Research Paper

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The Effect of Prostaglandin Analogues on Central Corneal Thickness in Patients with Glaucoma

Medical Science

KEYWORDS : Latanoprost, Central corneal thickness, Open-angle glaucoma

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ABSTRACT

Introduction: Recent studies have shown that central corneal thickness (CCT) may be affected by anti-glaucoma medications.In this study, we evaluated the effect of Latanoprost on CCT in patients with open-angle glaucoma.

Methods: One hundred seventy one eyes of 90 glaucoma patients in two groups, recipients of Latanoprost and other anti-glaucoma medications were enrolled. The main measure in both groups of study was CCT.

Results: Regardless of the type of glaucoma, a statistically significant reduction in the mean CCT was observed in the Latanoprost group at all time-intervals of the study (p<0/001). CCT was significantly reduced at all time-intervals in primary open-angle glaucoma patients which were treated with Latanoprost. Regardless of the type of medication, CCT at all time intervals significantly decreased in secondary glaucoma.

Conclusion: The use of Latanoprost significantly decreases the CCT in patients with open-angle glaucoma.

Introduction

Open angle glaucoma (OAG) is the second-leading cause of permanent blindness worldwide, affecting more than 60.5 million people aged over 40 years, increasing to 79.6 million by 2020(1).

Central corneal thickness (CCT) has become an important factor in the management of glaucoma after understanding its influence on IOP measurements. The importance of CCT as a potential risk factor for glaucoma and ocular hypertension has also been studied (2).

The Ocular Hypertension Treatment Study, which focuses on risk factors for glaucomatous visual field loss and optic nerve head changes in patients with ocular hypertension, suggested that CCT is the strongest predictive factor. They found that 40-µm decrease in CCT resulted in 1.71-fold more glaucoma conversion (2,3).

More recent studies have also suggested that CCT may be an independent risk factor for progression in patients with open-angle glaucoma. Many studies have demonstrated that single measurement of CCT is not sufficient for a proper glaucoma practice because the measurements vary when performed on separate occasions (4,5). Given this, the possible effects of topical anti-glaucoma medications on CCT values during the follow-up of glaucoma patients have been investigated in different studies (6-9).

To lower intraocular pressure (IOP) with prostaglandin analogs (PGAs), topical antiglaucoma therapy is the treatment of choice for millions of patients. PGAs reduce IOP through enhancing the aqueous humor through the uveoscleral pathway to the suprachoroidal space and episcleral veins. Although the exact mechanism of action of prostaglandin analogs is still not fully understood, it has been theorized that they act primarily through the activation of matrix metalloproteinases (MMPs) and a reduction of different collagen types in the eye(10-12). Because the cornea is mainly composed of collagen fibers and taking into account the importance of corneal thickness in the evaluation of glaucoma ,it is important to determine the CCT values serially during the follow-up of glaucoma patients due to the longitudinal changes that might occur owing to the medication .

Regarding the discrepancy in the results of the previous studies and the significance of the effect of corneal thickness variation in measuring IOP using Goldmann tonometry, and in the follow-up of the therapeutic process of the patients, we decided to investigate the effect of latanoprost on CCT in patients with OAG in a 1-year follow-up period.

Materials and Methods

This prospective study was performed in the Department of Ophthalmology at Tabriz University of Medical Sciences, Iran . The study was approved by the institutional review board of the Nikookari Eye hospital, and all study procedures adhered to the tenets of the Declaration of Helsinki. After a detailed explanation of the study benefits and risks, informed consent was obtained from all patients.

A total of 171 eyes from 90 patients were included in this study. The study cases were selected from patients receiving care at glaucoma clinic and took the initial diagnosis of primary open angle glaucoma and open angle glaucoma secondary to pseudoexfoliatin. Moreover their glaucoma was medically well controlled . Of these, 116 eyes from 62 patients were treated with latanoprost, and 55 eyes from 62 patients were treated with anti-glaucoma drops other than latanoprost. Exclusion criteria included patients unwilling to participate in the study, inability to follow up the patient for an extended period, patients with any other ocular pathology such as corneal opacities, dry eye, contact lens wear, preexisting ocular hypotensive medication, previous surgical intervention, those with any type of open angle glaucoma other than primary and pseudoexfoliative.

