

## Prostaglandin vs Dorzolamide/Timolol Effect on Anterior Scleral Thickness in Patients with Primary Open Angle Glaucoma By Using Anterior Segment Optical Coherence Tomography

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### Abstract

**Background:** analogues of prostaglandin are usually the first-line prescribed drops therapy in patients with glaucoma, but the mechanism of their action is not completely understood.

**Objectives:** Our study aims to compare anterior scleral thickness in glaucoma patients taking prostaglandins vs dorzolamide/timolol combinations

**Patients and methods:** This was a interventional prospective randomized study that included 60 adults with primary OAG randomized to receive either PG analogues or Dorzolamide/Timolol fixed combination drugs. The AST was evaluated manually by the built-in calipers of a platform provided in the OCT tools at three locations (scleral spur, 1000  $\mu$ m, and 2000  $\mu$ m behind the scleral spur) in the temporal and nasal meridians.

**Results:** The AST at the nasal area showed a decrease of 15.5 microns (SD = 21.4, p = .000). 1000-micron posterior to it, a decrease of 11.5 microns (SD = 5.5, p = .000), and 2000-micron posterior to it, 9.3 (SD = 6.3, p = .000). The AST at the temporal area demonstrated a decrease of 22.3 microns (SD = 8.6, p = .000). 1000-micron posterior to it, 20.9 microns (SD = 14, p = .000), and 2000-micron posterior to it, 20 microns (SD = 13.2, p = .000)

**Conclusion:** The use of prostaglandin analogues and dorzolamide/timolol showed a significant decrease in anterior scleral thickness in all measured points; over the nasal and temporal scleral spurs, and 1000 microns posterior to them, and 2000 microns posterior to them with no statistically significant difference between the two drugs.

**Keywords:** Glaucoma; Prostaglandin; Dorzolamide/Timolol.

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DOI: 10.21608/SVUIJM.2023.209912.1583

Received: 15 June, 2023.

Revised: 5 July, 2023.

Accepted: 11 July, 2023.

Published: 16 May, 2024

**Cite this** article as: Aya Mostafa Abozeid Makled, Wael Elshazly Eida, Ahmed Ali Ahmed Ammer, Ahmad Hassan Aldghaimy.(2024). Prostaglandin vs Dorzolamide/Timolol Effect on Anterior Scleral Thickness in Patients with Primary Open Angle Glaucoma By Using Anterior Segment Optical Coherence Tomography. *SVU-International Journal of Medical Sciences*. Vol.7, Issue 1, pp: 753-767.

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## Introduction

The aqueous humor exits the eye in one of two ways: either through the conventional or trabecular outflow pathway, which makes up between 70 and 95 percent of the aqueous humor outflow and consists of the trabecular meshwork, the Schlemm canal, intrascleral channels, and episcleral and conjunctival veins (Allingham et al., 2012), or the uveoscleral or unconventional outflow, in which the aqueous humor leaves the eye by passing through the root of iris, between the ciliary muscle bundles, and to the suprachoroidal and scleral tissues (Tamm, 2009). Almost, 5–30% of the aqueous humor outflow is caused by the uveoscleral outflow route (Toris, 1999). It is well established that cholinergic agonists decrease uveoscleral outflow while prostaglandin [PG] analogues, cycloplegic, and adrenergic drugs increase it (Allingham et al., 2012).

Multiple kinds of antiglaucoma drugs are currently available that lower Intraocular Pressure (IOP) by increasing aqueous outflow and/or decreasing aqueous production (McLaren et al., 2003); including,  $\beta$ -adrenergic receptor antagonists, the PG analogues, carbonic anhydrase inhibitors, adrenergic receptor agonists, cholinergic drugs, and rho-kinase inhibitors. Because of their once-daily dosage benefit and efficient IOP lowering, PG analogues are typically the ones prescribed as a first-line therapy in patients with glaucoma (Kim, 2017; Garway-Heath, 2015; Prum, 2016).

However, the mechanism of action of PG analogues is not fully understood, and earlier research has produced contradictory results (Toris et al., 2008). Although researchers (Crowston et al., 2004; Lim, 2008; Tieme, 2001) showed that the trabecular outflow facility improved after using PG, the majority of animal and human studies revealed that prostaglandins' ocular hypotensive effect is best explained by

enhancing the uveoscleral aqueous outflow rather than by decreasing aqueous production or increasing conventional aqueous outflow. (Toris et al., 2008).

After PG bind and activate the receptors of PG in sclera, iris root and ciliary muscle, they stimulate activity of Matrix Metalloproteinase (MMP) (Gaton, 2001; Weinreb et al., 1997; Ocklind, 1998) and change several components of the Extracellular Matrix (ECM) in such structures (Ocklind, 1998; Sagara, 1999), leading to a decrease in resistance of hydraulic to the aqueous movement, as a result reducing the IOP (Kim, 2001; Weinreb, 2001; Lindsey et al., 2007). Hence, the structures incorporated in the uveoscleral outflow may display alteration of structural or histologic following the application of topical PG.

Numerous research have examined the appearance of the microstructures of the aqueous outflow channel as anterior segment imaging techniques have developed recently (Kagemann, 2010; Li, 2017; Tun, 2013). Spectral-Domain Optical Coherence Tomography (SD-OCT), a non-contact, non-invasive, three-dimensional (3D) imaging technique that performs optical sectioning at micrometer resolution to clearly visualize the sclera and measure the Anterior Scleral Thickness (AST), has been used in several studies to scan the corneoscleral limbus (Ebnetter et al., 2015; Pekel, 2015; Woodman-Pieterse et al., 2018).

Histologic analyses have displayed the existence of transscleral fluid flux through the stroma of the sclera (Li et al., 2018) and elevated permeability of the sclera exposed to PG analogues (Kim, 2001; Lindsey et al., 2007); however, the in vivo impact is relatively not known of PG on the human sclera. So, we assessed the influence of topical PG analogues using SD-OCT on the AST for the treatment-naïve primary open-angle glaucoma (OAG) subjects.

