

## Effect of Topical Anti-glaucoma Treatment on Central Corneal Thickness. Long-Term Follow-up

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**Abstract:** The purpose of this study is to evaluate the long-term effect of different types and combinations of topical anti-glaucoma treatment on central corneal thickness (CCT) and comparing this effect in primary open angle glaucoma (POAG), normal tension glaucoma (NTG) and ocular hypertension (OHT) patients. This is a prospective comparative non-randomized study including newly diagnosed patients with POAG, NTG and OHT. Patients were categorized into three groups. Group A, included patients with POAG, Group B, included patients with NTG and Group C, included patients with OHT. In each group patients were further classified into 3 sub-groups; classes 1, 2 & 3 according to the number of topical anti-glaucoma treatment they are using, whether  $\beta$ -blockers, CAI and PGAs (class 1), or  $\beta$ -blocker, & CAI (class 2), or PGAs only (class 3). Main outcome measure was change in CCT. Results: Statistical analysis was performed on 200 patients. Group A included 66 patients with POAG. Mean baseline CCT was 550.7 $\mu$ . Group B included 70 patients with NTG. Mean baseline CCT was 542.05 $\mu$ . Group C included 64 patients with OHT. Mean baseline CCT was 582.7 $\mu$ . At the 6-month visit, mean CCT values in Groups A, B, & C were 544.7  $\mu$ , 538.1  $\mu$ , & 575.6  $\mu$ , respectively. The mean CCT value continued to decrease over the follow-up period in groups A, B, & C to reach mean values of 539  $\mu$ , 532.6  $\mu$ , & 570  $\mu$  at the 36-month visit, respectively. The mean percent reduction of CCT at the end of the follow-up period was 1.08%, 0.7% and 1.2% in groups A, B, & C respectively. The difference between CCT values at baseline and all time periods of follow-up was statistically significant in all 3 groups,  $p \leq 0.001$ . The use of combined regimen including  $\beta$ -blockers, CAI, & PGAs, or PGAs monotherapy was associated with significant decrease in CCT value in comparison with  $\beta$ -blockers & CAI only,  $p \leq 0.001$ . In conclusion, long-term use of topical anti-glaucoma treatment especially PGAs is associated with corneal thinning. Serial CCT measurement is recommended in patients submitted to extended use of anti-glaucoma agents to avoid underestimation of IOP and carry on necessary adjustments.

**Key words:** Central corneal thickness • Topical prostaglandins analogues

### INTRODUCTION

Intra-ocular pressure is an important risk factor for the development of glaucoma in patients with ocular hypertension (OHT) and for the progression of established glaucoma cases [1]. Since decades the Goldmann applanation tonometer is considered the gold standard for IOP measurement. However, it has been proven recently that its accuracy is influenced by central corneal thickness (CCT) variation, in the sense

that thick corneas lead to IOP over-estimation, whereas thin corneas result in IOP underestimation [2,3]. Subsequently, accumulating evidence from several studies established the importance of CCT measurement in correlating IOP value to clinical findings in glaucoma patients [1,4].

The formulation of topical anti-glaucoma drops relies on penetrating the cornea into the anterior chamber to be able to exert their action in modifying the IOP. Several reports suggested that the long-term use of different

anti-glaucoma agents particularly PGAs could cause alteration of CCT. PGAs are known to down-regulate different collagen types through activation of matrix metalloproteinases (MMPs) [5-7], eventually leading to reduction of CCT [8-10].

The current study aims at detecting the long-term effect of different types and combinations of topical anti-glaucoma treatment on CCT and comparing this effect in primary open angle glaucoma (POAG), normal tension glaucoma (NTG) and OHT patients.

