Al-Azhar International Medical Journal

Manuscript 2326

Section: Ophthalmology

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ORIGINAL ARTICLE

Adverse Side Effects of Prostaglandin Analogs Antiglaucoma Medication on Precorneal Tear Film

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Abstract

Background: **Glaucoma is a prevalent ocular disorder characterized by progressive damage to the optic nerve, leading to irreversible vision loss if left untreated.**

Aim: **This research aims to evaluate the quantity and quality of the precorneal tear film in primary open-angle glaucoma-studied cases that are using topical prostaglandin analogs, by conducting Schirmer and break-up time (BUT) tests.**

Patients and methods: **It was a prospective case−control clinical trial that involved 120 eyes divided into two groups. The first group consists of 30 age-matched healthy individuals, while the second group comprises 30 patients diagnosed with primary open-angle glaucoma and are under control with topical prostaglandin analogs attending the Ophthalmology Department at Al-Azhar University hospitals. Glaucoma patients under prostaglandin analogs are subdivided into three subgroups based on the duration of drug intake: early (1 month), 3, and 6 months.**

Results: **The BUT test outcomes indicate significant variation between the two groups, with group 1 (control) having a mean BUT of 17.67 s and group 2 (patients) having a significantly lower mean BUT of 4.1 s. Group 2 also had a significantly lower mean Schirmer test value of 8.43 ± 3.75, suggesting reduced tear production in these individuals.**

Conclusion: **Overall, the data suggests that primary open-angle glaucoma under prostaglandin analogs has significant effects on various aspects of eye health, including intraocular pressure, cup-to-disc ratio, tear film stability, and tear production.**

Keywords: Antiglaucoma medication, Precorneal tear film, Prostaglandin analogs

1. Introduction

Glaucoma is a prevalent ocular disorder characterized by progressive damage to the optic nerve, leading to irreversible vision loss if left untreated. Prostaglandin analogs have become a widely used class of antiglaucoma medications because of their efficacy in lowering intraocular pressure (IOP).[1]

The most common reason for irreversible blindness in the world, glaucoma, is a set of eye conditions that harm the optic nerve and cause visual loss.[2]

The main glaucoma risk factor is IOP. IOP and glaucoma incidence and progression have a similar dose−response connection, according to earlier prevalence surveys and longitudinal investigations.[3]

Unless other factors, like costs, side effects, intolerance, or patient refusal forbid use, prostaglandin analogs are frequently considered as the first line of medical treatment.[4]

Studied cases with topically treated glaucoma are significantly more likely to develop ocular surface disease when several variables are present. For instance, the length of the treatment and the quantity of drops infused are closely connected to the frequency and seriousness of ocular surface disease.

2. Patients and methods

The research design had been a prospective case−control clinical trial research. This study aims to assess the quantity and quality of the precorneal

Accepted 2 December 2023.
Available online 1 November 2024

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https://doi.org/10.58675/2682-339X.2326

tear film in primary open-angle glaucoma-studied cases that are using topical prostaglandin analogs, by conducting Schirmer and break-up time (BUT) tests.

The prospective case–control clinical trial that involves 60 persons, divided into two groups. The first group consists of 30 age-matched healthy individuals, while the second group comprises 30 patients diagnosed with primary open-angle glaucoma and are under control with topical prostaglandin analogs attending the Ophthalmology Department at Al-Hussien University Hospitals. Glaucoma patients under prostaglandin analogs are subdivided into three subgroups based on the duration of drug intake: early (1 month), 3, and 6 months.

2.1. Ethical approval

Before enrolling in the research, all participants gave their written informed consent to participate in the research and to have their data published. The research received approval from the Medical Research Ethical Committee of the Department of Ophthalmology, Faculty of Medicine, Al-Azhar University, and was been carried out in compliance with the unique standards outlined in the Helsinki declaration.

2.2. Inclusion criteria

Age group between 50 and 60 years old, cases diagnosed primary open-angle glaucoma of both sexes and under control with preservative-free prostaglandin analogs (travoprost, latanoprost, and bimatoprost).

2.3. Exclusion criteria

Studied cases with systemic causes of dry eyes, such as Sjogren syndrome and Parkinson's disease, patients with local causes of dry eye, such as trachoma and chemical injury, patients with ocular surface diseases, such as allergic conjunctivitis, patients with conjunctival blistering diseases, patients with a history of intraocular inflammation, patients with a history of past ocular operations, patients talking drugs causing dry eye such as antihistamines, beta-blockers and diuretics, other causes of glaucoma (angle-closure glaucoma and secondary open-angle glaucoma) and other medications other than prostaglandin analougs.

