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Comparison of Effects of Preserved and Preservative Free Anti-Glaucoma Drugs in Causing Dry Eye

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[1]Conception and design, drafting of the manuscript
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ABSTRACT

Objective: The aim of this study was to assess the potential impact of antiglaucoma medication preservatives on ocular surface health and the subsequent development of dry eye symptoms.

Methods: A non-randomized controlled trial study was conducted from March 2023 to June 2023. The study enrolled 108 patients, with 54 participants in each group. Patients meeting the inclusion criteria, including confirmed diagnosis of glaucoma and stable ocular health, were allocated to Group A (preserved medication) or Group B (preservative-free medication). Tear Film Break-Up Time(TBUT) and Schirmer's test were employed as objective indicators of tear film stability and tear production respectively. Measurements were recorded at baseline and after a 3-month duration of medication use.

Results: At 1st visit, mean TBUT was 10.87 sec and mean Schirmer's test was 13.75 mm in group A while in group B it was 11.25 sec and 14.56 mm respectively. After 3 months of medication use, mean TBUT and mean Schirmer's was 9.62 sec and 11.81 mm respectively in group A while in group B it was 10.18 sec and 13.18 mm respectively. The results showed that initial ocular status was similar in both groups however the decrease in values showed ocular surface deterioration. Notably group A demonstrated a more substantial decline in tear production compared to group B.

Conclusion: This study underscores the importance of both preserved and preservative-free anti-glaucoma medications. Although both may potentially exacerbate dry eye symptoms to a greater extent, preservative-free anti-glaucoma may offer benefits in maintaining ocular surface health with long-term use.

Key words: *antiglaucoma agents, dry eye disease, glaucoma, prevalence*

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Introduction

Glaucoma is a condition which involves a long term, chronic and progressive optic neuropathy. Anti glaucoma medications are used to decrease the intraocular pressure and resultant vision loss in this condition.[1] Glaucoma is expected to affect more than 111.8 million people worldwide over the age of 40 by the year 2040.[2] In Pakistan alone, more than 1.8 million patients suffer from glaucoma and about half of them have suffered complete loss of vision. [3]

Dry eye syndrome (DES) is a multifactorial ocular condition characterized by discomfort, visual disturbance, and tear film instability, which can result in potential damage to the ocular surface. [4] It is a common clinical

problem affecting individuals worldwide, with various etiological factors contributing to its development. The use of topical anti-glaucoma medications are one of the most potent causes of dry eyes.[5] However, the use of preservatives in preparation of these anti-glaucoma medications present a challenge and contribute to development of dry eye symptoms.

These preservatives contribute towards making the ophthalmic solutions safe from microbial contamination. However, they have been found to cause ocular surface toxicity and adverse effects. These include eye irritation, ocular discomfort and result in exacerbation of dry eye symptoms.[6,7] Multiple efforts have been made at minimizing the use of preservatives in anti-glaucoma drugs while maintaining the therapeutic efficacy. As a result, conducting studies on this matter becomes imperative. This necessity has spurred the development of preservative-free formulations of anti-glaucoma drugs, with the aim of minimizing potential ocular surface damage while retaining therapeutic efficacy. Thus, it is imperative to study the adverse effects of preservatives commonly present in glaucoma medications, especially concerning dry eyes.

One such preservative which is noted to have adverse effects is benzalkonium chloride (BAK). It has the potential to cause inflammation and disrupt the integrity of the ocular surface. [8] Primarily it is the detergent-nature and property of BAK that can decrease TBUT by affecting tear film's lipid layer. [9]

The prevalence of dry eye syndrome and its potential exacerbation using preserved anti-glaucoma medications (10), a condition which affects 1.8 million Pakistanis provide a strong rationale for this study. [3] Currently, there is no recent original research on this topic in the Pakistani population, except a correspondence paper which reviewed the potential connection of a preservative free eye drops to for glaucoma with P. aeruginosa infections in published literature. [11] This study employs a randomized controlled trial design to compare the effects of preserved and preservative-free anti-glaucoma drugs in causing dry eyes among patients with glaucoma. The research aims to provide valuable insights that contribute to the optimization of glaucoma management, balancing therapeutic efficacy with ocular surface health.