## MATERIALS AND METHODS

**Study Design & Patient Grouping:** This is a prospective comparative non-randomized study including 210 eyes of 210 patients (one eye per patient) recruited from the glaucoma clinic of the Research Institute of Ophthalmology – Egypt. The study was conducted during the period from January 2011 to March 2014. Recruited patients were newly diagnosed patients with glaucoma, either POAG or NTG and OHT who had not received topical anti-glaucoma treatment prior to recruitment. Patients were categorized into three groups each comprising 70 patients. Group A, included patients with POAG, Group B, included patients with NTG and Group C, included patients with OHT. In each group patients were further classified into 3 sub-groups; classes 1, 2 & 3 according to the number of topical anti-glaucoma treatment they were using, whether  $\beta$ -blockers, CAI and PGAs (class 1), or  $\beta$ -blocker, & CAI (class 2), or PGAs only (class 3). All patients recruited in the OHT group had their IOP reading  $\geq 24$  mmHg with an anatomically normal open angle and absence of visual field defects on automated perimetry or nerve fiber layer (RNFL) changes on OCT. Patients with diabetes mellitus, concomitant corneal disease that could induce abnormal corneal thickness, those who had history of keratorefractive or cataract surgery, & contact lens wearers were excluded from the study.

**Examination & Follow-Up Protocol:** All patients were examined at the start of recruitment and 6-monthly thereafter. Follow-up period was set at 36 months. Each visit included Snellen BCVA measurement, slit-lamp anterior segment examination, Goldmann applanation tonometry, direct gonioscopy using Zeiss 4-mirror lens, fundus examination using indirect ophthalmoscopy and slit-lamp biomicroscopy using +90D lens for examining the optic nerve head (ONH) and the macula centralis.

Automated perimetry for visual field assessment was done using Swedish Interactive Threshold Algorithm (*SITA standard 24-2, Humphrey Field Analyzer 745i – Carl Zeiss Meditech, AG, Jena - Germany*). OCT scans for ONH assessment were performed using the fourier domain RTVue-100 OCT machine (Optovue Inc., Fremont, CA, USA). We employed the glaucoma protocol that included NHM4 protocol (ONH map 4mm in diameter), & RNFL scan (3.45mm diameter circular scan), which calculates the average over 4 consecutive scans. CCT was measured using pentacam (*Wavelight Allegro Oculyzer II, Alcon, TX - USA*). All measurements were carried out at the same time of day, between 9 and 12 AM by the same qualified operator. Six readings were taken and then averaged. Main outcome measure was change in CCT.

All procedures and follow-up visits were done at the Research Institute of Ophthalmology (R.I.O.) - Ministry of Scientific Research, Egypt. The study was performed in accordance with the tenets of the Declaration of Helsinki of 1975 (the 2008 revision). The Research Committee of the Research Institute of Ophthalmology approved the protocol of the study. All patients received a thorough explanation of the procedures entailed in the study and signed an informed consent prior to enrollment.

**Statistical Analysis:** All statistical tests were performed using the SPSS 18.0 software. The Kolmogorov–Smirnov test was used to check the normal distribution of quantitative data. Categorical variables are presented as numbers and percentages. Chi-square test was used in order to evaluate any association between categorical variables. The qualitative variables are presented as means and standard deviations SDs or medians and inter-quartile ranges (IQRs) depending on their distribution. Either analysis of variance (ANOVA) or its non- parametric analogues, Kruskal-Wallis test was used to compare continuous data. Wilcoxon signed-rank test (non- parametric test) was used to compare CCT at different time periods of follow up in relation to that of baseline, while Mann–Whitney U (non- parametric test) was used to compare percent change in CCT between the treatment subgroups within each type of glaucoma. Bonferroni correction was used setting the significance level at  $p < 0.007$  to adjust for the inflation of type I error because of multiple comparisons.

