Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (9) Issue (8) (2024), (29- 36) **online: ISSN 2356–976x**
http://bjas.bu.edu.eg

Ocular Surface Disease and Glaucoma Medications

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Abstract
Background: Patients with glaucoma often have other health conditions, such as ocular surface disease (OSD), since the illness is characterized by a gradual and persistent damage to the optic nerve that often leads to elevated intraocular pressure. This study aims to examine the surface effects of a fixed combination of timolol and dorzolamide in both preservative-and non-preservative-containing glaucoma medications.
Methods: Forty people diagnosed with open angle glaucoma and seen by the ophthalmology team at Benha University Hospital participated in this prospective randomized trial. A preservative-containing group (PC) and a preservative-free group (PF) were randomly assigned to the participants. Eye drops containing the preservative (BAK) or a mixture of dorzolamide 2% and timolol 0.5% were administered to patients daily for 24 weeks.
Results: At W20 and W24, there was a notable rise in the amount of conjunctival stain found in the PC group when compared with the PF group (P=0.037, <0.001). There was a substantial increase in conjunctival staining test results compared to baseline at W4, 8, 12, 16, 20, and 24 in both the PC and PF groups (P<0.05). From Week 12 to Week 24, there was a notable decrease in intraocular pressure (IOP) in the PF group when compared to the PC group (p<0.05). At Weeks 4, 8, 12, 16, 20, and 24, the intraocular pressure (IOP) in the PC and PF groups was considerably lower than at baseline (P<0.05).
Conclusions: In comparison to patients whose drugs were kept, those whose medications were not showed improved outcomes in the following areas: OSDI scores, Schirmer test findings, tear break-up time, corneal and conjunctival staining, and intraocular pressure (IOP).

Keywords: Ocular Surface Disease; Glaucoma; Medications; Benzalkonium chloride; intraocular pressure.

Introduction

Many different parts of the eye's exterior may be affected by a collection of conditions known as ocular surface disease (OSD). It is thought of as a condition that impacts the tear film's stability and function in many ways. Symptoms often experienced by patients with OSD include a generalized ache, redness, burning, dryness, sense of a foreign body, visual disruption, and photophobia. [1]. Tear film problems are the most prevalent cause of OSD, however defective corneal and conjunctival cells are also potential culprits. Therefore, issues with the corneal epithelium, conjunctival epithelium, or tear film might cause OSD. [2].

Because glaucoma is a chronic, progressive optic neuropathy that often comes with elevated intraocular pressure (IOP), and because the therapy aims at reducing IOP and preserving vision, OSD is a frequent comorbidity in glaucoma patients. Preservatives added to multidose pharmaceutical bottles to prevent the danger of microbial contamination are the main cause of the rise in OSD symptoms after the use of intraocular pressure (IOP) reducing drugs. [3]. Topical glaucoma drugs may either exacerbate preexisting OSD or cause new OSD to manifest at the beginning of treatment. [4].

One of the most prevalent preservatives used in ophthalmology since the 1940s, benzoyl chloride (BAK) is included in around 70% of eye drops. Detergent that lyses cell membranes and kills microbes, it is a quaternary ammonium molecule. [5]. A number of surface eye problems were linked to long-term use of topical intraocular pressure (IOP)-lowering medications preserved in benzalkonium chloride, such as tear film instability, decreased density of superficial epithelial cells, impaired function of the corneal epithelial barrier, and inflammation of the conjunctiva. [6].

Obviously, removing the benzalkonium chloride and other preservatives from the eyedrops is the only method to fully eradicate any negative effects associated with them. Since using non-preserved eyedrops in multidose bottles might increase the danger of contamination, this strategy raises concerns among both industry and regulators. One solution to this problem is the prevalence of preservative-free formulations sold in single-dose packages. Products containing a single dosage of pilocarpine, timolol, dorzolamide, or the prostaglandin analogue tafluprost have recently entered the market. [7].

The objective of this study was to examine the surface effects of glaucoma medicine on the eye using both preservative-containing and preservative-free formulations of a fixed combination of timolol and dorzolamide.

Patients and Methods

This prospective randomized trial included 40 open angle glaucoma patients who visited Benha University Hospital's ophthalmology department from May 2022 to February 2023. The Benha University Faculty of Medicine Research Ethics Committee reviewed the work.