### Patients and methods

This was a prospective interventional randomized study performed in Qena University Hospitals, Ophthalmology Department. The current research was approved by the Ethics Committee of Faculty of Medicine, South Valley University, Qena, Egypt (SVU-MED-OPH026-1-22-6-414). An official letter was taken to approach the director of ophthalmology department in SVU hospital for permission to conduct the study. Written consent was obtained from all patients.

Inclusion criteria for our patients included adult patients with primary OAG. Exclusion criteria included children and uncooperative patients with disturbed conscious level or invisible trabecular meshwork in any quadrant on static gonioscopy, previous ocular surgery except uncomplicated cataract surgery more than one year before recruitment, patients with recurrent attacks of scleritis or episcleritis or rheumatoid arthritis, patient with pterygium.

Our study patients were randomized to receive either PG analogues or Dorzolamide/Timolol fixed combination drugs. 60 patients of both sexes with primary open angle glaucoma enrolled in the study and were followed up for about 6 months. Initial assessment included full history and clinical examination, IOP measurement, as well as SD-OCT of the anterior segment.

SD-OCT was performed using OCT-Spectralis by Heidelberg Engineering (SN: TR-KT-2069) with the software Heidelberg Eye Explorer version 1.9.10.0. At three locations in the nasal and temporal meridians (scleral spur, 1000 m, and 2000 m posterior to the scleral spur), the AST was

manually measured by one blinded observer using the built-in calipers of the software included in the OCT equipment. The scleral spur, which frequently appears as an inward protrusion of the sclera, was chosen as the location of the change in curvature of the inner surface of the angle wall. The interface between the sclera, which is highly reflective, and ciliary body, which is less reflective, was thought to be the inner limit of the AST, while the first high reflecting tissue signal of the episclera was thought to represent the outer limit. The inter-observer variability and intra-observer repeatability of 20 randomly chosen pictures of 20 eyes were evaluated using the AST. The intraclass correlation was used to evaluate the measurements' intra- and inter-observer agreements.

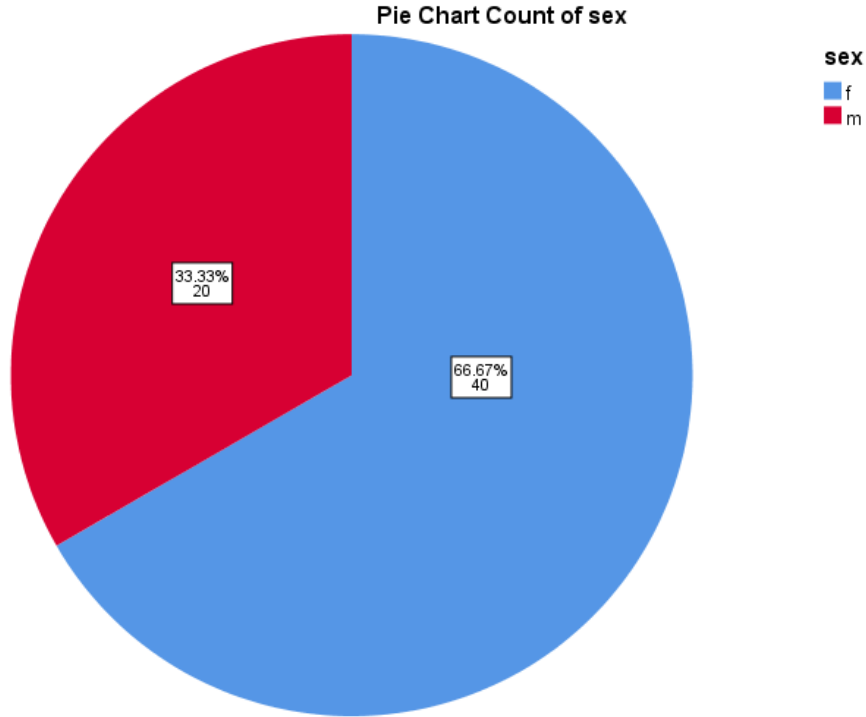
Our main outcome was anterior scleral thickness and our secondary outcomes included visual acuity and IOP measurements.

### Statistical analysis

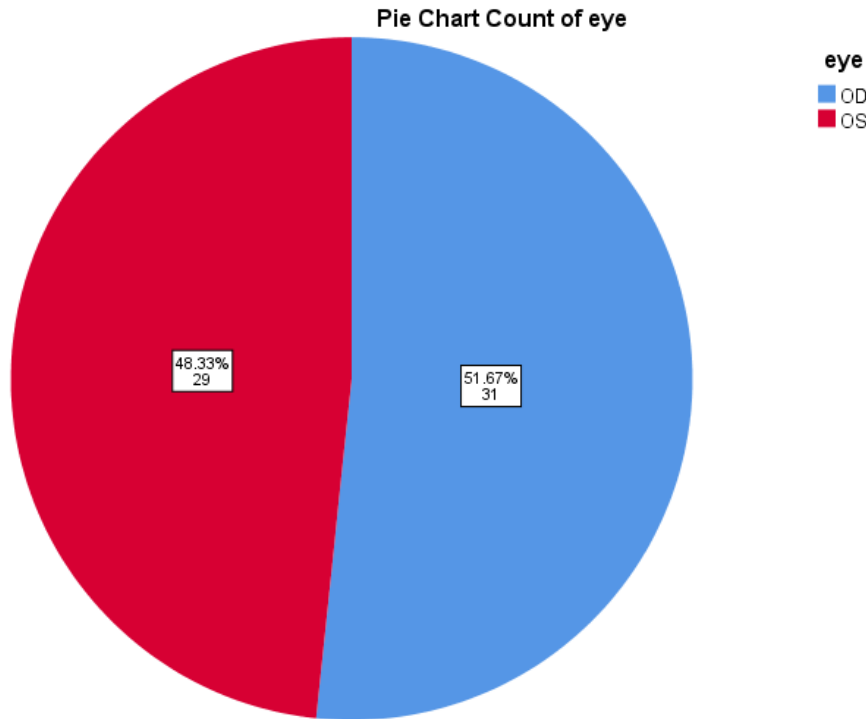
Data were processed by SPSS program (version 20). Categorical variables were recorded as number and proportions and using chi-square test for comparison. Numerical measures were presented as means  $\pm$  standard deviation (SD) and comparison performed using Student t- test. P-value  $< 0.05$  was considered significant.