Participants were divided into 2 groups: group 1 was composed of patients under treatment only with Latanoprost; group 2 was composed of patients under treatment with drugs other than Latanoprost such as timolol, dorzolamide, brimonidine or any combination of these drugs.

Complete ocular examination were performed at initial diagnosis ,6th and 12th months of treatment with the same clinician(R,S). All measurements were carried out between 10 AM and 1PM using Goldmann applanation tonometer for IOP and Tomey SP-3000 ultrasound biopachymeter (Tomey corporation, Nagoya, Japan) for CCT by the same physician recording the average of five consecutive readings. CCT measurements were carried out after IOP measurements.

All the statistical analyses were carried out using SPSS 16.0 (SPSS Inc; Chicago, IL). Data are described as percentages and mean values ± SD. The Wilcoxon or paired T test and Fisher exact test or X2 were used to assess the significance of differences between the two groups. Pearson correlation analysis was used to evaluate the correlation between the CCT and IOP values. In this study, P<0.05 was considered statistically significant.

Results

Ninety patients (116 eyes) with OAG were enrolled according to the above-cited inclusion/exclusion criteria. With regard to the medication, the patients were divided into 2 groups: group 1 involved 62 patients (116 eyes) being treated with Latanoprost, and group 2 consisted of 28 patients (55 eyes) being treated without Latanoprost.

The type of glaucoma in 47 patients (90 eyes, 52.6%) was primary and in 43 patients (81 eyes, 47,4%) was secondary to pseudoexfoliation. Sixty two patients (116 eyes, 67.8%) were treated with Latanoprost and 28 patients (55 eyes, 32.2%) with others.

As illustrated in Table 1, there was no statistically significant difference regarding age and sex distribution, between patients in any of the studied groups. Considering basic CCT, there was no statistically significant difference between patients with primary and secondary glaucoma and between groups treated with Latanoprost or other drugs.

Table -1: Characteristics of patients in both subgroups

	Number eyes (patients)	Age (years)	Sex male (percent)	Baseline CCT (µm)
POAG	**90(47)**	**62.45±10.86**	**35(74.5%)**	**537.49±25.46**
SOAG	**81 (43)**	**68±10.73**	**31(72.1%)**	**535.73±23.1**
P value	**–**	**0.09**	**0.79**	**0.74**
Latanoprost+	**116(62)**	**64.5±10.86**	**46 (74.2%)**	**537.49±25.46**
Latanoprost–	**55(28)**	**66.43±11.69**	**20 (71.4%)**	**534.24±29.65**
P value	**–**	**0.07**	**0.78**	**0.46**

Table -2 shows CCT in all patients before treatment and 6 month and 1-year following the treatment. In all patients, irrespective of the type of glaucoma, in the Latanoprost-treated group, CCT values decreased at 6 and 12 months (P<0.001) in comparison with the baseline, whereas in the group treated with other drugs, CCT values decreased at 12 month (P<0.007) compared to the baseline.

Table -2: Central Corneal Thickness values in patients treating with and without Latanoprost

	Baseline (µm)	6th month (µm)	12th month (µm)	P values
Latanoprost+	**537.49±25.46**	**529.97±27.1**	**517.8±48.86**	*** P<0.001 ** P<0.001 *** P<0.001**
Latanoprost–	**534.24±29.65**	**533.5±26.67**	**528.8±27.93**	*** P=0.52 ** P=0.007 *** P<0.001**

*P: Comparison of the baseline CCT with the 6th month,**P: Comparison of the baseline CCT with the 12th month,***P: Comparison of the 6th month with the 12th month

Table -3 displays CCT in patients with POAG prior to and following the treatment. In POAG patients receiving Latanoprost, a significant reduction in the CCT occurred at all follow-up intervals. Nevertheless, inPOAG patients treated with drugs other than Latanoprost, a significant decrease in CCT occurred merely after 12 months

Table -3: Central Corneal Thickness values in POAG patients treated with and without Latanoprost

	Baseline (µm)	6th month (µm)	12th month (µm)	P values
Latanoprost+	**539.84±28.57**	**531.9±29.78**	**526.5±29.83**	*** P<0.001 ** P<0.001 *** P=0.001**
Latanoprost–	**532.77±31.84**	**531.6±28.17**	**529.29±30.19**	*** P=0.69 ** P=0.04 *** P<0.001**

*P: Comparison of the baseline CCT with the 6th month,**P: Comparison of the baseline CCT with the 12th month, ***P: Comparison of the 6th month with the 12th month

With reference to Table -4, in patients with SOAG in both groups, a significant decrease in CCT occurred after 6 months of drug consumption.