Inclusion criteria were patients of either sex whose age between 45 -60 years with mild to

moderate primary open angle glaucoma (not on IOP lowering medications for at least 6 months before the study).

Exclusion criteria were autoimmune connective tissue diseases. chronic autoimmune blistering disorder. diabetes mellitus having clinically significant symptoms and signs of OSD, LASIK and other corneal refractive surgery, eyelid problems and other causes of sever DED and unfitting for using a combination of dorzolamide and timolol.

Randomization:

The preservative and preservative-free formulations of dorzolamide and timolol combination medicines for open-angle glaucoma may affect ocular surface health. Preservative-free formulations improved OSDI scores, Schirmer test findings, tear break-up time, corneal and conjunctival staining, and IOP.

In outpatient clinic visits, ocular surface parameters were assessed monthly for up to 6 months.

All patients had a complete history and ophthalmological exam. Dorzolamide 2%/timolol 0.5% preservative-free or preservative-containing eye drops were used daily for 24 weeks. Use one drop twice day on afflicted eyes. Artificial tears and other glaucoma therapies were banned throughout the experiment.

Efficacy assessment:

OSDI is a reliable method for assessing dry eye symptoms and visual performance. Three subscales—ocular symptoms, visual function, and environmental triggers—make up the 12-item questionnaire. Regular, mild-to-moderate, and severe OSDI are distinguished by acceptable to excellent test–retest reliability.[٨ ,٩]

To measure tear film break-up time (TBUT), sodium fluorescein dye was injected into the eye and examined under the slit lamp while the patient resisted blinking until little dry spots developed. Usually, >10 seconds is considered normal, 5-10 seconds mild to moderate, and <5 seconds severe .[١٠]

Schirmer tested whether the eye produces enough tears to keep moist. Filter paper was inserted into the lower eyelid for the test without anesthetic. After 5 minutes, paper was removed and moisture tested [11]. Schirmer test results: Regular: >10 mm paper soaks in 5 minutes. Dryness might be modest (6-10 mm moisture after 5 minutes) or severe (≤ 5 mm wetness).

Evaluation of safety:

MedDRA recorded and categorized all study medication-related adverse events (AEs) by System Organ Class (SOC) and Preferred Term .

We assessed corneal and conjunctival surface damage using fluorescein-impregnated strips and Lissamine green. This staining approach may reveal ocular surface disease-related conjunctival changes. Standards were employed to grade conjunctival staining. Grading typically depends on staining location, extent, and intensity. Results were recorded for each eye.

OSDI score change from baseline to 24 weeks was the key efficacy measure. Secondary efficacy outcomes were baseline-to-24-week IOP changes.

Statistical analysis:

The statistical analysis was done using SPSS v28 (IBM©, Armonk, NY, USA). The Shapiro-Wilks test and histograms checked data normality. Mean and SD were used to evaluate parametric quantitative data using unpaired student t-test. Qualitative variables were presented as frequency and percentage (%) for Chi-square or Fisher's exact analysis. A two-tailed P value < 0.05 indicates significance.

Case 1:

50 years old female patient with mild primary open angle glaucoma she was completed an ocular surface disease index questionnaire and underwent evaluation by Schirmer test, tear breakup time with corneal and conjunctival staining. There were signs of possible shortage of tear production. Patient received preservative eye drop for 6 months then patient come with significant ocular surface disease. **Fig1**

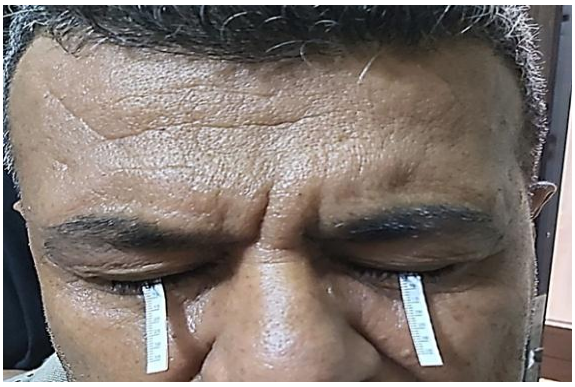
(A)

(B)

Fig. (1) (A) Schirmer test before using preservative medication, (B) Schirmer test after 12 weeks of using preservative medication