### Results

Our study included 60 eyes of 60 subjects, 20 (33.3%) men and 40 (66.7%) were women (**Fig.1**). It included 31 (51.7%) right eye and 29 (48.3%) left eye (**Fig.2**). The average age was 60.13 years (SD = 7.9). The mean period of follow up was 6 months (SD = 0.7).



**Fig.1. Male vs Female, F = female, m = Male.**



**Fig.2. Right (OD) vs Left (OS) eye.**

At baseline, the average IOP was 22.9 mmHg (SD = 2.1). Central Corneal Thickness (CCT) was 523 microns (SD =

13.5). The anterior scleral thickness at the nasal area was 799.8 microns thick (SD = 23.7). 1000-micron posterior to it, it was

675.3 microns (SD = 9.5), and 2000-micron posterior to it, it was 680.7 (SD = 8.6). The anterior scleral thickness at the temporal area was 881 microns (SD = 10.4). 1000-micron posterior to it, it was 711.8 microns (SD = 14.9), and 2000-micron posterior to it, it was 729.5 microns (SD = 14.5).

Post-treatment, the average IOP was 14.5 mmHg (SD = 2.5). Central Corneal Thickness (CCT) was 511.6 microns (SD = 14.8). The anterior scleral thickness at the

nasal area was 784.3 microns thick (SD = 20.8). 1000-micron posterior to it, it was 663.8 microns (SD = 9.2), and 2000-micron posterior to it, it was 671.4 (SD = 10.3). The anterior scleral thickness at the temporal area was 858.8 microns (SD = 10.7). 1000-micron posterior to it, it was 689 microns (SD = 14.39), and 2000-micron posterior to it, it was 709.3 microns (SD = 12.9) (Table.1).

**Table.1. Anterior Scleral Thickness at Various Locations before and after, showing the mean difference and the p value**

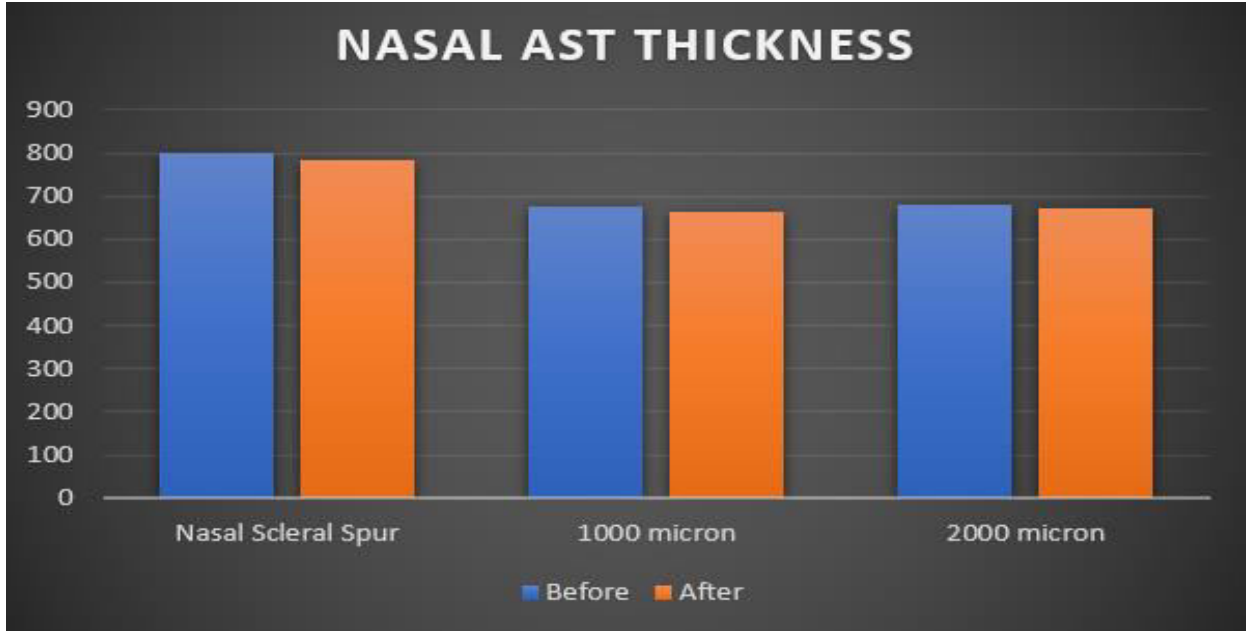
Variables	Pre Treatment	End of follow up period	Mean Difference	p value
Nasal Scleral spur	799.8	784.3	15.5	.000
Nasal 1000 microns	675.33	663.8	11.5	.000
Nasal 2000 microns	680.7	671.4	9.3	.000
Temporal Scleral spur	881	858.8	22.3	.000
Temporal 1000 microns	711.8	689	22.9	.000
Temporal 2000 microns	729.5	709.3	20	.000

The anterior scleral thickness at the nasal area showed a decrease of 15.5 microns (SD = 21.4, 95% CI = 10:21, p value = .000). 1000-micron posterior to it, there was a decrease of 11.5 microns (SD =

5.5, 95% CI = 10.1:12.9, p value = .000), and 2000-micron posterior to it, it was 9.3 (SD = 6.3, 95% CI = 7.6:10.9, p value = .000) (Fig.3, Table.2).