All groups were subjected to a complete ophthalmological evaluation as follows:

2.4. History taking

Personal history: age, sex, present history of ocular trauma, and systemic diseases as diabetes mellitus and hypertension, full ophthalmological history, and symptoms: headache, dizziness, deterioration of vision.

2.5. Clinical examination

General examination: including anthropometric measurements like height, weight, and BMI.

2.6. Standard ophthalmological examination

Visual acuity uncorrected, best-corrected visual acuity: measured using a Snellen chart with the patient's glasses or contact lenses on, slit lamp examination: to evaluate: anterior chamber, cornea, iris, lens, and retina, IOP using the Goldmann applanation tonometry, the field of vision using automated perimetry, fundus biomicroscopy, and ophthalmoscopy using a 90 D lens, AC angle using gonioscope, Schirmer test: the test may be carried out anesthetic-free (Schirmer 2) or anesthetic-induced (Schirmer 1). Schirmer 1 should theoretically assess baseline secretion, whereas Schirmer 2 (without anesthesia) should assess baseline plus reflex secretion. A Schirmer test result of less than 5 mm wetting in 5 min is generally considered abnormal and indicates reduced tear production. Results between 5 and 10 mm may indicate borderline tear production, while results greater than 10 mm are considered normal. The BUT: a BUT test result of less than 10 s is generally considered abnormal and indicates an unstable tear film. Results between 10 and 15 s may indicate borderline tear stability, while results greater than 15 s are considered normal.

2.7. Statistical analysis

Version 20.0 of the IBM SPSS software program (IBM Corp., Armonk, New York, USA) was used to analyze the data once it had been loaded into the computer. Numbers and percentages were used for defining qualitative data. The normality of the distribution had been examined using the Kolmogorov–Smirnov test. The range (minimum and maximum), mean, SD, and median of quantitative data had been used to explain the data. At the 5% level, the significance of the findings had been determined.

3. Result

The demographic data shows that the mean age for group 1 was 53.53 ± 3.73, while the mean age for group 2 was 54.97 ± 3.03, and the variation was not been statistically significant ($P = 0.109$). The age range was the same for both groups, with participants ranging from 50 to 60 years old. Overall, the demographic data suggests that the two groups were well-matched in terms of age and sex, which is important for minimizing the influence of these factors on the study results (Table 1).

The data shows that the mean IOP for group 1 was 16.17 ± 3.62 mmHg, while the mean IOP for group 2 was 17.12 ± 2.21 mmHg, and the difference was nonstatistically significant as shown in Figs 1 and 2.

The data shows that the mean cup-to-disc (C/D) ratio in the left eye for group 1 was 0.23 ± 0.12, while the mean C/D ratio in the left eye for group 2 was 0.61 ± 0.22, and the variation had been statistically significant with a P value of less than 0.0001. Similarly, the mean C/D ratio in the right eye for group 1 was 0.26 ± 0.12, while the mean C/D ratio in the right eye for group 2 was 0.63 ± 0.2, and the variation had also been statistically significant with a P value of less than 0.0001. These results suggest that the C/D ratio had been significantly smaller in control patients compared to primary open-angle glaucoma under prostaglandin analougs individuals. The C/D ratio is an important parameter in the diagnosis and management of glaucoma, as it reflects the amount of optic nerve cupping and damage. A higher C/D ratio indicates a larger C/D ratio, which can be a sign of glaucoma or other optic nerve damage. The significantly smaller C/D ratio observed in group 1 suggests that these patients had less optic nerve damage than the glaucoma group. However, the outcomes of this research suggest that the C/D ratio is significantly different between studied cases with primary open-angle glaucoma under prostaglandin analougs and age-matched healthy individuals and may be useful in the diagnosis and management of glaucoma (Fig. 3).

The Schirmer test is a diagnostic test used to measure tear production in the eye. The test involves placing a small filter paper inside the lower eyelid, which absorbs tears over a period. In this data, the Schirmer test was performed on both group 1 and group 2, and the results were compared.

The mean Schirmer test value for group 1 was 17.67 ± 1.84, while for group 2, it was 8.43 ± 3.75. This defines a statistically significant variation among the two groups ($P < 0.0001$).