Methodology

This study was a non-randomized controlled trial, conducted at the Department of Ophthalmology, Fauji Foundation Hospital, Rawalpindi from March 2023 to June 2023. A total of 108 patients were enrolled divided in 2 groups of 54. The sample size was calculated via comparing the incidence of moderate Schirmer test in patients treated with preservative free (0%) and preservative containing (13.3%) eye drops. [12] The sample size was calculated via the online Med Calc sample size calculator (https://clincalc.com/stats/samplesize.aspx) .[13]

The inclusion criteria encompassed adults aged 18 years and older who had a confirmed diagnosis of open angle glaucoma, necessitating treatment with anti-glaucoma medication. Exclusion criteria excluded individuals below the age of 18, those with secondary glaucoma or ocular hypertension not requiring medical treatment, participants who had switched between preserved and preservative-free anti-glaucoma medications within the preceding 3 months, as well as those with active ocular infections, ocular surface disease, or other significant ocular pathology.

Informed consent was obtained from all participating patients. Patients were divided into two groups, with 54 patients allocated to each of the two groups. The first group (Group A) received the anti-glaucoma drug containing preservatives while the second group (Group B) was administered the preservative-free version of the drug. Both drugs had same combination i.e dorzolamide 2% and timolol 0.5%.

To assess the impact of the different formulations on ocular health, TBUT and Schirmer's test were performed at baseline. Following the baseline measurements, participants from both groups received their respective medications for a duration of 3 months. Subsequently, TBUT and Schirmer's tests were repeated.

Schirmer 1 Test is performed to measure the total tear flow with the help of a filter paper sheet. The filter paper was inserted into the conjunctival sac right in between the middle and lateral one third of the eyelid. The sheet absorbed the tears which were them measured in millimeters. The classification was defined as: 'Normal'; >10 mm, Moderate: 6-10 mm whereas 'Severe: 3-5mm.

Furthermore, TBUT test was performed using a fluorescein containing paper that was already dipped in a drop of normal saline. The paper was introduced inside the inferior fornix. The patients were asked to not to blink and the time between the last blink and the first black point or breaking of tear fil was observed. The classification was defined as: Normal: >10 sec; Moderate 6-10 sec and Severe: 5 seconds.[12]

In this way, we assessed the effectiveness of preservative free medication as compared to preservative containing medication. The effectiveness is defined here as the degree of healing effect i.e., TBUT test and Schirmer test scores on glaucoma patients caused by either intervention.[12]

Data was analyzed via SPSS version 26. The mean and standard deviation were calculated for age, TBUT score (sec), and Schirmer's test (mm). The p-value was obtained via the independent samples t-test. A p-value less than 0.05 was considered significant.

Results

The mean age of the patients enrolled in Group A was 34.88 ±10.22 years, whereas in Group B it was 34.44 ± 10.32 years. The TBUT score (sec) of the patients was checked upon their 1st visit. The mean TBUT score (sec) at 1st visit was 10.90 ± 1.43 sec (p<0.001) in patients of Group A whereas it was 11.22 ± 1.43 sec (p<0.001) in patients in Group B as shown in Table I.

After 3 months, the TBUT score was assessed again. It was observed that in Group A, the TBUT score was 9.68 ± 1.25 sec (p<0.001) whereas in Group B it was observed as 10.1 ± 1.16 sec (p<0.001). Thus, the TBUT score was observed to be decreased in both groups as shown in Table I.

Table I: Comparison of mean of TBUT score (sec) in patients prescribed the drug with preservative and without preservative at the 1st visit and after 3 months.

Case Type	Mean	SD	p-value
TBUT (sec) at 1st visit (N=54)			
Drug with preservative (Group A)	10.90	1.43	<0.001
Drug without preservative (Group B)	11.22	1.43	
TBUT (sec) at 3rd month (n=16)			
Drug with preservative (Group A)	9.68	1.25	<0.001
Drug without preservative (Group B)	10.1	1.16	

The results of the TBUT were further categorized as normal or abnormal based on the values. The TBUT score greater or equal to 10 sec was determined as normal whereas lower than 10 sec was considered abnormal. The frequency and percentage of categorization based on TBUT is given in Table II.