**Table 2. Anterior Scleral Thickness Before and After at the Nasal Area**

Variables	Nasal Scleral Spur	1000 micron	2000 micron
Before	799.8	675.33	680.7
After	784.3	663.8	671.4



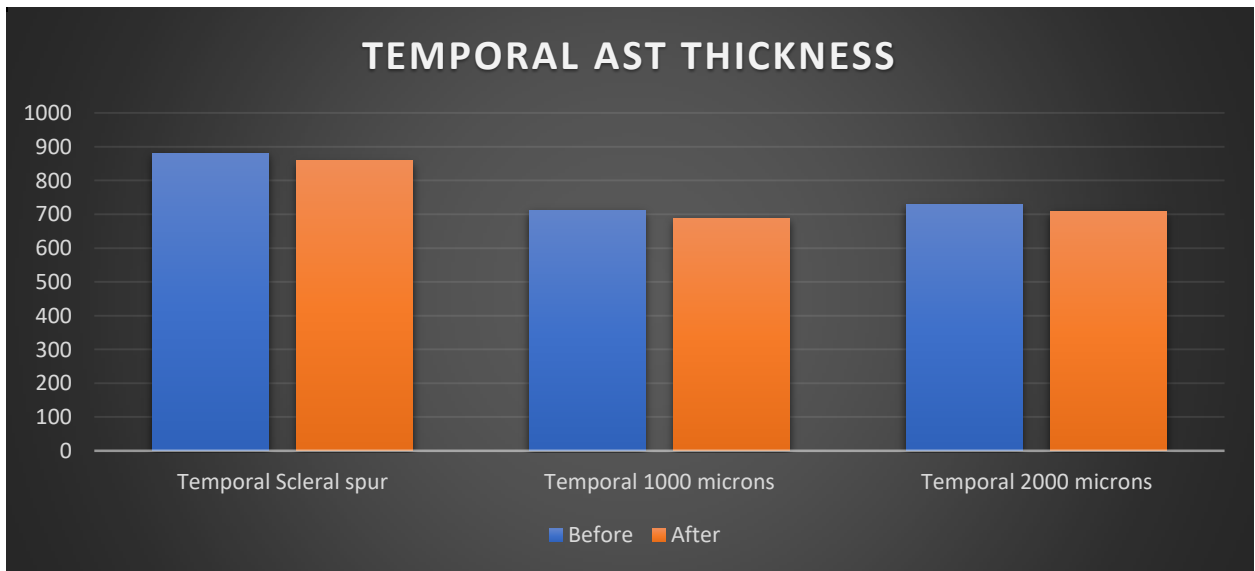
**Fig.3. Anterior Scleral Thickness Before and After at the Nasal Area.**

The anterior scleral thickness at the temporal area demonstrated a decrease of 22.3 microns (SD = 8.6, 95% CI = 20:24.5, p value = .000). 1000-micron posterior to it, it was 20.9 microns (SD = 14, 95% CI =

19.2:26.5, p value = .000), and 2000-micron posterior to it, it was 20 microns (SD = 13.2, 95% CI = 15.8:24.2, p value = .000) (Fig. 4, Table.3).

**Table.3. Anterior Scleral Thickness Before and After at the Temporal Area**

Variables	Temporal Scleral Spur	1000 micron	2000 micron
Before	881	711.8	729.5
After	858.8	689	709.3



**Fig. 4. Anterior Scleral Thickness Before and After at the Temporal Area**

Our patients were divided into 32 patients that received PG formulations (Group A) and 28 patients that received Dorzolamide/Timolol combinations (Group B). For group A, there was 16 (50%) right eyes and 16 (50%) left eyes of 10 (31.3%) male patients and 22 (68.7%) female patients whose average age was 59.5 years (SD = 8.1). And for group B, there was 15 (53.6%) right eyes and 13 (46.4%) left eyes

of 10 (35.7%) male patients and 18 (64.3%) female patients whose average age was 60.8 years (SD = 7.8).

The IOP for group A was 18.3 mmHg (SD = 1.9) and at the end of the follow up period it was 14 mmHg (SD = 2.1, p = .000). For group B, it was 19.6 mmHg (SD = 2) and at the end of the follow up duration it became 15 mmHg (SD = 2.9, p = .000) (Fig.5, Table.4).

**Table 4. IOP Before and After the follow up period for both groups**

Variables	Prostaglandin	Dorzolamide/Timolol
Before	18.3	19.6
After	14	15



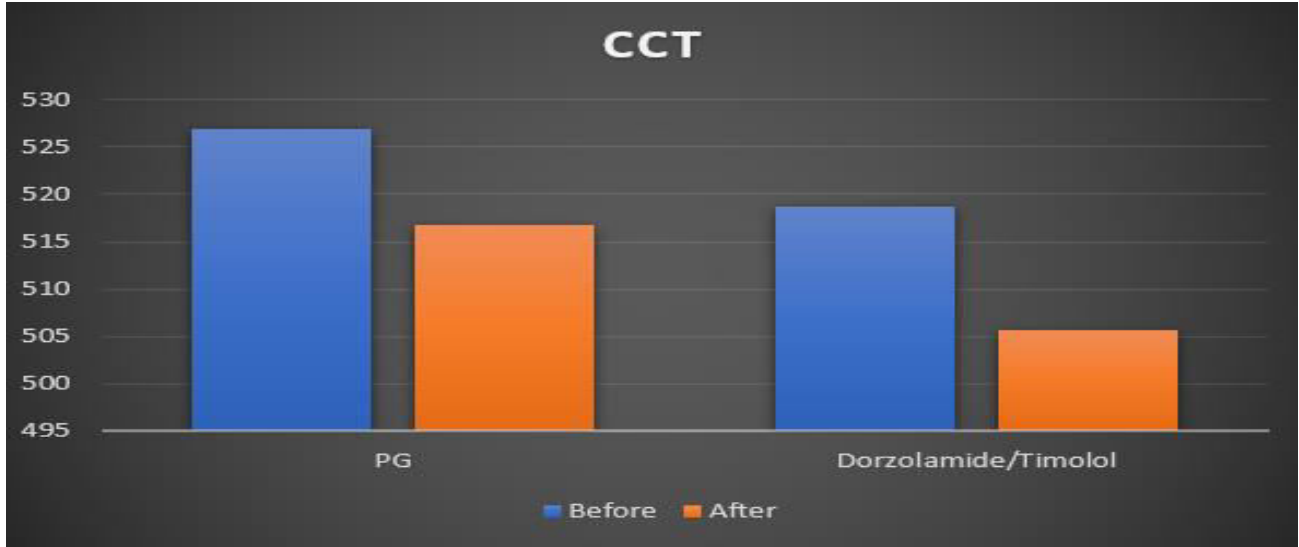
**Fig. 5. IOP Before and After the follow up period for both groups.**