Furthermore, the data was also analyzed based on the grading of the Schirmer test. In group 1, 90% of participants had normal tear production (>15 mm), while 6.66% had low normal tear production (10–15 mm) and 3.33% had borderline tear production (6–10 mm) while in group 2, only two out of 30 participants had normal tear production, while four had low normal tear production (10–15 mm), 16 had borderline tear production (6–10 mm), and eight had abnormal tear production (<6 mm). These differences in grading are also statistically significant ($P < 0.0001$).

These results suggest that group 2 has lower tear production than group 1 and that most participants in group 2 have abnormal or borderline tear production, which may be indicative of dry eye syndrome.

BUT test: in group 1, the mean BUT was 17.67 s with a SD of 1.84. In group 2, the mean BUT had been 4.1 s with a SD 2.26. The P value for comparing the means using a two-sample t test is less than 0.0001, indicating a statistically significant variation among the groups. The interpretation suggests that there are significant differences between group 1 and group 2 in terms of BUT test results (Figs 4 and 5).

4. Discussion

Understanding the precise impact of prostaglandin analogs on the precorneal tear film is crucial for optimizing glaucoma treatment and ensuring the ocular surface remains healthy. Our study aims to investigate the adverse side effects of prostaglandin analogs on the precorneal tear film, contributing valuable insights to the field of ophthalmology.[5]

Table 1. Demographic data distribution in all study populations.

	Group 1	Group 2	*P* value	Statistically significant
	$N = 30$	$N = 30$		
Age				
Mean ± SD	53.53 ± 3.73	54.97 ± 3.03	0.109	NS
Range (minimum–maximum)	50–60	50–60		
Sex [*n* (%)]				
Male	19 (63.33)	20 (66.67)	0.7866	NS
Female	11 (36.67)	10 (33.33)		

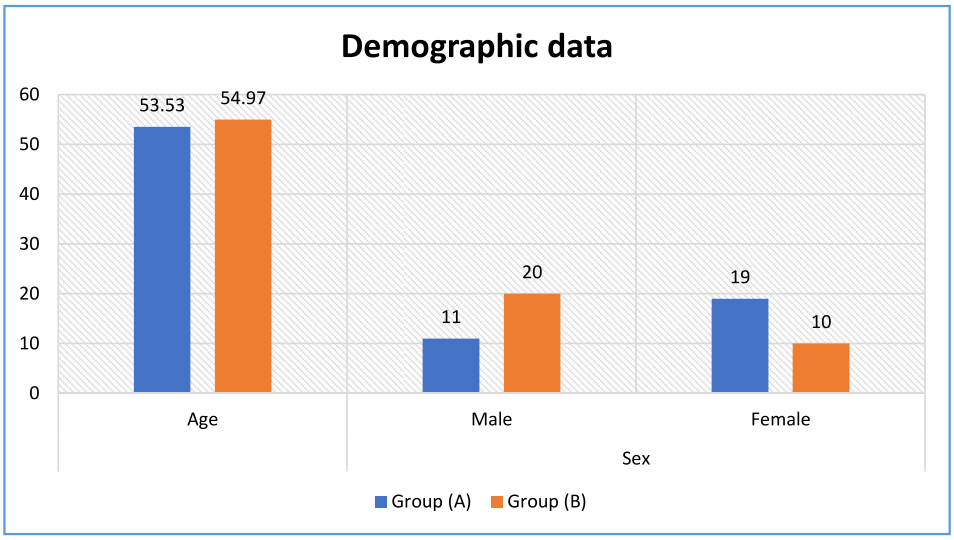

Fig. 1. Age data distribution in all study populations.

The proposed prospective case–control clinical trial aims to build upon the existing knowledge about the impact of prostaglandin analogs on the precorneal tear film. By dividing glaucoma patients into subgroups based on the duration of drug intake, the study can better understand the cumulative effects of these medications over time. The Schirmer test and tear break-up time (TBUT) test will provide valuable data on tear quantity and stability, respectively.

If the study confirms the adverse side effects of prostaglandin analogs on the precorneal tear film, it could have significant implications for the management of glaucoma. Ophthalmologists may need to closely monitor patients on long-term prostaglandin therapy for ocular surface changes and consider alternative treatment options in cases where tear film disruption is evident. Developing strategies to mitigate tear film instability in these patients could help improve treatment outcomes and patient comfort.

