

## Original Article

## Effects of preservative-free and preservative prostaglandin analogs on ocular surface by impression cytology in glaucoma patients

Ophthalmology

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### ABSTRACT

**Background:** Glaucoma represents a significant health problem and is an important cause of blindness worldwide. In order to delay the onset of advanced irreversible optic nerve injury and visual field abnormalities, topical medication treatment is typically used as first-line therapy.

**Objectives:** To compare the effects of preservative-free and preservative-containing prostaglandin analogs on ocular surface by using impression cytology (IC) in newly diagnosed primary open angle glaucoma (POAG) patients.

**Methodology:** A prospective randomized controlled clinical trial was done on 60 eyes of 30 patients with POAG and randomly divided into group A (n = 30) received preservative-free prostaglandin analogs and group B (n = 30) received preservative-containing prostaglandin analogs.

**Results:** Clinical assessment of ocular surface features showed a significant difference between two study groups after 3 months of treatment. Schirmer test, tear film break up time (TBUT) and Fluorescein corneal staining ( $P < 0.001$ ). IC was significantly different between the two groups ( $P < 0.001$ ). Also, the ocular surface disease index (OSDI) questionnaire score was significantly different between the two groups ( $P < 0.001$ ). There was a significant difference in intra ocular pressure (IOP) between the two study groups ( $P = 0.018$ ).

**Conclusion:** Our study concluded that glaucoma patients treated with preservative-free prostaglandin analogs have less ocular surface side effects than those treated with preservative-containing prostaglandin analogs. This finding suggests improving the tolerability of the topical medications that reflected on the patient compliance, efficacy of treatment, and control of glaucoma.

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**Keywords:** Primary open angle glaucoma, tear film breakup time test, impression cytology, prostaglandin analogs, preservative-free antiglaucoma.

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### INTRODUCTION

Glaucoma is a serious disease and a leading cause of blindness in the world. In order to delay the onset of advanced irreversible optic nerve injury and visual field abnormalities, topical medication treatment is typically used as first-line therapy<sup>[1]</sup>. Glaucoma drugs' lifespan are increased by the addition of preservatives. Some studies revealed that their detergent characteristics facilitated the penetration of the glaucoma drops' active components. Moreover, it has powerful bactericidal and fungicidal

properties that can reduce the development of pathogenic organisms<sup>[2]</sup>. Benzoalkonium chloride (BAK) might cause harmful effects include a worsening of dry eyes and a minor inflammatory reaction in the epithelial cells of the conjunctiva and cornea. Additionally, it may result in tear film instability, decreased tear secretion, impaired Schirmer's test, accelerated tear evaporation, shortened tear film break up time (TBUT), apoptotic of conjunctival cells, destruction of corneal epithelial cells and damage

of conjunctival goblet cells [3]. Conjunctiva is a semi-permeable natural barrier to topical medications. In response to stressful conditions, the conjunctiva gets irritated, loses its vascularization, and displays a range of metaplasia, including the loss of goblet cells along with stratification and keratinization. Ocular toxicity symptoms including superficial punctate keratitis are a sign of persistent cell injury [4]. Impression cytology (IC) was regarded as a secure, non-invasive technique. It is simple to repeat and may be used to diagnose and track progress at the cellular level caused by a variety of diseases. The principle IC is to collect epithelial samples by affixing cellulose filter paper to the conjunctival surface. It examines the cytological level of conjunctival surfaces. This approach aims to assess a variety of the ocular surface according to the cell morphology of the conjunctival epithelium, the ratio of cytoplasm nucleus and the goblet cell density [5]. The aim of this work is to compare the effects of preservative-free and preservative-containing BAK prostaglandin analogs (PGAs) on ocular surface by using IC in newly diagnosed primary open angle glaucoma (POAG) patients.