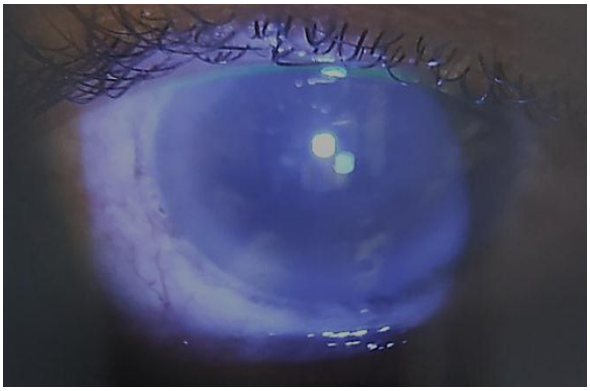
Case 2:

59 years old male patient with moderate open angle glaucoma. patient came with blurred vision, itching, redness and intolerance to windy conditions received preservative free eye drop for 6 months and there was improvement of symptoms and signs of OSD. **Figure 2**

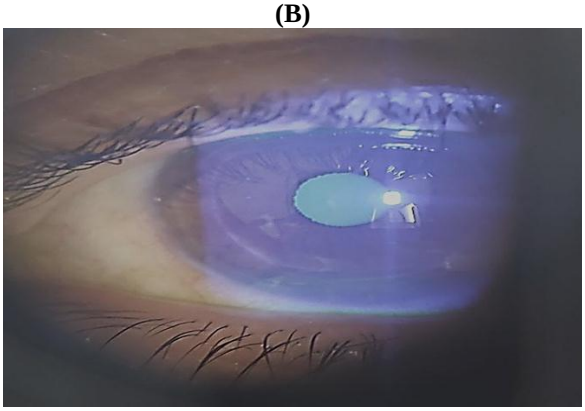


(A)

(B)



(C)



(D)

Fig. (2) (A) Schirmer test before using preservative free medication, (B) Schirmer test after using preservative free medication, (C, D) Tear breakup test

Results

According to ocular assessment, the mean OSDI severity score was 12.3. Schirmer teat mean measurement was 9.6 mm. The mean tear breaks up time was 9.7 sec, mean corneal staining score was 0.9 and Conjunctival staining score was 0.8±0.4. The comparison of age and gender distribution between the groups did not show a statistically significant difference. **Table 1**

Table(1)Demographic data compared in the studied groups

		PC (n=20)	PF (n=20)	Test	p
Age (years)		51.25±4.03	53.8±5.47	T=1.709	0.087
Gender	**Female**	10(50%)	13(65%)	X^2=0.921	0.337
	Male	10(50%)	7(35%)		

Data presented as mean ± SD or frequency (%), T = independent t test, X2= Chi-Square test, Group PF (preservative-free), Group PC (preservative).

OSDI score at baseline, W4, W8 and W12 didn't show significant difference between the studied groups. A significant higher OSDI scores were detected in PC group compared to PF group from W16 to W24 ($p<0.05$). In both PC and PF groups, OSDI score was significantly increased at W8, 12, 16, 20 and 24 compared to baseline ($P<0.05$).

Schirmer test at baseline, W4, 8, 12 and 24 didn't show significant difference between the studied groups. A significant lower Schirmer test were detected in PC group compared to PF group at W16 and W20 (p=0.036, 0.030). In PC group, Schirmer test was significantly decreased at W12, 16, 20 and 24 compared to baseline ($P<0.05$), with no significant difference at W4 and 8 compared to baseline. In PF group, Schirmer test was significantly decreased at W24 compared to baseline (P=0.008), with no significant difference at W4, 8, 12, 16, and 20 compared to baseline. **Table 2**