## RESULTS

**Patient Characteristics:** At recruitment the study included 210 patients distributed evenly among 3 groups.

Table 1: Patient characteristics

Baseline patient characteristics	N (%)
Total number of patients	200(100)
Male	104 (52)
Female	96 (48)
<b>Group A (POAG)</b>	
Number of Patients	66 (33)
Mean Age (years)	59.18
Mean CCT ( $\mu$ )	550.7
Subgroup (class 1- $\beta$ -blockers, CAI, PGAs)	22
Subgroup (class 2 - $\beta$ -blockers, CAI)	22
Subgroup (class 3 - PGAs)	22
<b>Group B (NTG)</b>	
Number of Patients	70 (35)
Mean Age (years)	56
Mean CCT ( $\mu$ )	542.05
Subgroup (class 1- $\beta$ -blockers, CAI, PGAs)	23
Subgroup (class 2 - $\beta$ -blockers, CAI)	23
Subgroup (class 3 - PGAs)	24
<b>Group C (OHT)</b>	
Number of Patients	64 (32)
Mean Age (years)	53.4
Mean CCT ( $\mu$ )	582.7
Subgroup (class 1- $\beta$ -blockers, CAI, PGAs)	25
Subgroup (class 2 - $\beta$ -blockers, CAI)	23
Subgroup (class 3 - PGAs)	16

At completion of the study 10 patients were excluded from the study because they did not complete the required follow-up period, those were 4 patients from Group A (POAG), & 6 patients from Group C (OHT). Statistical analysis was therefore performed for the remaining 200 patients.

Group A included 66 patients with POAG, 33 men and 33 women. Mean age was 59.18 years (range 44-78, SD 7.6). Mean baseline CCT was 550.7 $\mu$  (range 523-574  $\mu$ , SD 13.1). Subgroup (class 1) included 22 patients using  $\beta$ -blockers, CAI and PGAs. Subgroup (class 2) included 22 patients using  $\beta$ -blockers and CAI. Subgroup (class 3) included 22 patients using PGAs monotherapy.

Group B included 70 patients with NTG, 40 men and 30 women. Mean age was 56 years (range 44-70, SD 6.4). Mean baseline CCT was 542.05 $\mu$  (range 529-555  $\mu$ , SD 4.5). Subgroup (class 1) included 23 patients using  $\beta$ -blockers, CAI and PGAs. Subgroup (class 2) included 23 patients using  $\beta$ -blockers and CAI. Subgroup (class 3) included 24 patients using PGAs monotherapy.

Group C included 64 patients with OHT, 31 men and 33 women. Mean age was 53.4 years (range 42-68, SD 6.5). Mean baseline CCT was 582.7 $\mu$  (range 543-643  $\mu$ , SD 22.8). Subgroup (class 1) included 25 patients using  $\beta$ -blockers, CAI and PGAs. Subgroup (class 2) included 23 patients using  $\beta$ -blockers and CAI. Subgroup (class 3) included 16 patients using PGAs monotherapy. Patient characteristics are summarized in Table 1.

**Change in CCT in Response to Topical Anti-glaucoma Treatment:** At the 6-month visit, mean CCT values in Groups A, B, & C were 544.7  $\mu$  (range 516-569  $\mu$ , SD 12.7), 538.1  $\mu$  (range 525-551  $\mu$ , SD 4.7), & 575.6  $\mu$  (range 539-632  $\mu$ , SD 21.8), respectively. The mean CCT value continued to decrease over the follow-up period in groups A, B, & C to reach mean values of 539  $\mu$  (range 512-569  $\mu$ ,