The findings of this research might contribute to a better understanding of the ocular surface health in glaucoma-studied cases under prostaglandin analog

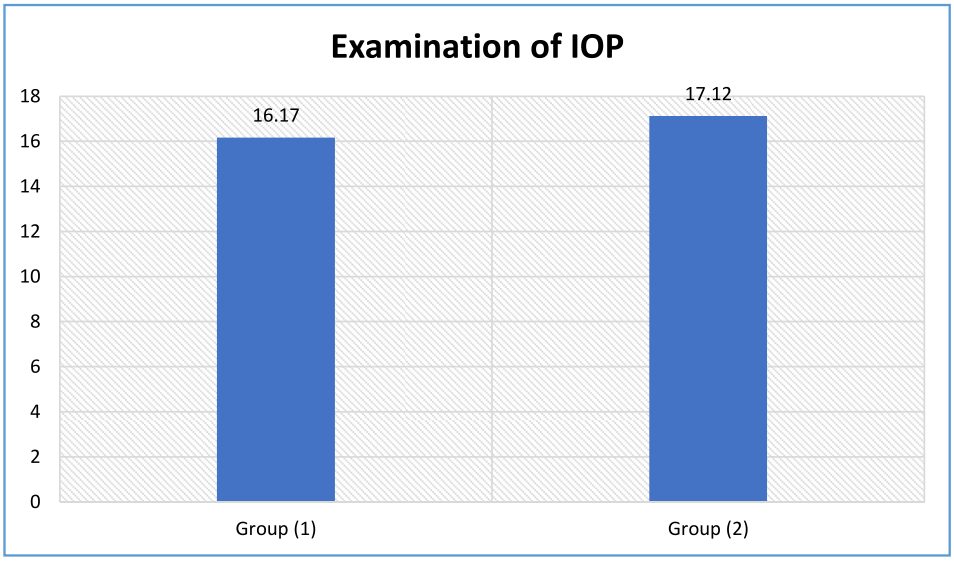

Fig. 2. Examination of intraocular pressure (IOP) data distribution in all study populations.

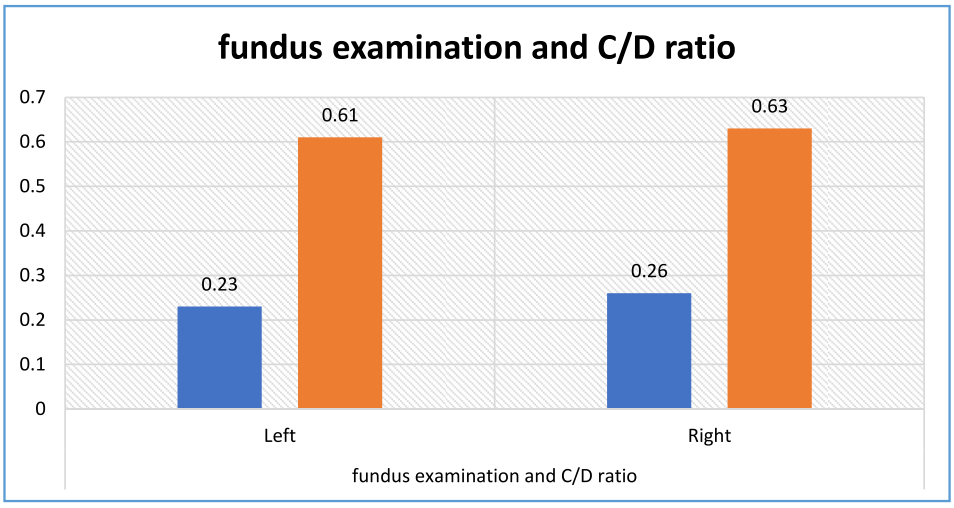

Fig. 3. Fundus examination and cup-to-disc (C/D) ratio. Data distribution in all study populations.

treatment and potentially lead to the development of new approaches to manage or prevent adverse side effects associated with these medications.

Our research aimed to assess the quantity and quality of the precorneal tear film in primary open-angle glaucoma-studied cases under control with topical prostaglandin analogs. We conducted a prospective case–control clinical trial involving 120 eyes, divided into two groups: group 1 comprised 30 age-matched healthy individuals, and group 2 included 30 studied cases diagnosed with primary open-angle glaucoma who had been under control with topical prostaglandin analogs attending the Ophthalmology Department at Al-Azhar University hospitals. Tear film assessment was conducted using the Schirmer and TBUT test. The patients in group 1 were further subdivided based on the duration of prostaglandin analog intake, with sub-groups including early (1 month), 3, and 6 months of drug intake.

