) did not exhibit any symptoms of dry eye syndrome. As per the results of the Basal Schirmer test, a significant proportion of the patient cohort exhibited symptoms of dry eye disease. Specifically, 13 patients (16.1%) were diagnosed with severe dry eye disease, 29 patients (39.9%) exhibited moderate symptoms, and 18 patients (18.89%) presented with mild dry eye syndrome. The results were consistent with the findings of the previous study. As per the findings of a study conducted by Manusaini et al in the medical and academic domain, it has been observed that a total of 66 patients who were prescribed anti-glucidal medication were included in the study (13). Of these, 17 eyes (34%) exhibited dryness at levels 2 or 3. A further investigation conducted by Leung and colleagues (14) indicated that 29% of the subjects did not manifest the clinical manifestations of xerophthalmia. A study found that 27% of glaucoma patients exhibited mild to moderate ocular surface disease, while 35% of patients had a significant tear deficiency. This suggests a potential correlation between glaucoma and ocular surface disease (10). Glaucoma is a prevalent ocular disorder that ranks second in the list of leading causes of visual impairment. It exerts a chronic influence on an individual's quality of life. Discontinuation of prescribed medications is not feasible due to the manifestation of adverse effects, including xerophthalmia. Compliance with treatment regimens for dry eye disease is a subject of debate due to its association with the condition. Timely identification and simultaneous management may result in a better prognosis.

V. Conclusion

The application of glaucoma medication topically has been associated with the development of dry eye syndrome and has been observed to affect the stability of the tear film. Non-adherence to treatment regimen and ocular surface disease are common issues encountered in patients diagnosed with glaucoma who are prescribed antiglaucoma medications. Our research findings indicate that individuals undergoing antiglaucoma therapy are more susceptible to ocular surface disease and dry eye. The presence of preservatives in pharmaceuticals and a prolonged duration of therapy were the primary factors that contributed to the outcome

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