## PATIENT AND METHODS

A Prospective randomized controlled clinical trial was performed at the ophthalmology department and Histopathology department, Al-Zahraa University Hospital, Al-Azhar University from September 2021 to April 2022. This study was approved by the Ethics Board of Al Azhar University and was conducted in accordance with the World Medical Association Declaration of Helsinki Guidelines. All participants received a full explanation about the study with informed consent was obtained. Study population: The study included 60 eyes of 30 newly diagnosed POAG who randomly divided into two groups:

- **Group A (30 eyes):** received preservative-free PGAs eye drop Tafluprost 0.015% (Taflupro; Orchidia, Pharmaceuticals Industries, Cairo, Egypt).
- **Group B (30 eyes):** received preservative-containing PGAs eye drop Latanoprost 0.005% (Ioprost; Orchidia, Pharmaceuticals Industries, Cairo, Egypt).

**Inclusion criteria:** Age between 40 and 70 years old and patients newly diagnosed with POAG.

**Exclusion criteria:** Patients younger than 40 or older than 70, patient incontinent for treatment or follow up, patient received other topical ocular treatment, history of ocular surgery, ocular surface diseases, collagen vascular disease, hypersensitivity to therapy, contact lenses wearer, allergic conjunctivitis, ocular surgery within 3 months prior to the study, corneal abnormalities affecting tonometry including refractive corneal surge.

## Methods

Every patient was scheduled for 4 visits throughout the study: a baseline visit, visits at 30, 60, and 90 days of therapy.

### At baseline visit, Patients underwent full clinical examination including:

Detailed medical and surgical history of the patient about family history of glaucoma, history of receiving any topical or systemic treatment previously and history of symptoms of dryness like burning, stinging, foreign body sensation, tearing, or itching were taken.

Measurement of best corrected visual acuity (BCVA), full ophthalmological examination by TOPCON slit-lamp bio-microscopy using +90 D noncontact lens, intraocular pressure (IOP) measurement was done using Goldmann applanation tonometer.

Examination of anterior chamber angle using Gonio lens 3mirror; after installation of topical anesthesia, the angle was examined for its width and presence of pigmentation, angle grades were classified according to the Shaffer-Etienne scale, based on the visibility of angle structures and giving numerical grade (0-4) to each angle with corresponding anatomical description. Angle should be graded 3 or 4 for diagnosis of POAG.

Investigations include; Field of vision (Automated perimetry central 24-2) using Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Jena, Germany), spectral-domain optical coherence tomography (OCT) of the optic disc using RTVue XR Avanti instrument (AngioVue; Optovue, Inc, Fremont, California, USA), were done for every patient at the baseline visit.

### Recording symptoms and signs of Ocular surface disease as follow:

Ocular symptoms including: tears, itching, foreign body feeling, irritation, burning, and dry eye sensation. The ocular surface disease index (OSDI) questionnaire organized into three parts. Questions regarding ocular symptoms of dry eye syndrome, ocular symptoms when reading or watching television, and questions about ocular symptoms brought on by environmental variables make up the first category of questions. The OSDI questionnaire was rated on a scale from 0 to 4, where 0 denotes never, 1; represents occasionally, 2; represents half of the time, 3; represents the majority of the time, and 4; represents always [6].

### Ocular signs including

**Schirmer 1 test:** Measures the amount of total tear flow that are produced when a filter sheet is inserted into the conjunctival sac at the intersection of the middle and lateral 1/3 of the lower eyelid. The amount of sheet wet by tear during 5 minutes was measured in millimeters. Normal; >10 mm soaking of the paper, moderate; 6-10 mm soaking of the paper and severe; 3-5 mm soaking of the paper [7].

**TBUT:** Using a fluorescein paper dipped in a drop of normal saline, a little amount of fluorescein was inserted into the inferior fornix. The patient was instructed to maintain open eyelids after a few blinks, and the time between the last completed blink and the first black point, or breakage of the tear film, which observed through the use of a cobalt blue filters, was noted. Normal; >10sec; Moderate; Severe; 6-10sec; and 5 sec [8].

**Fluorescein corneal staining:** Assessing corneal epitheliopathy. Using a scale of 0-3, the van Bijsterveld grading method was used to assess the amount and distribution of the spots. On the cornea and two exposed conjunctival zones, intensity was assessed using the VAN BIJSERVELD scale. Each zone is scored 0–3, with a maximum score of 9. (1 indicates no staining, 2 indicates significant staining, and 3 indicates extensive staining) [9].