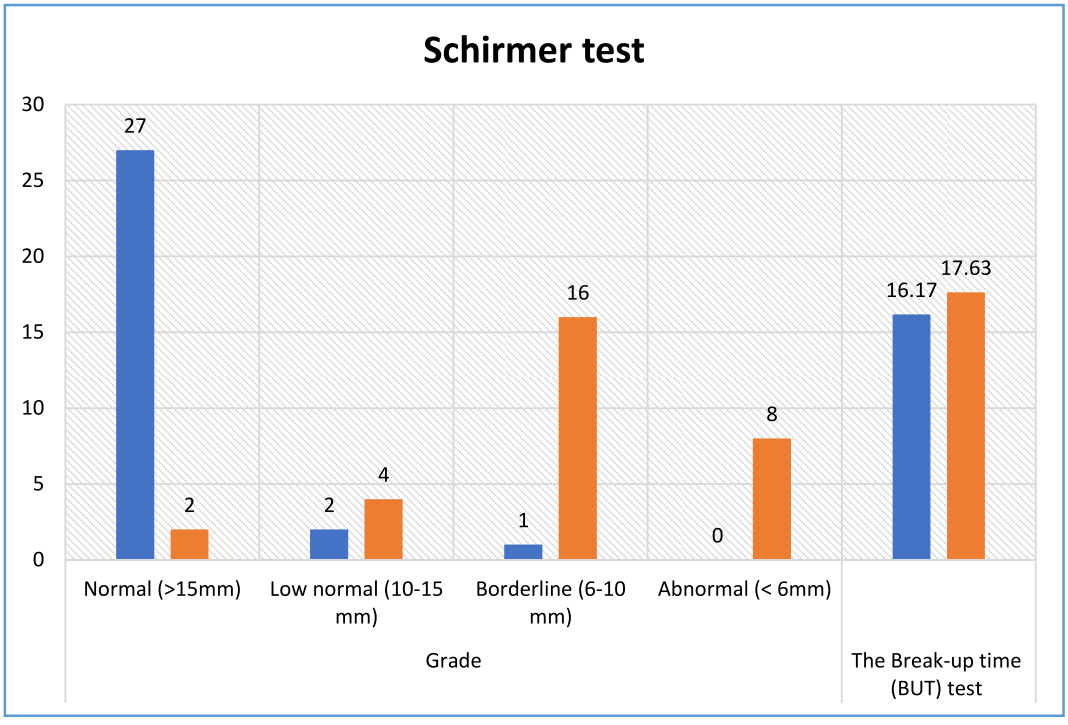

Fig. 4. Schirmer test. Data distribution in all study populations.

