Original Article

Effects of Prostaglandin Analogue on the Central Retinal Thickness in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Purpose: To determine the central macular thickness in patients with type 2 Diabetes using Latanoprost eye drops and to compare with type 2 diabetic patients using Timolol eye drops.

Study Design: Quasi experimental study.

Place and Duration of Study: Al-Noaman Teaching Hospital from February 2023 to April 2023.

Methods: One hundred diabetic patients were divided into two equal groups (Timolol group and Latanoprost group). Visual acuity was tested using Snellen chart, IOP was measured with Goldmann Applanation Tonometer, central corneal thickness (CCT) measurement was done to correct IOP for CCT. Optical coherence tomography (OCT) was used to measure central retinal thickness (CRT).

Results: The mean age of Timolol group was 57.91±1.6 years, which was very close to the mean age of Latanoprost group (57.57±1.63 years). There were 30 females and 20 males in each group. HbA1Cwas 8.99±0.47% in Timolol and 6.28±0.08% in Latanoprost group (p <0.001). The IOP showed statistically lower levels in Timolol group in comparison to Latanoprost group, 28.81±0.93 mmHg in comparison to 29.56±1.04 mmHg, respectively. In Timolol group, visual acuity significantly improved, the IOP was reduced, and the CRT was significantly lowered. However, in Latanoprost group, the pre and post treatment values showed that only the IOP significantly improved. Visual acuity and CRT were statistically and clinically the same.

Conclusion: Latanoprost may increase the central retinal thickness in diabetic patients without diabetic macular edema, however the rationale for stopping the medication in low-risk patients is still lacking.

Key Words: Diabetes mellitus, Latanoprost, Diabetic retinopathy, central retinal thickness, Prostaglandin analogues.

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INTRODUCTION

Prostaglandin analogues lower intraocular pressure (IOP) by increasing the outflow of aqueous humor from the eye.[1] They are commonly used to treat glaucoma and ocular hypertension.[2] However, they may also cause some adverse effects, such as uveitis and cystoid macular edema (CME).[3,4] CME leads to blurred vision and may lead to permanent vision loss if left untreated.[5] CME can be caused by ocular inflammation, surgery, trauma or vascular diseases.[6] Diabetes mellitus is one of the most common vascular diseases that affect retina.[7] Diabetic retinopathy damages the retinal blood vessels and leads to leakage of fluid and blood into the macular area resulting in diabetic macular edema (DME) or CME.[8] There is a possible link between prostaglandin analogues, macular edema, and diabetes mellitus.[9] However, the exact causal relationship and the risk-benefit profile of

these eye drops in people with or at risk of DME require further research.[10,11]

This study was conducted to assess the possible role of Latanoprost in causing CME in an already high-risk group with diabetes mellitus. The study aimed to investigate the central retinal thickness in diabetic patients using Latanoprost eye drops in comparison to diabetic patients using Timolol eye drops.

METHODS

This was a quasi-experimental study aimed to investigate the effects of prostaglandin analogues eye drops on macular thickness in patients with type 2 diabetes mellitus. The study was conducted at Al-Noaman Teaching Hospital during a three-month period from February 2023 to April 2023.

The study participants had diabetes mellitus for at least 10 years. They were divided into two groups: Timolol group and Latanoprost group. Both groups were matched by age, sex, and duration of diabetes. All patients were diagnosed with primary open angle glaucoma by a glaucoma specialist and were on prostaglandin analogue treatment (Latanoprost) for at least 6 months. In group one, Latanoprost eye drops were stopped and replaced with Timolol eye drops. They were followed for two months, while in Latanoprost-group, latanoprost eye drops were continued throughout the study duration.

Visual acuity was tested using Snellen chart, IOP was measured with Goldmann Applanation Tonometer, central corneal thickness (CCT) measurement was done to correct IOP for CCT. Optical coherence tomography (OCT)was used to measure central retinal thickness (CRT), and fundus examination was carried out for all patients.

The independent samples T-test was used to study the difference in means between Latanoprost and Timolol groups, while Paired Sample T-test was used to study the difference after replacing Latanoprost with Timolol. The level of significance was set at $p<0.05$.

To estimate the sample size, we used the single proportion formula:

$$\frac{Z^2 * P\ (1-P)}{d^2}$$

Where, Z = 1.96, P = 0.0014 according to results of Hu et al. 2020 [3], d = 0.01

$$\frac{1.96^2 * 0.0014\ (1-0.0014)}{0.001^2} = 54$$

However, to increase the statistical yield and sample power we enrolled 50 (100 eyes) subjects in each study group.