Table (2) OSDI and Schirmer test score between the studied groups

	PC (n=20)	PF (n=20)	Test	p
	OSDI			
Base	12.05 ± 0.94	12.2 ± 0.89	0.921	0.609
W4	12.25 ± 0.91	12.45 ± 0.76	0.763	0.455
W8	12.6 ± 0.88	12.70 ± 0.66	0.874	0.687
W12	13.2 ± 1.4	13.10 ± 0.79	5.843	0.778
W16	15.1 ± 1.02	13.90 ± 0.64	5.786	**<0.001***
W20	16.3 ± 1.4	14.60 ± 0.75	6.054	**<0.001***
W24	17.25 ± 0.85	15.45 ± 0.51	5.837	**<0.001***
P value within group	P1= 0.507	P1= 0.262		
	P2=0.024*	**P2=0.047***		
	P3=0.006*	**P3=0.003***		
	P4<0.001*	**P4<0.001***		
	P5<0.001*	**P5<0.001***		
	P6<0.001*	**P6<0.001***		
	Schirmer test			
Base	9.7 ± 0.3	9.5 ± 0.1	0.655	0.513
W4	9.65± 0.49	9.55 ± 0.51	0.374	0.531
W8	9.40 ± 0.50	9.45 ± 0.5	1.579	0.757
W12	9.25 ± 0.44	9.45 ± 0.51	0.374	0.194
W16	9.0 ± 0.65	9.40 ± 0.50	0.322	**0.036***
W20	8.95 ± 0.39	9.25 ± 0.44	0.593	**0.030***
W24	8.9 ± 0.49	9.1 ± 049	1.476	0.060
P value within group	P1= 0.772	P1= 1.00		
	P2=0.055	P2=0.494		
	P3=0.001*	P3=0.541		
	P4<0.001*	P4=0.419		
	P5<0.001*	P5=0.083		
	P6<0.001*	**P6=0.008***		

Data presented as mean ± SD, *: statistically significant as p value <0.05, P1: p value between base and W4, P2: p value between base and W8, P3: p value between base and W12, P4: p value between base and W16, P5: p value between base and W20, P6: p value between base and W24

In terms of TBUT test, at baseline, W4, 8 and 12 didn't show significant difference between the studied groups. A significant lower TBUT were detected in PC group compared to PF group from W16 to W24 ($p<0.05$). In PC group, TBUT test at W16, 20 and 24 was significantly decreased compared to baseline ($P<0.05$), with no significant difference at W4, 8 and 12 compared to baseline. In PF group, TBUT test at W20 was significantly decreased compared to baseline (P=0.031), with no significant difference at W4, 8, 12, 16 and 24 compared to baseline.

The corneal staining test at baseline, W4 and 8 didn't show significant difference between the studied groups. A significant increase in level of corneal stain detected in PC group compared to PF group from W12 to W24 ($p<0.001$). In PC group, corneal staining test at W8, 12, 16, 20 and 24 was significantly increased compared to baseline ($P<0.05$), with no significant difference at W4 compared to baseline. In PF group, corneal staining test at W4, 8, 16, 20 and 24 was significantly increased compared to baseline ($P<0.05$), with no significant difference at W12 compared to baseline. **Table 3**

Table(3) Tear breakup time mean measurements and Corneal staining (Oxford grading scale) compared in the studied groups

	PC (n=20)	PF (n=20)	Test	p
	TBUT			
Base	9.6 ± 0.2	9.7 ± 0.2	0.781	0.437
W4	9.4 ± 0.3	9.5 ± 0.3	0.000	1.000
W8	9.2 ± 0.3	9.4 ± 0.3	0.684	0.539
W12	9 ± 0.3	9.3 ± 0.3	3.464	0.194
W16	9.1 ± 0.3	9.3 ± 0.4	0.781	**0.035***
W20	8.1 ± 0.3	9.1 ± 0.3	5.785	**<0.001***
W24	7.5 ± 0.4	9.2 ± 0.3	5.689	**<0.001***
P value within group	P1= 0.772	P1= 0.772		
	P2=0.789	P2=0.330		
	P3=0.789	P3=0.267		
	P4=0.001*	P4=0.104		
	P5<0.001*	**P5=0.031***		
	P6<0.001*	P6=0.258		
	Corneal staining			
Base	0.9 ± 0.0	0.8 ± 0.0	0.000	1.000
W4	1.15 ± 0.37	1.4 ± 0.50	0.987	0.080
W8	1.30 ± 0.57	1.2 ± 0.41	0.865	0.529
W12	2.05 ± 0.51	1.3 ± 0.66	3.025	**<0.001***
W16	2.25 ± 0.72	1.4 ± 0.68	4.254	**<0.001***
W20	2.60 ± 1.05	1.4 ± 0.68	4.628	**<0.001***
W24	2.90 ± 1.12	1.65 ± 1.09	4.112	**0.001***
P value within group	P1= 0.083	**P1= 0.002***		
	P2=0.030*	**P2=0.042***		
	P3<0.001*	P3=0.055		
	P4<0.001*	**P4=0.017***		
	P5<0.001*	**P5=0.017***		
	P6<0.001*	**P6=0.015***		

Data presented as mean ± SD, *: statistically significant as p value <0.05, P1: p value between base and W4, P2: p value between base and W8, P3: p value between base and W12, P4: p value between base and W16, P5: p value between base and W20, P6: p value between base and W24

The conjunctival staining test at baseline, W4, 8, 12, and 16 didn't show significant difference between the studied groups. A significant increase in level of conjunctival stain detected in PC group compared to PF group at W20 and W24 (P=0.037, <0.001). In both PC and PF groups, conjunctival staining test at W4, 8, 12, 16, 20 and 24 was significantly increased compared to baseline (P<0.05).