Table II: Categorization of TBUT scores in Groups A and B via Chi-square test.

		TBUT Scores Categorization		
		Normal	Abnormal	p-value
Case Type	Drug with preservative	31	23	0.007
	Drug without preservative	44	10	
Total		75	33	

Schirmer's Test (mm) was observed at the 1st visit of the patients. In group A, the mean of Schirmer's test score (mm) was 13.77 ± 2.27 mm (p<0.001) and in group B, the mean was observed to be 14.51 ± 2.35 mm (p<0.001) as depicted in Table III.

Schirmer's test (mm) was also observed after 3 months of the initial visit. In group A, the mean of Schirmer's test score (mm) was 11.94 ± 2.54 mm (p<0.001) and in group B, the mean was observed to be 13.18 ± 1.37 mm (p<0.001) as depicted in Table III.

Table III: Comparison of mean of Schirmer's Test score (mm) in patients prescribed the drug with preservative and without preservative at 1st visit.

Case Type	Mean	SD	p-value
Schirmer's Test (mm) at 1st visit (n=16)			
Drug with preservative (Group A)	13.77	2.27	
Drug without preservative (Group B)	14.51	2.35	<0.001
Schirmer's Test at 3 months			
Drug with preservative (Group A)	11.94	2.54	<0.001
Drug without preservative (Group B)	13.18	1.37	

The results of Schirmer's test were further categorized as moderate or severe based on the values. The Schirmer's score greater or equal to 10 mm was determined as moderate whereas lower than 10 mm was considered severe. The frequency and percentage of categorization based on Schirmer's is given in Table IV.

Table VI: Categorization of Schirmer's scores via Chi-square test.

		Schirmer Score Categories		
		Normal	Abnormal	p-value
Case Type	Drug with preservative	45	9	0.002
	Drug without preservative	54	0	
Total		99	9	

Discussion

In this study, we have compared the effects of preserved and preservative-free anti-glaucoma medications in causing dry eyes among patients diagnosed with glaucoma.

The TBUT test is widely used to assess tear film stability, with a reduced TBUT being indicative of poor tear film integrity. The initial TBUT measurements demonstrated comparable results in both groups, indicating that the ocular health of participants was relatively consistent at the onset of the study. The mean TBUT score (sec) at 1st visit was 10.90 ± 1.43 sec (p<0.001) in patients of Group A whereas it was 11.22 ± 1.43 sec (p<0.001) in patients in Group B. However, after 3 months, it was observed that in

Group A, the mean TBUT score was 9.68 ± 1.25 sec ($p<0.001$) whereas in Group B it was observed as 10.12 ± 1.16 sec ($p<0.001$). In line with these findings, Lee et al. also demonstrated that TBUT when using preserved-prostaglandins analogue (PGAs) tends to be worse compared to when using preservative-free prostaglandins analogues (PF-PGAs). After the 6th month follow-up, TBUT was 5.00 ± 1.88 (sec) while using preservative-free tafluprost (NPT). When switched to a preservative containing tafluprost (PT) for the next 6 months, TBUT was 3.60 ± 2.07 (sec) after utilizing PT (P-value = 0.06) (14). Kim KE et al. also reported that the TBUT score was 5.61 ± 1.72 in drugs with preservatives whereas it was 7.27 ± 2.96 ($p<0.05$) in a preservative-free group.[2] In another study, TBUT was increased from 5.1 ± 2.3 sec to 10.1 ± 3.6 sec at 12 weeks of shifting to of preservative free tafluprost. [15]

Mohamed et al. also reported that among the patients who were administered PF-PGAs, 80% exhibited normal values TBUT, which was defined as greater than 10 seconds. In contrast, only 13.3% of patients who received preserved PGAs had normal TBUT values, and this difference was statistically significant (P-value<0.001).[12] These percentages are very similar to our study where 81.5% exhibited normal TBUT scores (10 seconds or greater) in a preservative-free group as compared to 57.4% in the preservative group after 3 months of administration.