This study was approved by the Ethical Approval Committee/ Al-Iraqia University/ Baghdad/ Iraq (number: FM.SA130). The research followed the ethical standards of the institutional research committee and was in compliance with the Helsinki declaration and its subsequent update of ethical standards (Code: 2019/C081). Every individual participant included in the study provided written informed consent.

RESULTS

This study enrolled 50 patients (100 eyes) in the Timolol group, and 50 patients (100 eyes) in Latanoprost group. The mean age of Timololgroup was 57.91±1.6 years, which was very close to the mean age of Latanoprost group (57.57±1.63 years). There were 30 females and 20 males in each group. However, there was a statistically significant difference in HbA1C, as its mean was 8.99±0.47% in Timolol and 6.28±0.08% in Latanoprost group ($p<0.001$). The IOP showed statistically lower levels in Timololgroup in comparison to Latanoprost group, 28.81±0.93 mmHg in comparison to 29.56±1.04 mmHg, respectively. However, it was not clinically significant. The CRT is shown in Table-1.

Table 1: *Characteristics of the study groups before intervention.*

Variables	Timolol Mean± SD	Latanoprost Mean± SD	P-value
Age	57.91±1.6	57.57±1.63	0.138
HbA1C	8.99±0.47	6.28±0.08	<0.001
Visual acuity (log MAR)	0.4±0.11	0.37±0.1	0.148
Intraocular pressure	28.81±0.93	29.56±1.04	<0.001
Central retinal thickness	269.67±5.6	269.6±5	0.920

After follow-up, the HbA1C was still higher in Timolol group. Visual acuity, IOP, and CRT are depicted in Table-2.

Pairwise comparison in-between groups before and after follow up showed that in Timolol group, visual acuity significantly improved, the IOP was reduced, and the CRT was significantly lowered. However, in Latanoprost group, the pre and post

treatment values showed that only the IOP significantly improved. Visual acuity and CRT were statistically and clinically the same, as illustrated in Figure-1.

Table 2: *Characteristics of the study groups after intervention.*

Variables	Timolol Mean± SD	Latanoprost Mean± SD	P-value
HbA1C	6.33±0.05	6.29±0.07	<0.001
Visual acuity (logMAR)	0.13±0.07	0.38±0.1	<0.001
Intraocular pressure	18.08±0.91	19.65±0.83	<0.001
Central retinal thickness	247.68±3.1	268.9±4.72	<0.001

DISCUSSION

This study showed that Latanoprost increases the CRT in diabetic patients without existing diabetic macular edema. However, a study by Patel et al, found that patients who did not use prostaglandin analogues were more likely to develop diabetic macular edema. However, among those who did use these medications, there was a tendency for the condition to resolve more slowly, regardless of the duration of their diabetes.[12] Since then, limited research has been published on this topic, with most of the literature focusing on macular edema following cataract surgery and the use of prostaglandin analogues.[13-14]