IOP at baseline, W4, W8 didn't show significant difference between the studied groups. A significant decrease in IOP was detected in PF group compared to PC group from W12 to W24 (p<0.05). In PC and PF groups, IOP at W4, 8, 12, 16, 20 and 24 was significantly decreased compared to baseline (P<0.05). **Table 4**

Table (4) Conjunctival staining (Oxford grading scale) and Intraocular pressure (IOP) compared between the studied groups

	PC (n=20)	PF (n=20)	Test	p
	Conjunctival staining			
Base	0.8 ± 0.2	0.7 ± 0.4	0.000	1.000
W4	1.15 ± 0.37	1.1 ± 0.31	0.983	0.446
W8	1.30 ± 0.47	1.2 ± 0.41	0.754	0.344
W12	1.50 ± 0.83	1.35 ± 0.67	3.577	0.459
W16	1.70 ± 0.86	1.35 ± 0.67	3.577	0.128
W20	2.1 ± 1.4	1.35 ± 0.67	2.161	**0.037***
W24	2.55 ± 1.10	1.4 ± 0.82	4.073	**<0.001***
P value within group	**P1= 0.042***	**P1= 0.030***		
	P2=0.005*	**P2=0.017***		
	P3=0.008*	**P3=0.008***		
	P4=0.001*	**P4=0.008***		
	P5<0.001*	**P5=0.008***		
	P6<0.001*	**P6=0.010***		
	IOP			

Base	23.3 ± 1.45	23.1 ± 0.64	0.420	0.674
W4	18.4 ± 3.5	18.3 ± 3.35	0.275	0.891
W8	17.6 ± 4.22	17.1 ± 3.57	0.583	0.718
W12	17.1 ± 0.90	16.4 ± 0.80	2.600	**0.014***
W16	17.2 ± 0.82	16.2 ± 0.80	3.904	**<0.001***
W20	17.5 ± 3.8	16.4 ± 3.22	4.480	**<0.001***
W24	17.8 ± 3.93	16.2 ± 3.72	2.554	**<0.001***
P value within group	**P1<0.001***	**P1<0.001***		
	P2<0.001*	**P2<0.001***		
	P3<0.001*	**P3<0.001***		
	P4<0.001*	**P4<0.001***		
	P5=0.001*	**P5=0.001***		
	P6<0.001*	**P6<0.001***		

Data presented as mean ± SD, *: statistically significant as p value <0.05, P1: p value between base and W4, P2: p value between base and W8, P3: p value between base and W12, P4: p value between base and W16, P5: p value between base and W20, P6: p value between base and W24.

Discussion

Preservatives keep multidose glaucoma medicines sterile and prevent contamination. On the other side, they may induce conjunctival inflammation, corneal epithelial cell damage, and tear film instability, among other eye surface concerns. [5].

Demographics showed no statistically significant variation in age or gender across groups.

These results agree with Akçay et al. [12], who found no significant age or gender differences across groups (P > 0.05).

Our investigation demonstrated no significant OSDI score difference between groups at baseline, w4, w8, and w12. The PC group had substantially higher OSDI ratings from w16 to w24 compared to the PF group (P<0.05). OSDI score substantially increased at W 8, 12, 16, 20, and 24 compared to baseline (P<0.05) in both groups. At the conclusion of the trial (w24), PC had a higher OSDI score.

Mohamed et al. [13] found that the OSDI score was significantly different between the two groups (46.7% of patients in preservative-free group had normal OSDI score compared to 0% in preservative group, 26.7% had mild complaints, 20% had moderate complaints, and 6.6% had severe complaints versus 6.7% &33.3% and 60.0% respectively) (P value=0.001).

Contrary to our findings, Cvenkel et al. [14] found no statistically or clinically significant difference in OSDI scores between glaucoma-treated and untreated patients, despite increased ocular surface changes in clinical tests and impression cytology.