Schirmer's test, a measure of tear production, revealed interesting trends in our study. At baseline, both groups exhibited relatively similar Schirmer's test scores. In group A, the mean of Schirmer's test score (mm) was 13.77 ± 2.27 mm ($p<0.001$) and in group B, the mean was observed to be 14.51 ± 2.35 mm ($p<0.001$). However, 3 months after the initial visit, in group A, the mean Schirmer's test score (mm) was 11.94 ± 2.54 mm ($p<0.001$) and in group B, the mean was observed to be 13.18 ± 1.37 mm. This discrepancy suggests that the presence of preservatives might contribute to a more pronounced reduction in tear production over time. Our results align with those of Mohamed et al. who found that the Schirmer test showed significant differences between the two groups. In the group that received PF- PGAs, 80% of patients had normal values (wetting of the Schirmer paper >10mm), while only 13.3% in the other group had normal values (p-value <0.001). Conversely, 13.3% of patients in the preservative-free group exhibited a moderate Schirmer 1 test result (≤10 mm wetting of the paper), and 6.7% had a severe decrease in Schirmer test values (>5 mm wetting of Schirmer paper). This was in contrast to the preservative group, where 66.7% had moderate results, and 20% had severe results.[12] A similar trend in percentages is shown in our study where 83.3% had moderate Schirmer 1 in preservative-loaded medication whereas 100% had moderate values without preservatives. Uusitalo et al. observed that the percentage of patients with abnormal Schirmer's test results at the beginning of latanoprost treatment was 71.5%. After the 6th and 12th week of treatment with preservative-free tafluprost, the percentages decreased to 61.5% and 59.4%, respectively (p-value = 0.003 at 12 weeks).[16]

The comparison of the two outcome measures—TBUT and Schirmer's Test—suggests that while both preserved and preservative-free medications might lead to decreased tear film stability and tear production, the impact appears to be more pronounced in the group receiving the preserved medication. In a study, prevalence of ocular surface disease was assessed to be higher in patients using preserved antiglaucoma medication as compared to those not using any topical medications.[17] A review article concluded that preserved formulations of ophthalmic medications limits their usage due to their adverse effects so preservative free formulations are needed for chronic ocular conditions.[7]

The main culprit behind the disruption of membrane integrity is considered to be BAK. In order to battle the cholera pandemic, Gustav Raupenstrauch developed BAK, the most extensively used preservative in eye drops today, as an antiseptic disinfectant in Germany in 1889 ([2]). BAK destabilizes the tear film when added to eye drops, causing inflammation, squamous metaplasia, and fibrotic alterations in the conjunctiva. It also destabilizes the lipid layer of pathogen cell membranes.[2]

Walsh K also observed that the ocular symptoms resulting from preservatives anti-glaucoma medications, encompassing sensations of discomfort during eye drop application, sensations of burning/stinging, a feeling akin to a foreign object in the eye, dryness, excessive tearing, and itching of the eyelids.[10]

However, it is essential to acknowledge the limitations of this study. The sample size was relatively small, and the study duration was limited to 4 months. Long-term effects of anti-glaucoma medications on dry eyes should be explored in larger, longitudinal studies. Additionally, individual variations in response to medications and potential confounding factors, such as environmental conditions and other concomitant medications, were not addressed in this study.

Conclusion

Conclusively, this study provides valuable insights into the effect of preservatives in anti-glaucoma medications on the Pakistani population. The study shows that addition of preservatives leads to significant adverse effects on tears contributing towards dry eye disease as is proved by the different outcomes of TBUT and Schirmer 1 test of the patient population. This study thus advocates the need for adoption of preservative free anti-glaucoma medications in clinical practice in Pakistan.