**IC:** After instillation of 0.4% benoxinate hydrochloride (Benox; International Pharmaceutical Industries Co.E.I.P.I.Co, Egypt), the conjunctival epithelium's outermost layers were removed from the ocular surface using 5 mm x 5 mm cellulose acetate filter paper (0.22 mm pore size), and the slides were stained with hematoxylin and eosin for examination under a light microscope. Grading by Nelson's grading system from 0 to III [5].

- **Grade 0:** shows small and rounded epithelial cells with excessive in the no. of goblet cells.
- **Grade 1:** shows bigger and polygonal epithelial cells and decrease in the no. of goblet cells.
- **Grade 2:** shows much bigger and polygonal epithelial cells and few goblet cells.
- **Grade 3:** shows biggest epithelial cells with basophilic cytoplasm. The nucleus is small, picnotic and goblet cells are totally disappeared [10].

**Statistical analysis**

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean± standard deviation and ranges. Also qualitative variables were presented as number and percentages. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk Test. Independent-samples t-test of significance was used when comparing between two means & Mann Whitney U test: was used for comparisons between two-group with non-parametric data. The Comparison between groups with qualitative data was done by using Chi-square test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant p- <0.05, and p >0.05 was considered insignificant.

**RESULTS**

**Table (1): Comparison between group A and group B according to severity of glaucoma**

Severity of glaucoma	Group A n =15 patients	Group B n =15 patients	Stat. test	p-value
Advanced	1 (6.6%)	2 (13.3%)	X <sup>2</sup> = 0.410	0.815
Early	7 (46.7%)	7 (46.7%)		
Moderate	7 (46.7%)	6 (40.0%)		

X<sup>2</sup>: Chi-square test

**Table (2): Comparison between group A and group B based on IOP**

IOP	Group A n = 30 eyes	Group B n = 30 eye	Stat. test	P-value
<b>Baseline</b>				
- Mean ± SD	24.80±2.66	25.10±3.64	t = -0.364	0.717
- Range	20-29	15-32		
<b>After 1 month</b>				
- Mean ± SD	20.34±2.88	22.11±1.85	t =2.832	0.006*
- Range	14-26	16-27		
<b>After 2 month</b>				
- Mean ± SD	18.20±2.97	20.24±1.97	t =3.135	0.003*
- Range	12-25	14-26		
<b>After 3 month</b>				
- Mean ± SD	16.17±3.35	18.03±2.51	t = 2.440	0.018*
- Range	10-23	12-22		

t: t-Independent Sample t-test , \* Significant p-value (<0.05), IOP: Intraocular pressure

**Table (3): Comparison between group A & group B pre-treatment based on clinical features**

Pretreatment of clinical features	Group A n=30 eyes	Group B n=30 eyes	Stat. test	p-value
	n (%)	n (%)		
<b>TBUT</b>			$X^2 = 2.411$	0.121
- Normal	26 (86.7)	30 (100.0)		
- Moderate	4 (13.3)	0 (0.0)		
- Severe	0 (0.0)	0 (0.0)		
<b>Schirmer test</b>			$X^2 = 2.411$	0.121
- Normal	26 (86.7)	30 (100.0)		
- Moderate	4 (13.3)	0 (0.0)		
- Severe	0 (0.0)	0 (0.0)		
<b>Fluorescein stain</b>			$X^2 = 2.411$	0.121
- Normal	26 (86.7)	30 (100.0)		
- Moderate	4 (13.3)	0 (0.0)		
- Severe	0 (0.0)	0 (0.0)		
<b>OSDI</b>			$X^2 = 0.079$	0.778
- Normal	22 (73.3)	20 (66.7)		
- Mild	8 (26.7)	10 (33.3)		
- Moderate	0 (0.0)	0 (0.0)		
- Severe	0 (0.0)	0 (0.0)		
<b>Impression cytology</b>			$X^2 = 2.411$	0.121
- Grade G1	26 (86.7)	30 (100.0)		
- Grade G2	4 (13.3)	0 (0.0)		
- Grade G3	0 (0.0)	0 (0.0)		

$X^2$ : Chi-square test, \* Significant p-value (<0.05)

In the present study, the two study groups did not have significant difference in glaucoma severity. Group A had 7(46.7%) mild cases similar to 7 (46.7%) in group B. In group A, there were 7 (46.7%) moderate cases and 1 (6.6%) severe case compared to 6 (40%) and 2 cases (13.3%) respectively in group B. P=0.0815 (table 1).