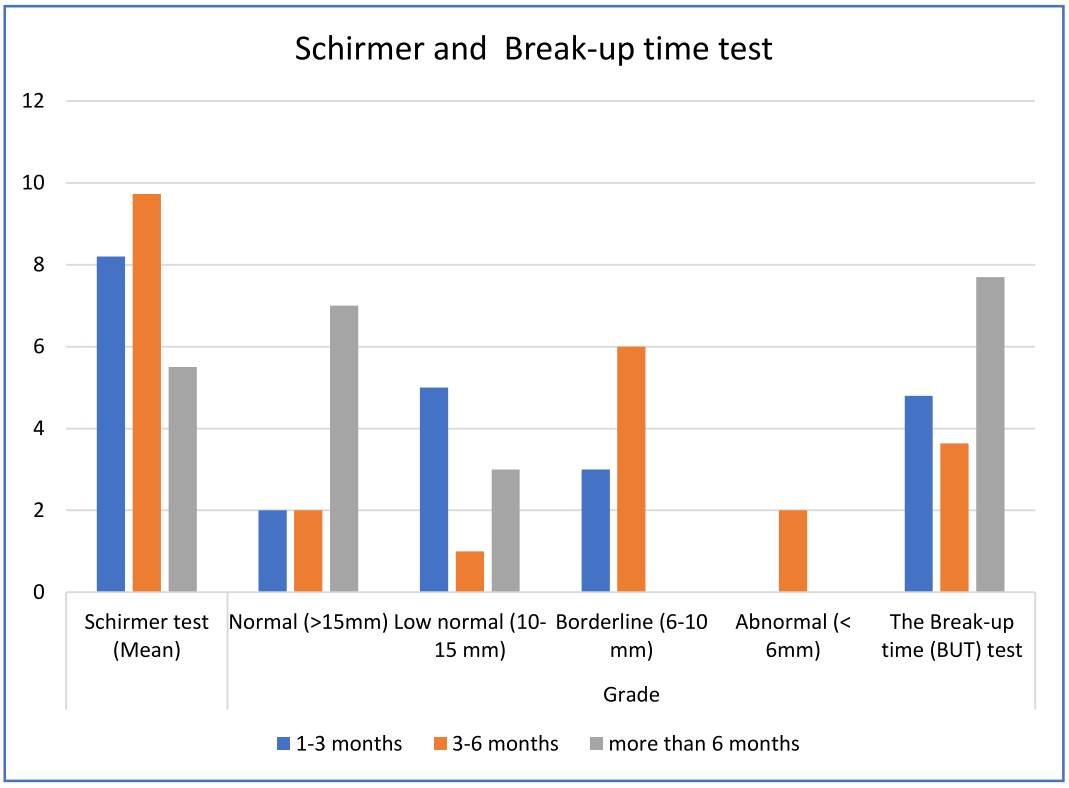

Fig. 5. Schirmer test. Data distribution in glaucoma patients under prostaglandin analougs.

Our data suggests that significant variations in Schirmer test results are observed when analyzed across distinct temporal intervals, with the 3-month cohort exhibiting the highest mean value, while the 6-month cohort demonstrates the lowest mean value.

The distribution of Schirmer test grades exhibits pronounced dissimilarities across these temporal intervals. Over time, the proportion of patients categorized as 'normal' experiences an incremental rise, while the prevalence of individuals classified as 'low normal' and 'borderline' concurrently experiences a decrement.

Likewise, the BUT test results manifest substantial divergence across the specified temporal intervals, with the 6-month cohort displaying the highest mean value and the 3-month cohort presenting the lowest mean value.

Numerous studies have explored the impact of prostaglandin analogs on tear film stability and ocular surface health in glaucoma-studied cases. Lee *et al.*,[6] investigated tear film stability using TBUT in glaucoma-studied cases treated with prostaglandin analogs. They reported a statistically significant reduction in TBUT, indicating potential tear film instability associated with these medications.

Wong *et al.*,[7] conducted prospective research to assess tear volume differences in glaucoma patients on prostaglandin analogs. They found a significant decrease in Schirmer test values in patients using prostaglandin analogs for 6 months, suggesting a reduction in tear production over time.

The findings from our study regarding the IOP in both groups are crucial in understanding the efficacy of prostaglandin analogs in managing glaucoma. The data revealed a significant variation in the mean IOP among the two groups. In group 1, consisting of glaucoma patients under control with topical prostaglandin analogs, the mean IOP was 16.17 ± 3.62 mmHg. In contrast, in group 2, which comprised healthy individuals, the mean IOP was 17.12 ± 2.21 mmHg.

The observed distinction in mean IOP between these cohorts was deemed statistically nonsignificant, substantiated by a P value of 0.488. This indicates the absence of a significant disparity in IOP levels between the control group and the cohort of glaucoma patients employing prostaglandin analogs.

Previous inquiries conducted by Koca and Inan[8] and Zaleska-Żmijewska *et al.*[17] have reported reductions in IOP among glaucoma patients subjected to the therapeutic regimens involving prostaglandin analogs.

The findings from our study regarding the field of vision in both groups provide important insights

into the impact of primary open-angle glaucoma and prostaglandin analogs on visual function. The data revealed a stark contrast in the distribution of the field of vision between the two groups.

The field of vision abnormalities observed in group 2 provides further understanding of the visual challenges faced by glaucoma patients. The most common field of vision abnormalities in this group were upper arcuate scotoma and scattered scotoma, each accounting for 33.33% of the cases. This finding is consistent with previous research on glaucoma-related visual field defects.[9] Additionally, generalized constriction of the visual field was observed in 30% of group 2 participants, indicating a more widespread visual impairment.[9]

The differences in the field of vision between the two groups are of great clinical importance. The significant number of fields of vision abnormalities observed in patients emphasizes the necessity of regular eye examinations, even in the absence of glaucoma. Additionally, it highlights the importance of early glaucoma detection and prompt initiation of treatment, such as prostaglandin analogs, to preserve visual function and prevent further vision loss.