Table -4: Central Corneal Thickness values in SOAG patients treated with and without Latanoprost

	Baseline(µm)	6th month(µm)	12th month(µm)	P values
Latanoprost+	**535.38±22.32**	**528.1±24.58**	**508.69±60.18**	*** P<0.001 ** P<0.001 *** P=0.005**
Latanoprost–	**536.8±25.94**	**531.5±24.47**	**527.9±24.18**	*** P<0.001 ** P<0.001 *** P<0.001**

*P: Comparison of the baseline CCT with the 6th month,**P:Comparison of the baseline CCT with the 12th month, ***P: Comparison of the 6th month with the 12th month

Discussion:

In this study, we measured patients' CCT with OAG after receiving antiglaucoma medication with special focus on Latanoprost. This study found that regardless of glaucoma type, taking this drug significantly resulted in the thinning of the cornea over time.

As mentioned earlier, CCT has a significant effect on detection and measurement of IOP. Measuring the IOP with Goldmann aplanation tonometer in the limit of CCT=500µm has been accepted as a golden standard method in measuring IOP. Outside this limit, various studies have suggested the corrective factor of 1-0.19 for every 10 µm change in CCT (12). Moreover, the measurement of CCT is influenced by factors such as the type of the used device, the measuring individual, age, sex, daily variations, and history of intra-ocular surgery (13).

In the present study, in order to decrease these factors, all pachymetry information of the patients was provided by one individual and with the use of one pachymetry device (Ultrasound Pachymetry-SP-3000, Tomey Company, Japan) and at specific hours of a day (10 AM to 1 PM). Moreover, patients of different groups had appropriate distribution regarding age and sex. Another influential factor on CCT is IOP-lowering drugs in glaucoma patients. Numerous studies have been conducted to investigate the effects of these drugs. These studies have shown different results regarding the timing of CCT variations and the nature of changes in response to different medications (14-18).

In our study, in the patients treated with Latanoprost , regardless of the type of glaucoma, CCT at all intervals significantly

decreased and the mean CCT in this group, at the end of the 12thmonth went down by 3.73%.

This finding corresponds to Sen et al (19) in which they evaluated the effect of Latanoprost and Bimatoprost on the patients' CCT and found that both drugs caused a significant decline in the CCT in a 24-month follow-up interval, not considering the type of glaucoma.

In another study by Weizer et al (6), the longitudinal variations of CCT in open-angle glaucoma patients were investigated. They reported that in two visits done with an average of 8.2-year interval, the average CCT had decreased 17μm in the right eye and 23μm in the left eye. Because of the presence of normal individuals in this study, they reported that the decrease of CCT was greater in glaucoma patients than that of normal people and this difference is statistically meaningful. The design of this study was further improved by Brandtet al (20). They similarly considered the effects of drugs. In this study, 1191 patients were followed up in a period of 3-4 years. The average CCT in these individuals not receiving medical treatment had decreased 2μm, whereas this reduction in individuals under IOP-lowering treatments was reported to be 3.5μm. A noteworthy point in this study was a decrease of 5.1μm in average CCT in the group treated with prostaglandin analogues.

Of course, some other studies have repudiated this finding. For instance, Tsikripiset al (21), in a study published in 2013, considered the effect of prostaglandin analogues on the CCT of patients with open-angle glaucoma for 3 years. The findings of this study are at odds with the previous ones. These results signify that in the Latanoprost–receiving group, at all considered intervals, the CCT has slowly but significantly increased. The curious point about this study is that the average CCT of the patients considered by Tsikripsis et al. was significantly higher than the one in our study. Moreover, unlike our study, their studied patients were not differentiated according to the type of glaucoma.