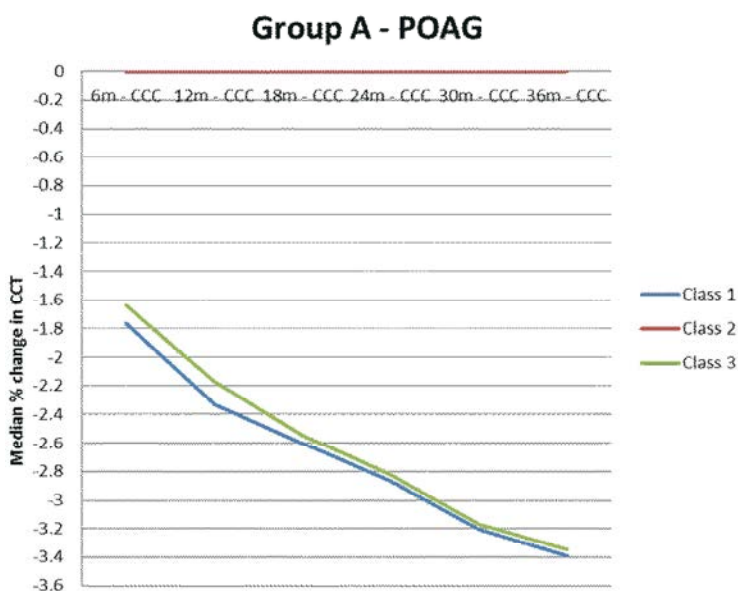


Fig. 1: Change of CCT over the follow-up period in Group A - POAG

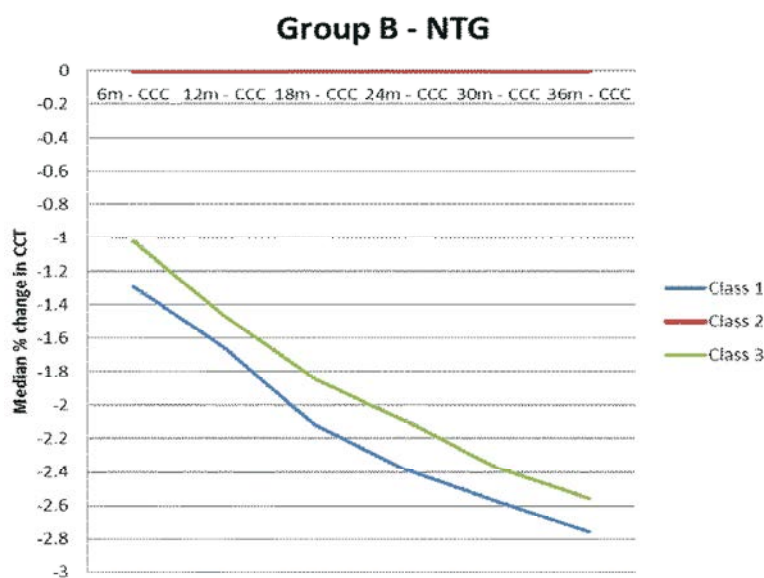


Fig. 2: Change of CCT over the follow-up period in Group B-NTG

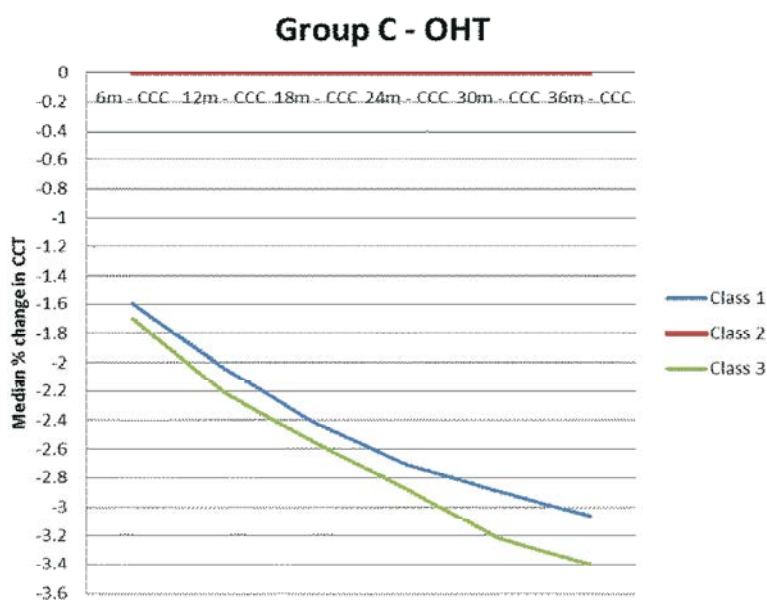


Fig. 3: Change of CCT over the follow-up period in Group C-OHT

SD 13.4), 532.6  $\mu$  (range 519-551  $\mu$ , SD 7.2), & 570  $\mu$  (range 533-620  $\mu$ , SD 21.4) at the 36-month visit, respectively. The mean percent reduction of CCT at the end of the follow-up period was 1.08%, 0.7% and 1.2% in groups A, B, & C respectively. The difference between CCT values at baseline and all time periods of follow-up was statistically significant in all 3 groups,  $p \leq 0.001$ .