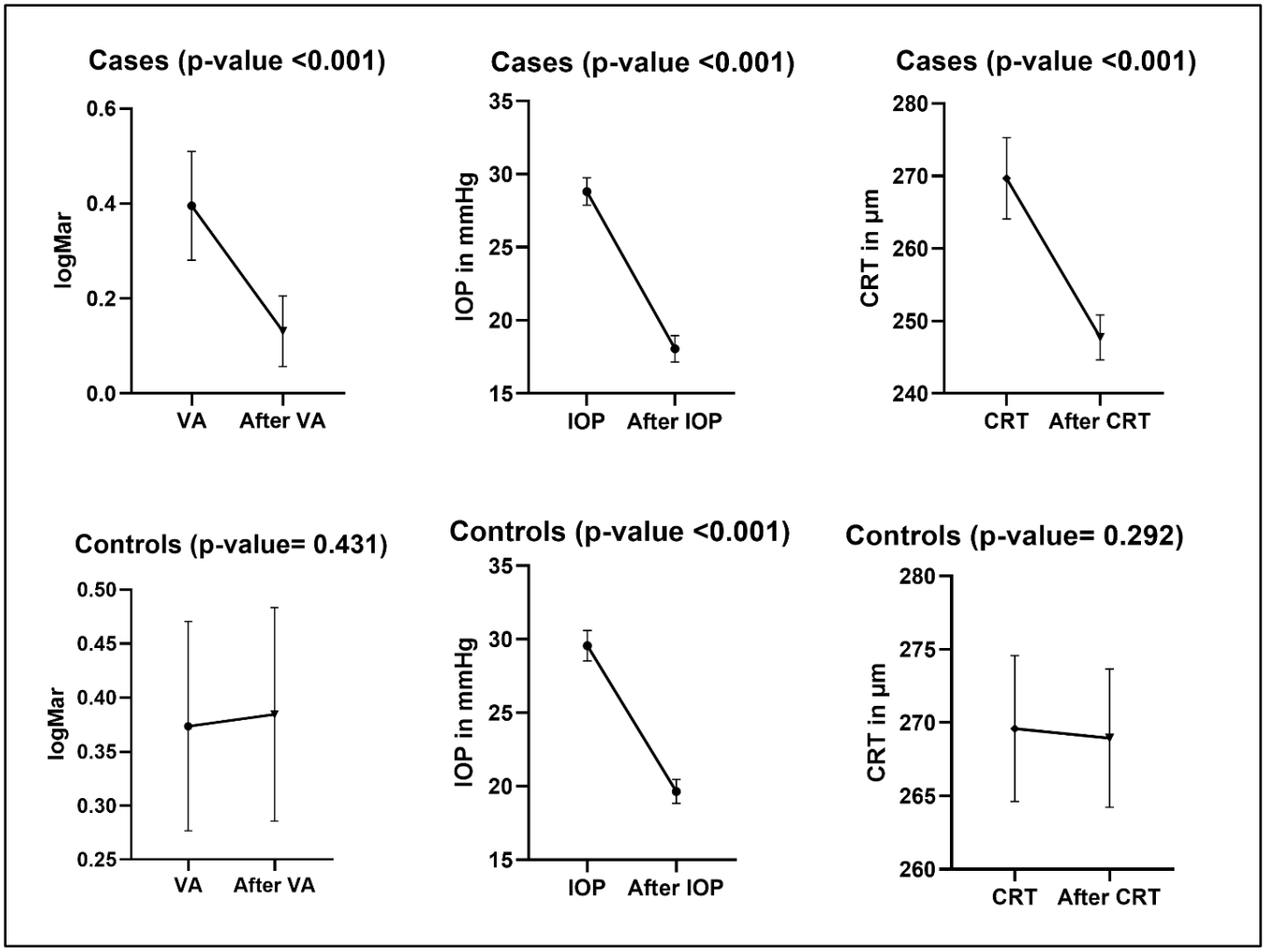

Figure1: Ingroup-analysis before and after intervention in Timolol (cases) and Latanoprost (control) groups.

Two meta-analyses reported that macular edema rates showed no statistically significant differences among the patients using Travoprost, Bimatoprost, or Latanoprost.[15,16]

In the current study, CRT significantly reduced

after replacing Latanoprost with Timolol, although both groups did not have diabetic macular edema. Kalpana et. al., studied a diabetic patient with cystoid macular edema who was using Travoprost. They were able to manage CME only by stopping Travoprost.[17] Another study by Veselovska et. al., studied the effects of Tafluprost eye drops on patients with diabetes. They reported that it did not increase the risk of developing diabetic eye disease. However, they did not report effect on CRT.[18]

In a study by Schoenberger et al., vitreous levels of prostaglandin E2 were significantly higher in diabetic eyes as compared to the non-diabetic eyes.[19] These levels were correlated with VEGF-levels. Tilma and Bek reported that one-week treatment with Latanoprost caused vascular narrowing in the inflamed, but not in the normal vessels.[20] Zhang et al., studied the levels of 8-iso-prostaglandin-F2α (a prostanoid related to prostaglandin F2α) and reported that its levels were closely related to the onset and progression of diabetic retinopathy.[21]

The relationship between Prostaglandin analogues and CME is still in debate, and there is no definite causal relationship between the two. However, some authors have recommended to use caution when administering PGAs to any patient with high risk of CME, including those with diabetic retinopathy.[6]

Limitations of this study include short duration of follow up which might not be sufficient to observe long-term changes in central macular thickness or intraocular pressure. It was a single center study which limits the diversity of the population and reduces the external validity of the findings. There was limited assessment of confounding factors. In the Latanoprost group, the medication was stopped and replaced with Timolol without a washout period, which might introduce variability due to the carryover effects of Latanoprost. Addressing these limitations in future studies can provide a more robust understanding of the relationship between glaucoma medications and macular thickness in diabetic patients.

CONCLUSION

Latanoprost may increase central retinal thickness in diabetic patients without diabetic macular edema. However, there is still a lack of evidence to support discontinuing Latanoprost in low-risk diabetic patients, indicating that further research is needed to establish a clear rationale for such a practice.

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Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(2019/C081)**.

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Authors Designation and Contribution

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