In the same vein, Bafa et al. (22) obtained results in 2009 similar to the above reported study. These researchers found an increase in the concentration of free calcium and the activation of the protein Kinase C of the corneal stroma following instilling of Latanoprost and some change in the shape of stromal cells, as justifying reasons for the increase of corneal thickness in their studied patients.

In another study by You JY et al. (23) in 2013, a control group was established. As far as research findings are concerned, this studyis congruent with our study. They evaluated the effect of Latanoprost on the corneal thickness of patients with unilateral glaucoma under normal pressure. This study, in which the control group was the other eye, indicated that the variation rate of CCT in a 24-month period had significantly decreased but at the ninth month this change was not significant relative to the basic value, but generally it had a decreasing rate. They reported in their findings that using Latanoprost after 24 months can lead to a decrease in CCT.

Furthermore, Kim et al (24)investigated the effect of Latanoprost on corneal thickness over 12 months in 2011. Likewise, they stated in the conclusion of this study that long-term use of Latanoprost in glaucoma patients can result in the decrease of corneal thickness, and this requires more attention by the clinician to CCT variations and thus its effect on IOP.

In our study, in the group receiving drugs other than Latanoprost, regardless of the type of medication, CCT decreased by 1.12% after the 12th month, which is one third of the Latanoprost-receiving individuals. This can be due to variations of CCT in glaucoma patients, regardless of the type of the taken medication.

Therefore, glaucoma may singularly result in CCT decrease, and this effect may be aggravated in case of using prostaglandin analogues such as Latanoprost.

The effect of prostaglandin analogues, mainly Latanoprost, on CCT is through its effect on extracellular corneal stroma and the up-regulation of the matrix-metaloproteinases. It has also been demonstrated in experimental studies that when corneal stroma fibroblasts are confronted with Latanoprost in the culture environment, they undergo contraction. However, they do not show such a reaction in the presence of timolol. (25)

Considering the possible role of glaucoma and its type in the variation of CCT in the study patients, we also classified the patients based on the type of glaucoma and studied the results separately in each group and concluded that in both groups similar results are obtained for all patients.

Therefore, the effects of Latanoprost on CCT are independent of the type of glaucoma. Nonetheless, considering the relative effects of Latanoproston on CCT, in the secondary open angle glaucoma group, these effects have a greater intensity. It is noteworthy that this is itself a thought-provoking point that may be indicative of greater variations of CCT over time in patients with secondary glaucoma (pseudoexfoliative) in comparison to primary open-angle glaucoma.

Of course, in the case of patients who have taken medications other than Latanoprost, if we pay attention to the results of CCT study in the subclass primary and secondary open-angle glaucoma, we realize that there are similar CCT changes in patients with primary open-angle glaucoma after at least 12 months of using medication but in secondary open-angle glaucoma, such variations have been demonstrated to occur more rapidly and intensely.

Moreover, in a cross-sectional study, the receivers of Prostaglandin analogues were compared with the receivers of carbonic anhydrase inhibitors, and it was found that there is no significant difference between these two pharmaceutical groups concerning the effect on CCT (26).

Our study has some limitations: patients were not classified according to the drugs they received other than Latanoprost. Definitely, more precise and accountable findings in this respect require another study. Due to ethical considerations, we had to choose the control group from patients receiving other medications. Finally, we restate that despite the high statistical power of the study, the unequal number of the participating patients in the study groups is also another limitation of this study.

In conclusion, Latanoprost in patients with open-angle glaucoma leads to a considerable reduction in the CCT value which begins from the 6th month after the initiation of the treatment. In patients who use drugs other than Latanoprost, CCT variation is less severe than the receivers of Latanoprost and had a longer onset (after 12 months). Moreover, patients with secondary glaucoma are exposed to more severe CCT changes.

Therefore, while setting the target IOP levels in glaucoma practice, the falsely lower IOP values owing to the thinning effects of prostaglandin analogs has to be taken into account. CCT evaluation along with IOP measurement at all control visits may be beneficial for this purpose.

Further prospective, large scale, multicentered studies with longer follow-up intervals using all prostaglandin analogs with a control group are needed to arrive at more robust and conclu-

sive findings in this line of inquiry.

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