For group A, the preoperative CCT was 526.9 microns (SD = 7.5) and postoperatively it became 516.8 microns (SD = 7.5, p = .000). For group B, The CCT

at baseline was 518.8 microns (SD = 17) and post-treatment it became 505.6 microns (SD = 19, p = .000) (Fig. 6, Table. 5).

**Table 5. CCT Before and After the follow up period for both groups.**

Variables	Prostaglandin	Dorzolamide/Timolol
Before	526.9	518.8
After	516.8	505.6



**Fig.6. CCT Before and After the follow up period for both groups.**

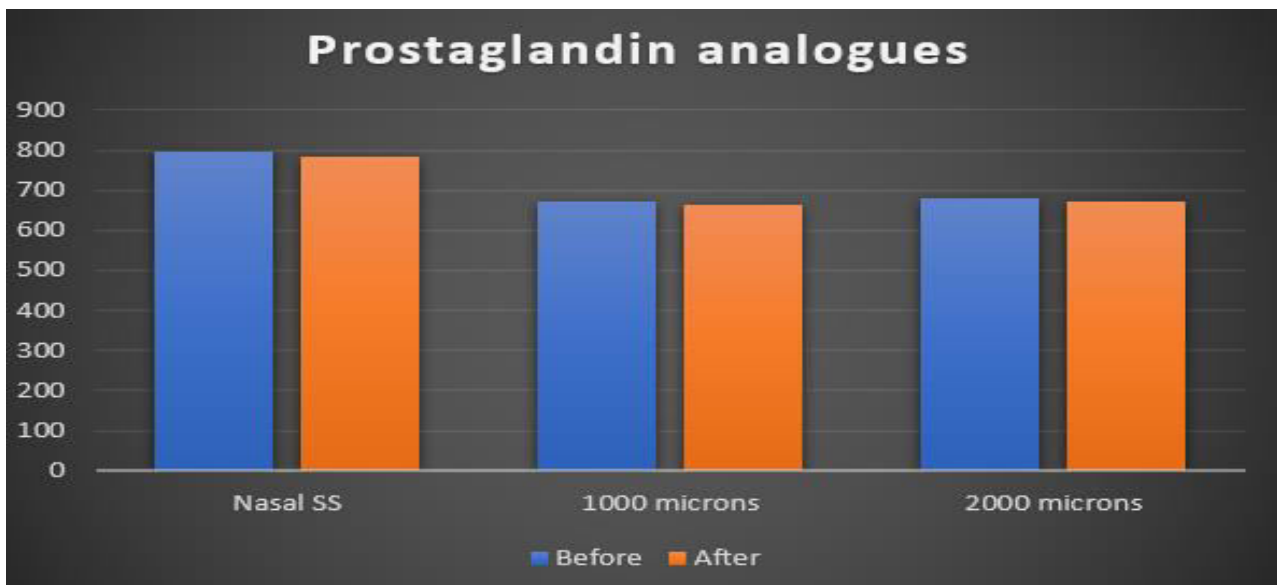
For group A, at baseline, the mean AST thickness at the nasal scleral spur was 796.6 microns (SD = 23.4), 1000 microns posterior to it, it was 673.4 (SD = 9.7), and 2000 microns posterior to it, it was 680.6 (SD = 8.4). The temporal scleral spur was 879.8 microns (SD = 10.7), 1000 microns posterior to it, it was 711.6 microns (SD =

13.6), and 2000 microns posterior to it, it was 728.1 microns (SD = 14).

For group A, post-treatment, the mean AST thickness at the nasal scleral spur was 781.6 microns (SD = 24.7, p = .000), 1000 microns posterior to it, it was 662.8 (SD = 10.2, p = .000), and 2000 microns posterior to it, it was 670.5 (SD = 10.5, p = .000) (Fig. 7, Table.6).

**Table 6. Nasal AST Before and After the follow up period for Group A.**

Variables	Nasal Scleral Spur	1000 micron	2000 micron
Before	796.6	673.4	680.6
After	781.6	662.8	670.5