Schirmer test mean readings at baseline, W4, 8, 12, and 24 were not significantly different across groups in our research. PC group had a poorer Schirmer test at W16 and W20 than PF group (p=0.036, 0.030). Schirmer test dropped considerably in PC group at W12, 16, 20, and 24 compared to baseline (P<0.05). PF group Schirmer test reduced at W24 compared to baseline (P=0.008). Schirmer test mean measurements indicated no significant difference between groups at study end (w24).

Mylla Boso et al. [15] found that 64.71% of treated glaucomatous eyes had normal Schirmer test tear production (>10 mm). None of the eyes exhibited severe tear insufficiency, whereas 17.65% had mild and moderate. His result may be explained by OSD's compensating reflex stimulation to tear production. Restoring ocular surface homeostasis may reduce reflective lacrimation and enhance lipid layer, lowering TMH and Schirmer test readings.

Our baseline, W4, 8, and 12 TBUT test findings showed no significant difference between groups. TBUT was significantly lower in PC group compared to PF group from W16 to W24 (p<0.05). The TBUT test at W16, 20, and 24 was considerably lower in the PC group compared to baseline (P<0.05). At W20, PF group TBUT test was considerably lower than baseline (P=0.031). At study conclusion (w24), PC group TBUT mean values were considerably lower than PF group.

Baseline corneal staining test findings showed a substantial rise in PC group compared to PF group from W12 to W24 (p<0.001). The PC group showed substantial increases in corneal staining at W 8, 12, 16, 20, and 24 compared to baseline (P<0.05). The PF group showed substantial corneal staining increases at W4, 8, 16, 20, and 24 compared to baseline (P<0.05). The baseline, W4, 8, 12, 16, and 20 conjunctival staining tests showed no significant differences between groups. A substantial increase in conjunctival stain was seen in the PC group at W24 compared to the PF group (P<0.001). Both PC and PF groups showed substantial increases in conjunctival staining at W4, 8, 12, 16, 20, and 24 compared to baseline (P<0.05). At study conclusion (W24), PC group had significantly more corneal and conjunctival staining than PF group.

According to Mohamed et al. [13], the Schirmer test showed significant differences between the two groups. Patients who received preservative-free PGAs had normal values (>10mm

wetting of Schirmer paper) compared to 13.3% in the other group (P >0.001). Patients in the PF group had moderate Schirmer 1 (≤10 mm wetting) and severe decrease (>5 mm wetting) compared to (66.7% & 20% respec.). Baseline IOP was not statistically different between groups A and B (p = 0.717), however group A had substantially lower mean IOP after 1 month (p = 0.006), 2 months (p= 0.003), and 3 months (p = 0.018). TBUT, Schirmer test, Fluorescein stain, OSDI, and IC showed no significant variation in pretreatment ocular surface characteristics between the two groups. After 3 months of therapy, there was a very significant change in TBUT, Schirmer 1 test, F1uorescein stain, OSDI, and IC [13].

In contrast, Wong et al. [16] found significantly lower tear film osmolarity, TBUT, and tear meniscus height in treated eyes. Ocular surface staining was not statistically significant, unlike our research where preservative-free corneal staining was considerably decreased at weeks 20 and 24.

The PF group showed a substantial reduction in IOP from W12 to W24 compared to the PC group (p<0.05). At W4, 8, 12, 16, 20, and 24, IOP reduced considerably in PC and PF groups compared to baseline (P<0.05). IOP decreased more in PF than PC groups at the conclusion of the research.

Chamard et al. [17] found that switching from preserved to preservative-free eye drops improved OSDI.

Limitations: A single-center research with a limited sample size may restrict its generalizability. Longer-term observations were excluded from the 24-week follow-up.

To confirm our results, large-scale prospective investigations with multicenter collaboration and higher sample numbers are required. A longer follow-up would help determine how glaucoma drugs affect the ocular surface and late-onset adverse events.

Conclusions:

When it comes to treating open-angle glaucoma, the decision between preservative-containing and preservative-free versions of the combination drug dorzolamide and timolol may have a major influence on the health of the eye's surface. Results on OSDI scores, Schirmer tests, tear break-up time, corneal and conjunctival staining, and intraocular pressure (IOP) were all better in patients who received formulations without preservatives as compared to those who received preserved drugs.

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