In terms of sub-group analysis, the use of combined regimen including  $\beta$ -blockers, CAI, & PGAs, or PGAs monotherapy was associated with significant decrease in CCT value in comparison with  $\beta$ -blockers & CAI only,  $p \leq 0.001$ . Figures 1, 2, & 3.

## DISCUSSION

Long-term use of topical anti-glaucoma medication particularly PGAs has been linked to significant change in corneal morphology particularly CCT through up-regulation of matrix metalloproteinases [10-14].

In accordance with this finding, the current study detected reduction of CCT associated with using different topical anti-glaucoma agents over 3-year period. We have noticed that the percent reduction of CCT compared to the baseline value

was highest when PGAs were used either as monotherapy or in combination with other anti-glaucoma agents.

In congruity with our findings, Zhong *et al.* [8] detected significant reduction of CCT in patients submitted to PGAs monotherapy (latanoprost, travoprost, or bimatoprost). Their study included 69 patients with glaucoma or OHT. Mean follow-up period was 17 months. Similar results were reported by Sen *et al.* [9] in a prospective study including 188 eyes of 94 patients. These authors found significant reduction of CCT in patients submitted to PGAs monotherapy for 24 months. Bafa *et al.* [15] reported diametrically opposite results. In their prospective study they followed-up 129 glaucoma patients, of whom 108 patients were submitted to long-term PGAs. The authors reported significant increase of CCT associated with PGAs use especially latanoprost and brimatoprost. The findings of Bafa *et al.* are corroborated by a number of studies that suggested that PGAs especially latanoprost induce collagen gel contraction in the corneal stroma and rounding of corneal cells which would increase CCT [16-18].

On the contrary, Baratz *et al.* [19] found that chronic administration of anti-glaucoma medications does not affect keratocyte density or corneal endothelial characteristics. These authors used confocal microscopy and specular microscopy to evaluate the cornea of 38 patients with OHT submitted to either anti-glaucoma medication or observation. Their study had a follow-up period of 6 years. Likewise, Lester *et al.* [20] concluded that topical PGAs and CAI did not alter the CCT. These authors conducted an Italian multicenter study recruiting 316 patients receiving either topical PGAs or CAI. The authors did not find significant difference between baseline and post-treatment CCT neither did they find significant difference between the two classes of medication.

Another important finding in the present study was that long-term administration of  $\beta$ -blockers and CAI was associated with less degree of corneal thinning when compared to PGAs. This finding is corroborated by the Ocular Hypertension Treatment Study group (OHTS) which reported that the rate of CCT reduction in patients with OHT treated with PGAs over 3.8 years was more than those who were using beta blockers [12]. Further supporting evidence was presented by Viswanathan *et al.* [10]. These authors conducted a case-control study including 187 glaucoma patients on topical anti-glaucoma medications for at least 3 years. They found that PGAs

whether administered as monotherapy or in combination with other agents were associated with significant reduction of CCT over time. On the other hand the authors did not detect significant reduction of CCT in the cohort of patients using topical  $\beta$ -blockers only. The study recommended serial measurements of CCT in all glaucoma patients submitted to long-term topical anti-glaucoma agents particularly PGAs.

Limitations of the present study include absence of control group; ideally the study should have included a control group comprised of normal subjects or of glaucoma suspects who are being followed-up without receiving anti-glaucoma treatment. Another limitation is the relatively small sample size in each group, in addition to unequal sample size in sub-groups of Group C which might have biased the results.

## CONCLUSION

Long-term use of topical anti-glaucoma treatment especially PGAs is associated with corneal thinning. Serial CCT measurement is recommended in patients submitted to extended use of anti-glaucoma agents to avoid underestimation of IOP and carry on necessary adjustments.

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