**Fig.7. Nasal AST Before and After the follow up period for Group A.**

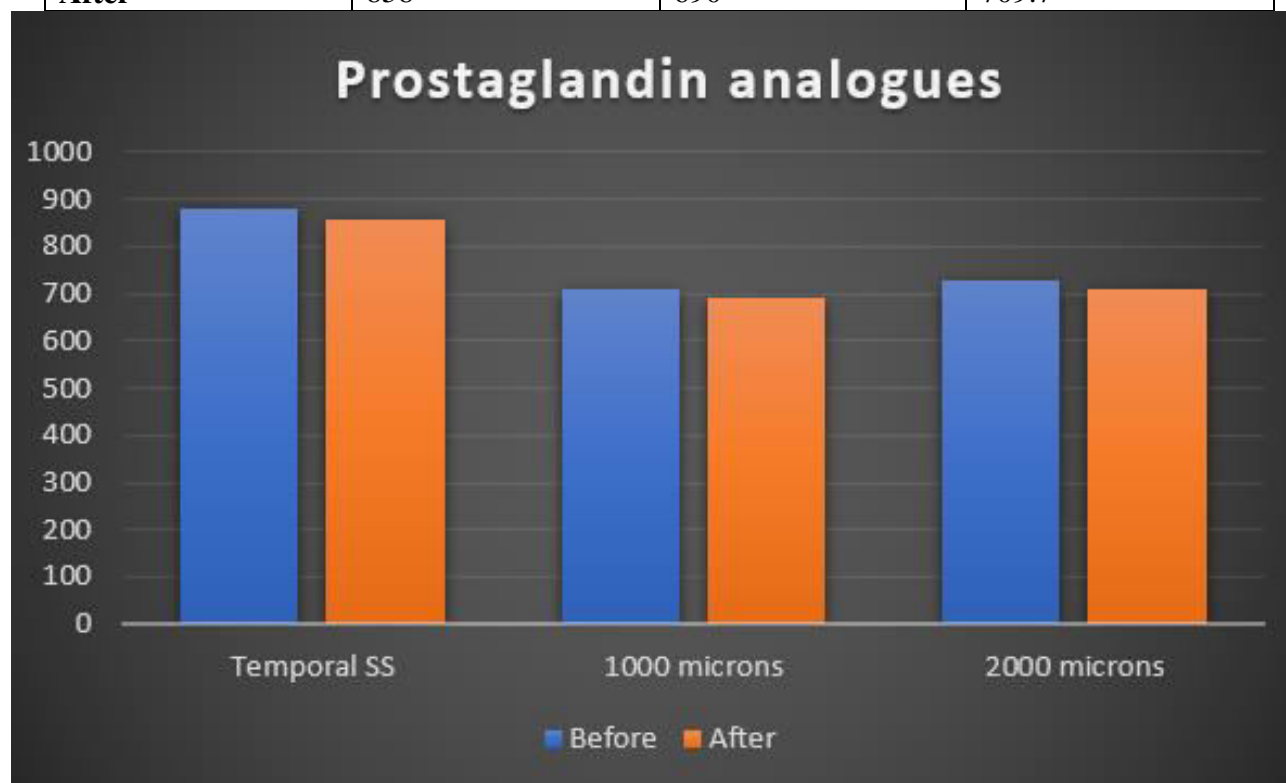


The temporal scleral spur was 858 microns (SD = 10.8, p = .000), 1000 microns posterior to it, it was 690 microns

(SD = 12.7, p = .000), and 2000 microns posterior to it, it was 709.7 microns (SD = 13.1, p = .000) (Fig. 8, Table.7).

**Table 7. Temporal AST Before and After the follow up period for Group A.**

Variables	Temporal Scleral Spur	1000 micron	2000 micron
Before	879.8	711.6	728.1
After	858	690	709.7



**Fig.8. Temporal AST Before and After the follow up period for Group A.**

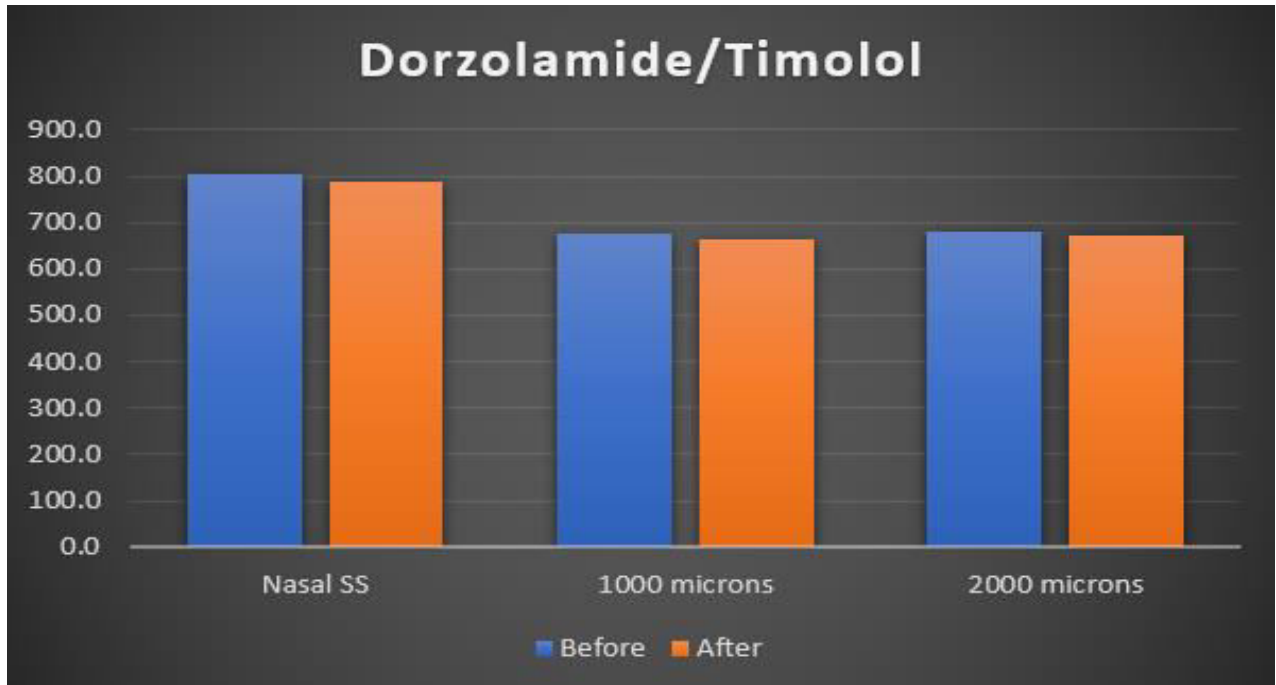
For group B, at baseline, the mean AST thickness at the nasal scleral spur was 803.4 microns (SD = 24), 1000 microns posterior to it, it was 677.5 (SD = 8.9), and 2000 microns posterior to it, it was 680.7 (SD = 9). The temporal scleral spur was 882.3 microns (SD = 10.1), 1000 microns posterior to it, it was 712 microns (SD =

16.4), and 2000 microns posterior to it, it was 730.4 microns (SD = 15).