The two study groups did not differ significantly in term of Baseline IOP (p = 0.717) but the mean IOP was highly significantly lower in group A than in group B throughout the study period of follow up after 1 month (p = 0.006) , 2 months (p= 0.003) and 3 months (p = 0.018) (table 2).

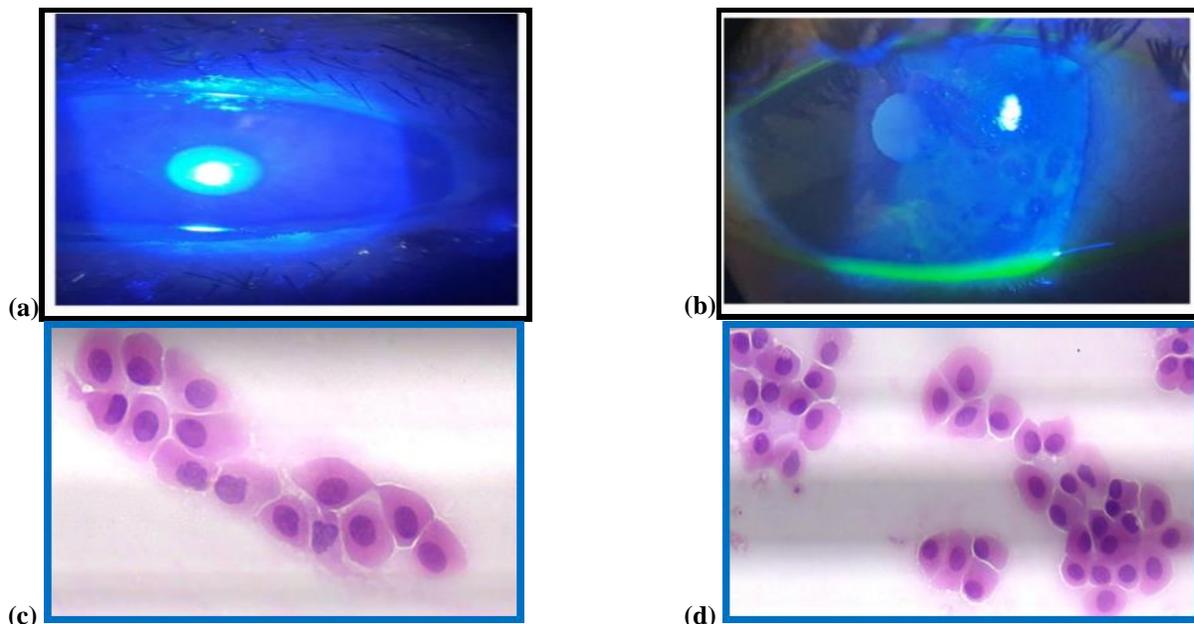
Regarding the clinical assessment of ocular surface features in the two groups pretreatment there was not a significant difference, TBUT (p= 0.121), Schirmer 1 test (p=0.121),Fluorescein stain (p= 0.121),OSDI (p= 0.778), IC (p=0.121) (table 3 and figure1, 2).

Regarding the clinical assessment of ocular surface features in the two groups after 3months of treatment there was highly significant difference TBUT (p<0.001), Schirmer 1 test (p<0.001), Fluorescein stain (p<0.001), OSDI (p<0.001), and IC (p <0.001) (table 4 and figure 1, 2).