The C/D ratio is a crucial parameter in glaucoma assessment, as it provides valuable information about the amount of cupping and damage to the optic nerve head. A higher C/D ratio indicates a larger cup-to-disk ratio, often associated with glaucoma or other optic nerve damage. The significantly smaller C/D ratio observed in group 1 suggests that glaucoma patients under control with topical prostaglandin analogs had more optic nerve damage compared to the healthy control group.

The outcomes of this research align with previous research that has consistently shown the diagnostic significance of the C/D ratio in glaucoma. Studies by Roberti *et al.*[10] and Fogagnolo *et al.*[11] also reported significant variations in the C/D ratio among glaucoma patients and healthy individuals.

The difference in the C/D ratio among the two groups has important clinical implications. This highlights the effectiveness of prostaglandin analogs in managing the progression of optic nerve damage and preserving visual function. It also emphasizes the importance of monitoring the C/D ratio in glaucoma patients as a valuable tool for disease management and treatment optimization.

Additionally, the BUT test results demonstrated a substantial difference between the two groups, with group 1 having a mean BUT of 17.67 s and group 2 having a significantly lower mean BUT of 4.1 s. The P value from the two-sample t test indicated a highly statistically significant variation in the tear film stability among the two groups ($P < 0.0001$).

Additionally, Steinsapir and Steinsapir,[12] assessed tear film dynamics in glaucoma patients and found a significant correlation between BUT and disease severity, further validating the significance of tear film stability in glaucoma management.

Several studies have investigated tear production and its association with glaucoma and prostaglandin analogs use. Nijm *et al.*[13] conducted a comparative study between glaucoma patients and healthy controls, assessing tear production using the Schirmer test. They reported a significant reduction in tear production in glaucoma patients, which is consistent with our findings.

Similarly, Arita *et al.*[14] performed cross-sectional research on glaucoma-studied cases treated with prostaglandin analogs and nonglaucomatous controls, observing a lower Schirmer test value in the glaucoma group, further supporting our results.

Additionally, Tomić *et al.*,[15] conducted a meta-analysis of various studies investigating tear production in glaucoma patients using prostaglandin analogs. They found a consistent trend of reduced tear production in glaucoma-studied cases compared to healthy individuals, which is in line with our observations.

Multiple studies have investigated the relationship between glaucoma and dry eye symptoms. Research by Aydin Kurna *et al.*[16] evaluated the prevalence of dry eye symptoms in primary open-angle glaucoma-studied cases. They observed that glaucoma-studied cases had been more likely to experience dry eye symptoms, including itchy eyes, gritty feeling, and increased tearing, supporting our results.

Additionally, Actis and Rolle,[5] conducted a prospective study on glaucoma patients and reported a significantly higher prevalence of dry eye symptoms, including itchy eyes and increased tearing, compared to healthy controls.

The findings from our study align with the results of previous research, collectively suggesting that glaucoma patients under prostaglandin analogs treatment (group 2) are more likely to experience dry eye symptoms compared to healthy individuals (group 1). The significant difference in the prevalence of itchy eyes, gritty feeling, redness, and increased watering between the two groups highlights the effect of glaucoma and prostaglandin analogs on ocular surface health and tear film dynamics.

Many studies have studied the effect of prostaglandin analog eye drops on dry eye symptoms, but they used eye drops that contain preservatives, which leads to mixing the effects of the active substance with the preservatives effect. However, this

study was distinguished by using eye drops free of preservatives to give more accurate results about the effect of the active substance on dry eye symptoms. However study did not focus on the effect of glaucomatous structural changes on the lacrimation system. We recommend further study to assess glaucomatous structural changes in secretory lacrimal glands.

4.1. Conclusion

Healthy controls exhibited a notably reduced C/D ratio, indicating less optic nerve damage than glaucoma patients under treatment. Glaucoma patients under prostaglandin analogs showed significant differences in tear film stability, are more likely to experience dry eye symptoms compared to healthy individuals, and reflect the impact of glaucoma on anterior chamber angle and tear film dynamics. Monitoring tear production and implementing dry eye management strategies for glaucoma patients are vital.

Ethics information

Its was approved by faculty.

Funding

The research was conducted without external funding or grants, relying solely on the authors' own resources.

Conflicts of interest

The authors declare no conflict of interest.

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