References

1. Keel S, Xie J, Foreman J, Lee PY, Alwan M, Fahy ET, et al. Prevalence of glaucoma in the Australian National Eye Health Survey. Br J Ophthalmol. 2019 Feb;103(2):191-5. https://doi.org/10.1136/bjophthalmol-2017-311786
2. Kim DW, Shin J, Lee CK, Kim M, Lee S, Rho S. Comparison of ocular surface assessment and adherence between preserved and preservative-free latanoprost in glaucoma: a parallel-grouped randomized trial. Sci Rep. 2021 Jul 22;11(1):14971. https://doi.org/10.1038/s41598-021-94574-x
3. Khan L, Ali M, Qasim M, Jabeen F, Hussain B. Molecular basis of glaucoma and its therapeutical analysis in Pakistan: an overview. Biomed Res Ther. 2017 Mar 23;4(03):1210-27. https://doi.org/10.15419/bmrat.v4i03.158
4. Messmer EM. The Pathophysiology, Diagnosis, and Treatment of Dry Eye Disease. Dtsch Ärztebl Int. 2015 Jan;112(5):71-82. https://doi.org/10.3238/arztebl.2015.0071
5. Maeng KJ, Lee K, Kim S, Park CK, Kim EW, Lee SY, et al. Effects of Glaucoma Medication on Dry Eye Syndrome and Quality of Life in Patients with Glaucoma. Korean J Ophthalmol KJO. 2021 Dec;35(6):467-75. https://doi.org/10.3341/kjo.2021.0068
6. Thygesen J. Glaucoma therapy: preservative-free for all? Clin Ophthalmol Auckl NZ. 2018;12:707-17. https://doi.org/10.2147/OPTH.S150816
7. Vasdev N, Chaudhari N, Polaka S, Rajpoot K, Gondaliya P, Sayyed AA, et al. Current progress in preservative-free topical ophthalmic formulations. J Drug Deliv Sci Technol. 2023 Jan 1;79:103996. https://doi.org/10.1016/j.jddst.2022.103996
8. Goldstein MH, Silva FQ, Blender N, Tran T, Vantipalli S. Ocular benzalkonium chloride exposure: problems and solutions. Eye. 2022 Feb;36(2):361-8. https://doi.org/10.1038/s41433-021-01668-x
9. Steven DW, Alaghband P, Lim KS. Preservatives in glaucoma medication. Br J Ophthalmol. 2018 Nov;102(11):1497-503. https://doi.org/10.1136/bjophthalmol-2017-311544
10. Walsh K, Jones L. The use of preservatives in dry eye drops. Clin Ophthalmol Auckl NZ. 2019;13:1409. https://doi.org/10.2147/OPTH.S211611
11. Mughal S, Sakina SK. Artificial tears: Promising treatment or silent threat to public health? Health Sci Rep. 2023;6(8):e1508. https://doi.org/10.1002/hsr2.1508
12. Mohamed S, Gamal El-Deen A, Abosaif A, El-Koussy N. Effects of preservative-free and preservative prostaglandin analogs on ocular surface by impression cytology in glaucoma patients. J Recent Adv Med. 2023 Jan 1;4(1):65-73. https://doi.org/10.21608/jram.2023.178388.1192
13. Rosner B. Fundamentals of Biostatistics. 2010;
14. Lee W, Lee S, Bae H, Kim CY, Seong GJ. Efficacy and tolerability of preservative-free 0.0015% tafluprost in glaucoma patients: a prospective crossover study. BMC Ophthalmol. 2017 Apr 28;17(1):61. https://doi.org/10.1186/s12886-017-0453-z
15. Hommer A, Schmidl D, Kromus M, Bata AM, Fondi K, Werkmeister RM, et al. Effect of changing from preserved prostaglandins to preservative-free tafluprost in patients with glaucoma on tear film thickness. Eur J Ophthalmol. 2018;28(4):385-92. https://doi.org/10.1177/1120672117753703
16. Uusitalo H, Chen E, Pfeiffer N, Brignole-Baudouin F, Kaarniranta K, Leino M, et al. Switching from a preserved to a preservative-free prostaglandin preparation in topical glaucoma medication. Acta Ophthalmol (Copenh). 2010 May;88(3):329-36. https://doi.org/10.1111/j.1755-3768.2010.01907.x
17. Awe OO, Onakpoya OH, Adeoye AO. Effect of Long-Term Topical Antiglaucoma Medication Use on the Ocular Surface. Niger Med J J Niger Med Assoc. 2020;61(4):184-8. https://doi.org/10.4103/nmj.NMJ_116_19