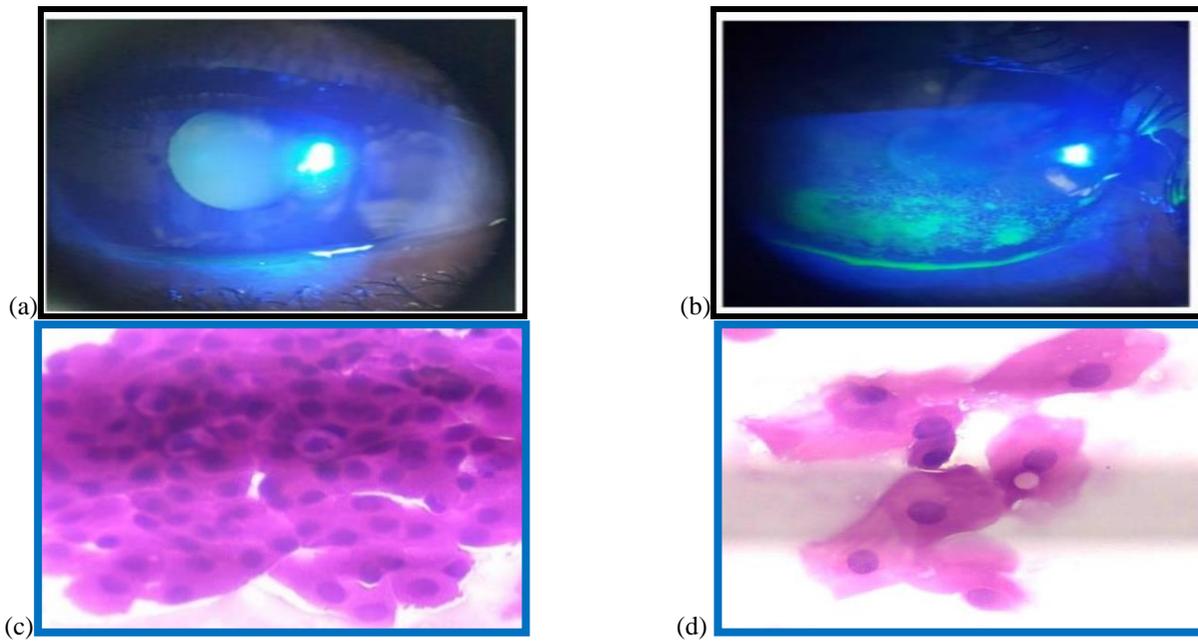
Table (4): Comparison between group A and group B post treatment based on clinical features

Post-treatment of clinical features	Group A n =30 eyes	Group B n =30 eyes	Stat. test	p-value
	n (%)	n (%)		
<b>TBUT</b>				
- Normal	24 (80.0)	4 (13.3)	$X^2 = 26.952$	<0.001*
- Moderate	4 (13.3)	20 (66.7)		
- Severe	2 (6.7)	6 (20.0)		
<b>Schirmer test</b>				
- Normal	24 (80.0)	4 (13.3)	$X^2 = 26.952$	<0.001*
- Moderate	4 (13.3)	20 (66.7)		
- Severe	2 (6.7)	6 (20.0)		
<b>Fluorescein stain</b>				
- Normal	24 (80.0)	4 (13.3)	$X^2 = 26.952$	<0.001*
- Moderate	4 (13.3)	20 (66.7)		
- Severe	2 (6.7)	6 (20.0)		
<b>OSDI</b>				
- Normal	14 (46.7)	0 (0.0)	$X^2 = 31.400$	<0.001*
- Mild	8 (26.7)	2 (6.7)		
- Moderate	6 (20.0)	10 (33.3)		
- Severe	2 (6.6)	18 (60.0)		
<b>Impression cytology</b>				
- Grade G1	24 (80.0)	4 (13.3)	$X^2 = 26.952$	<0.001*
- Grade G2	4 (13.3)	20 (66.7)		
- Grade G3	2 (6.7)	6 (20.0)		

X<sup>2</sup>: Chi-square test, \* Significant p-value (<0.05)



Figure(1):Images of Fluorescein stain in group A (a) pretreatment .(b) post treatment. Images of Impression cytology in group A (c) Pretreatment shows G1: small and polygonal cells with eosinophilic cytoplasm and bignucleus (H&E x200 magnification power). (d) Post treatment shows G1: small and polygonal cells with eosinophilic cytoplasm and bignucleus (H and E x200 magnification power).



**Figure (2):**Images of fluorescein stain in group B (a) Pretreatment .(b) post treatment. Images of Impression cytology in group B (c) pretreatment shows G1: small and polygonal cells with eosinophilic cytoplasm and big nucleus (H&E x200 magnification power). (d) Post treatment shows G3:Biggest and polygonal cells with eosinophilic cytoplasm and small nucleus (H&E x200 magnification power).