For group B, post-treatment, the mean AST thickness at the nasal scleral spur was 787.3 microns (SD = 15.2, p = .001), 1000 microns posterior to it, it was 665 (SD = 7.9, p = .000), and 2000 microns posterior to it, it was 672.5 (SD = 10, p = .000) (Fig.9, Table.8).

**Table 8. Nasal AST Before and After the follow up period for Group B.**

Variables	Nasal Scleral Spur	1000 micron	2000 micron
Before	803.4	677.5	680.7
After	787.3	665	672.5



**Fig.9. Nasal AST Before and After the follow up period for Group B.**

The temporal scleral spur was 859.6 microns (SD = 10.7, p = .000), 1000 microns posterior to it, it was 687.3 microns

(SD = 16.2, p = .000), and 2000 microns posterior to it, it was 708.9 microns (SD = 12.8, p = .000) (Fig.10, Table.9).

**Table 9. Temporal AST Before and After the follow up period for Group B.**

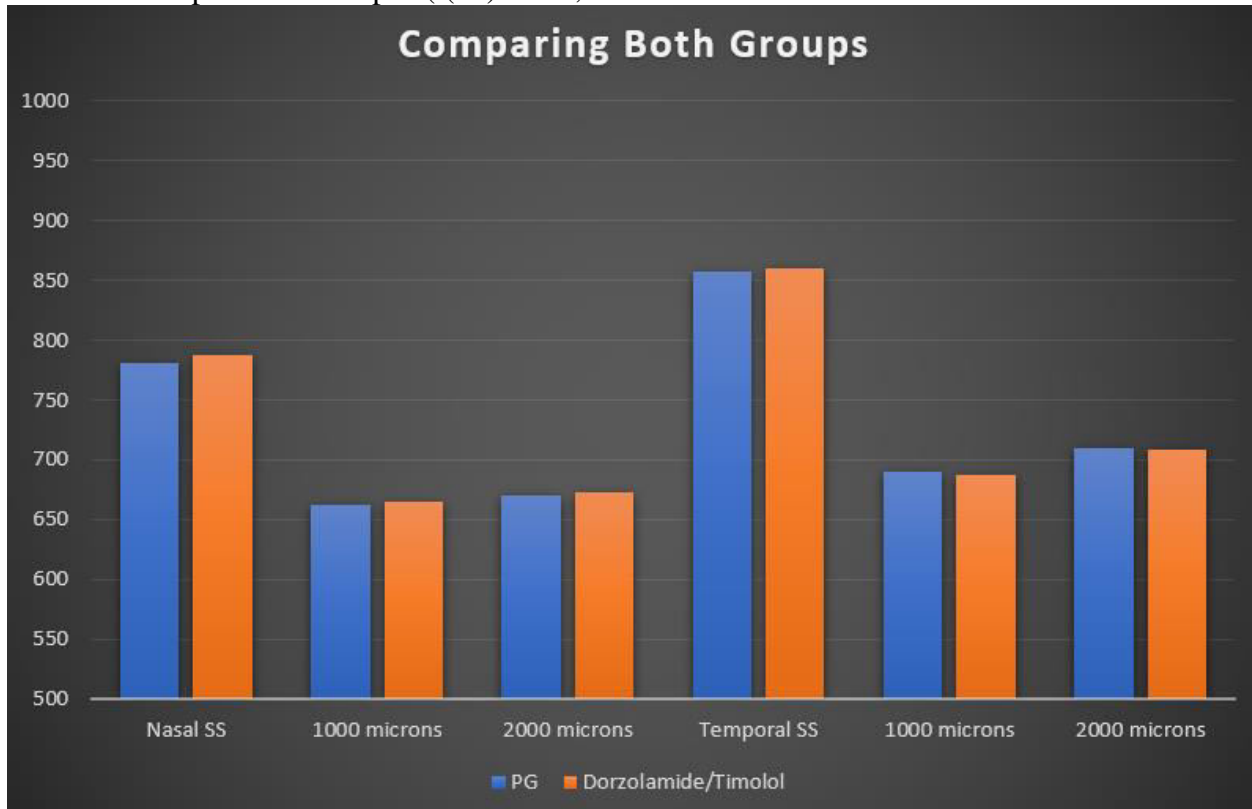
Variables	Temporal Scleral Spur	1000 micron	2000 micron
Before	882.3	712	730.4
After	859.6	687.3	708.9



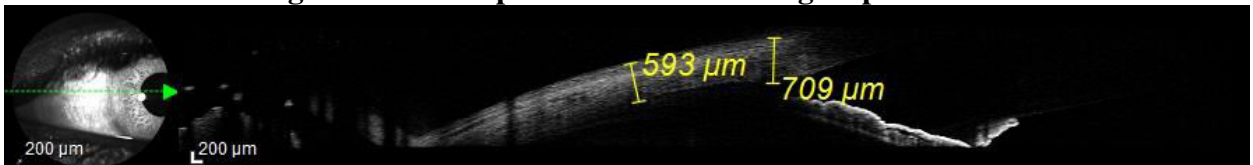
**Fig.10. Temporal AST Before and After the follow up period for Group B.**

When comparing the two groups of drugs at the end of the follow up duration, Group A (Prostaglandin analogues) showed a lower AST at the nasal scleral spur (t(58) = 1.067, mean difference = 5.75, 95% CI = -5:16.6, p = .291), 1000 microns posterior to it (t(58) = 0.915, mean difference = 2.2, 95% CI = -2.6:7, p = .364), 2000 microns posterior to it (t(58) = 0.763, mean difference = 2, 95% CI = -3.3:7.4, p = .449), and at the temporal scleral spur (t(58) = 0.6,

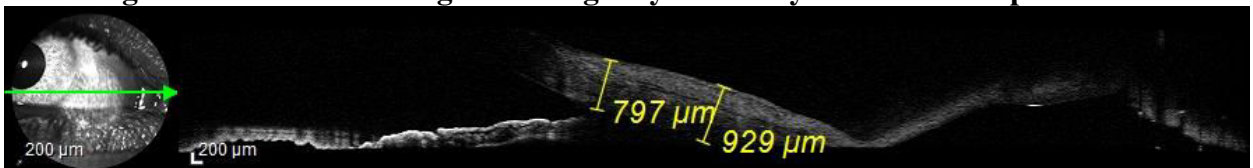
mean variation = 1.7, 95% CI = -3.9:7.3, p = .551). But Group B (Dorzolamide/Timolol) showed a lower AST 1000 microns posterior to the temporal scleral spur (t(58) = 0.818, mean difference = 3, 95% CI = -4.4:10.5, p = .417) and 2000 microns posterior to it (t(58) = 0.226, mean difference = 0.76, 95% CI = -6:7.5, p = .822) (**Fig.11, Table.1**) but none of the differences among the categories were significant (**Figs.12-14**).