## DISCUSSION

Glaucoma requires long-term, typically life-long therapy because it is a symptomless but sight-threatening disease. Gaining patient agreement and persistence to treatment is essential if chronic deterioration and possible vision loss are to be prevented. While there are many obstacles to effective adherence, one of the biggest is drug side effects. Initial evidence indicates that treating SD in glaucoma patients can enhance their clinical outcome and early treatment adherence patterns are associated with improved long-term adherence. Therefore, improvements in the tolerability of topical glaucoma medications are likely to have a positive effect on adherence as well as the quality of life of patients <sup>[11]</sup>.

The European Glaucoma Society (EGS) has authorized the use of PGAs as first-line glaucoma therapy due to their ability to effectively lower IOP and their well-established safety profile. These agents represent the basis of treatment for ocular hypertension and POAG <sup>[12]</sup>. But most PGAs contain BAKs as a preservative which is accused to be the cause of many ocular surface problems in patients receiving anti-glaucoma medications. In the present study, we aimed to clarify the effect of topical preservatives on ocular surface, and to compare the ocular surface adverse effects in patients receiving preservative-free and preservative-containing PGAs. In this study, regarding baseline IOP (mean± SD), no significant difference was found between the group received preservative-free PGAs (24.8±2.66) and the other group received preservative-containing PGAs (25.1±2.364). After three months of follow up, every patient in our study had been assessed clinically and histologically

to evaluate the efficacy of the drug in controlling IOP as a secondary outcome measure, and also to detect any side effect developed other than ocular surface effects.

Regarding the clinical evaluation of patient's ocular surface characteristics of the two groups in our study, Schirmer1 test was significantly different between the two groups (80% of patients who received preservative-free PGAs had normal values (>10mm wetting of the schirmer paper) compared with 13.3% in the other group (P <0.001); while, (13.3%) of patients in the PF group showed moderate schirmer 1 test (≤10 mm wetting of the paper) and (6.7%) showed severe decrease in schirmer test (<5 mm wetting of schirmer paper) compared to (66.7% & 20% respectively ) in preservative group. Similar results were obtained by Uusitalo et al. <sup>[13]</sup> who found that the percentage of patients exhibiting abnormal schirmer test at baseline during latanoprost treatment was (71.5%), and at 6 and 12 weeks of treatment with PF tafluprost was (61.5%) & (59.4%) respectively (p = 0.003 at 12 weeks).

Regarding TBUT test, the current results were significantly different among the two groups: 80% of patients received PF-PGAs had normal values (>10 seconds) compared to 13.3% of patients received preserved-PGAs (P value<0.001), in addition, 13.3% of patients received preserved-PGAs showed moderate (≤5 seconds) and 6.7% showed severe (immediate appearance of dry spot) dryness compared to (66.7% & 20% respectively) of patients received preserved-PGAs. In agreement, Leet al. <sup>[14]</sup> showed that TBUT using

preserved-PGAs was proportionally worse to that using PF-PGAs (P=0.06).

Regarding fluorescein corneal staining we found that there were significant differences between the two groups: 80% of patients received preservative-free PGAs (taflupro ED) had normal values compared to 13.3% of patients received preserved-PGAs (Ioprost ED) (P<0.001), 13.3% of patients received preserved-PGAs showed moderate increase in corneal staining score compared to 66.7% of patients received preserved-PGAs, and 6.7% of patients of patients received preservative-free PGAs showed severe increase in corneal staining compared to 20% of patients received preserved. Also, Walimbe et al. [15] revealed similar result in his study as he found that inferior corneal staining score decreased significantly (P=0.003) when patients switched to BAK-free Latanoprost ophthalmic solution.

Regarding the histological assessment of ocular surface features, conjunctival samples were obtained by IC and analyzed by light microscopy using Nelson's grading scheme (grades 0-3), and we found that IC differed significantly between the two groups after three months of treatment (P < 0.001). Similarly, Cvenkel et al. [16] found that IC grade in patients received preservative-containing anti-glaucoma medications was significantly higher than the control group (P < 0.001).

Concerning the OSDI Questionnaire in the two groups, the 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, also, 26.7% of patients in preservative-free group had mild complaints in OSDI questionnaire, 20% had moderate complaints and 6.6% had severe complaints versus (6.7% & 33.3% and 60.0% respectively) among preservative group (P value=0.001). Asiedu and Abu [17] found that the mean OSDI value was considerably decreased in the BAK free travoprost 0.004% group opposed to the BAK preserved-latanoprost 0.005% group.

Regarding IOP follow up, both preservative and preservative-free groups reduced IOP significantly, but with follow-up preservative-free taflupro showed more IOP reduction than the other medication. As we noticed in our study that some side effects in the preservative-containing eye drops caused patients to miss days without putting the eye drop which may be the cause of difference in IOP control in both groups. In agreement, Konstas et al. [18] found that comparing PF-tafluprost treatment to preserved latanoprost, PF-tafluprost showed statistically higher 24-hour efficacy and increased tolerability. It also resulted in a higher decrease in the mean, peak, and fluctuation of the 24-hour IOP, involving the 02:00 and 06:00 time periods (P<0.05).

## CONCLUSION

Glaucoma patients treated with PF-PGAs have less ocular surface side effects than those treated with preservative-containing PGAs. This may increase the tolerability of the topical medications which may be reflected on the patient compliance, efficacy of treatment, and control of glaucoma.

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## المخلص العربي

تأثير قطرات نظائر البروستاجلاندين الخالية وذات المواد الحافظة على سطح العين بواسطة علم الخلايا الانطباعي في مرضى الجلوكوما

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### ملخص البحث

**الخلفية:** تمثل الجلوكوما مشكلة صحية كبيرة وهو من أهم أسباب العمى في جميع أنحاء العالم. يعتبر العلاج الطبي وسيلة فعالة للسيطرة على الجلوكوما في مرحلته الأولية. يستخدم العلاج الطبي الدوائي الموضوعي بشكل أساسي كاختيار أول لتجنب ظهور المزيد من التلف الذي لا رجعة فيه في العصب البصري وعيوب المجال البصري.

**الهدف:** مقارنة تأثير قطرات نظائر البروستاجلاندين الخالية من المواد الحافظة والتي تحتوي على مواد حافظة (بنزلكونيم كلوريد) على سطح العين بواسطة علم الخلايا الانطباعي في مرضى تم تشخيصهم حديثاً بجلوكوما الزاوية المفتوحة الأولية.

**الطرق:** تمت الدراسة على 60 عين ل 30 مريض تم تشخيصهم حديثاً بجلوكوما الزاوية المفتوحة، تم تقسيمهم عشوائياً لمجموعتين، مجموعته أ (30 عين) استخدموا قطرة مشتقات البروستاجلاندين التي لا تحتوي على مادة حافظة و مجموعته ب(30 عين) استخدموا قطرة مشتقات البروستاجلاندين التي تحتوي على مادة حافظة.

**النتائج:** أظهر التقييم السريري لسطح العين فرقاً كبيراً بين المجموعتين الدراسيتين بعد 3 أشهر من العلاج. اختبار شيرمر، وقت تكسير الغشاء الدمعي وصبغة الفلوريسين. كان علم الخلايا الانطباعي مختلفاً بشكل كبير بين المجموعتين. أيضاً، كانت درجة استبيان مؤشر مرض سطح العين مختلفة بشكل كبير بين المجموعتين.

**الاستنتاجات:** إن مرضى الجلوكوما الذين عولجوا بنظائر البروستاجلاندين الخالية من المواد الحافظة لديهم آثار جانبية أقل على سطح العين من أولئك الذين عولجوا بنظائر البروستاجلاندين المحتوية على مواد حافظة. قد يزيد هذا من تحمل الأدوية الموضوعية مما قد ينعكس على امتثال المريض وفعالية العلاج والسيطرة على الجلوكوما.

**الكلمات المفتاحية:** جلوكوما الزاوية المفتوحة الأولية، وقت تكسير الغشاء الدمعي، علم الخلايا الانطباعي، نظائر البروستاجلاندين، مضاد الجلوكوما خالي من المواد الحافظة.

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