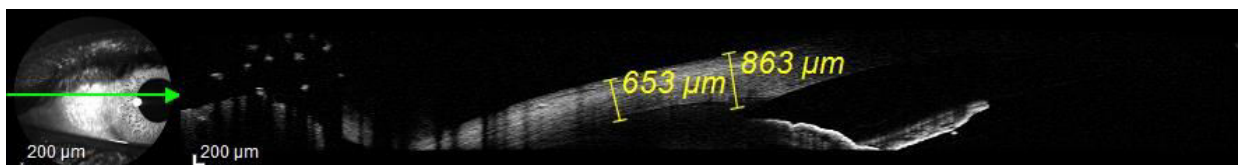
**Fig.11. AST Comparison between both groups.**



**Fig.12. Pretreatment image of the right eye of a 40-year-old female patient.**



**Fig.13. Pretreatment image of the left eye of a 40-year-old female patient.**



**Fig.14. Post treatment image of the right eye of a 40-year-old female patient.**

## Discussion

Our study showed that the use of prostaglandin analogues in treatment of open angle glaucoma showed a significant decrease in anterior scleral thickness in all measured points; over the nasal and temporal scleral spurs, and 1000 microns posterior to them, and 2000 microns posterior to them.

Our work is novel, with not many papers in the literature focusing on our area of interest. Some researchers compared AST between normal and POAG patients, and it was demonstrated to be considerably thinner in POAG subjects (Xiaoqin Yan et al., 2022).

However, a previous study found no difference between the two groups (Yoo et al., 2011). This is most likely attributed to difference in definition of AST, as the first study defined it as the assessed range between the episcleral blood vessels and the interface between the ciliary body and sclera, and the later study defined it as the measured distance between the first high reflective tissue signal of the episclera and the interface between the sclera and ciliary body. We defined it as follows; the interface between the sclera, which is highly reflective, and ciliary body, which is less reflective, was thought to be the inner limit of the AST, while the first high reflecting tissue signal of the episclera was thought to represent the outer limit.

Yoo et al., 2011 found that central corneal thickness was less in patients with normal tension glaucoma vs patients with primary open angle glaucoma and compared to normal controls while it was equal between primary angle glaucoma patients and normal

controls. Our study found that post treatment there was a decrease in central corneal thickness. The study of corneal biomechanics is vital in the discussion of glaucoma since not only does the cornea affect the measurements of IOP in glaucoma, but it also affects the pathogenesis (Sng et al., 2017).

Our findings agree with the previous literature which found that PG analogues lead to a decrease in AST thickness at 1-year postoperatively, which might contribute to increased drainage of the uveo-scleral outflow (Park et al., 2021). The unequal reduction between the nasal and temporal sclera was explained in their study by the nasal and temporal sectors' different ciliary body lengths and anterior sclera thicknesses, which affect how the sclera changes after taking PG medications. Second, investigations on animals revealed two routes for fluid to get through the sclera: through the scleral stroma and through small crevices near penetrating blood arteries and nerves (Inomata et al., 1977). Since the perforating blood vessel and nerves are rarest in the temporal sclera (Pardinielli et al., 2013), the transscleral fluid flux in this area may mainly rely on the pathway through the scleral stroma. As a result, the temporal sector's scleral stroma, which may be connected with scleral thickness, may have undergone more pronounced modifications as a result of topical PG. However, more research is required to confirm the aforementioned theories.

The effect of prostaglandin on scleral thickness has been discussed before (Park et al., 2021), however we are the first work to discuss Dorzolamide on scleral thickness.

Unlike Prostaglandin's unequal reduction in nasal and temporal scleral thickness, our findings support that equal reduction of scleral thickness in different regions when using Dorzolamide, probably contributing to a better antiglaucoma response, which is supported by the pressure drop in our Dorzolamide group being more than in the Prostaglandin group (4.6 vs 4.3,  $p < 0.001$ ). As interesting as these findings are, we would be erroneous if we were to correlate them with posterior scleral thickness since previous studies showed that there is no correlation between the two (Vurgese et al., 2012).

The strengths of our studies are the statistical significance of our findings ( $p = .000$ ) and the novelty of the area of research we're concerned with. However, our study is limited by a low follow up period of only 6 months. We recommend further studies with longer follow up periods to further ascertain the impact of PG analogues on anterior thickness of the sclera and to suggest useful clinical correlations between the two.

### Conclusion

The use of analogues of prostaglandin in treatment of open angle glaucoma showed a significant decrease in anterior scleral thickness in all measured points; over the nasal and temporal scleral spurs, and 1000 microns posterior to them, and 2000 microns posterior to them.

### Declarations

**Ethical approval:** The research granted an exemption from the research ethics committee of the Faculty of Medicine, South Valley University. Participated Patients signed a consent.

**Conflict of interest:** No competing interests.

**Data availability:** Data are available from the first author upon request.

**Funding:** No funding.

**Author Contribution:** All authors participated in the conception and design of the study. Patient collection was done by

Aya M. Makled. Data analysis was done by Aya M. Makled. Aya M. Makled wrote the first draft of the manuscript. Ahmad H. Aldghaimy, Wael E. Eida, and Ahmed A. Ammer revised and edited the manuscript. All authors read and approved the final manuscript.

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