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Research Article

Role of Central Corneal Thickness Measurement by Optical Coherence Tomography for Diagnosis of Primary Open Angle Glaucoma, Normal-Tension Glaucoma and Ocular Hypertension

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Abstract

Background and Objectives: Glaucoma is a disease of slow onset and progression which has relatively less symptoms in its early phase with or without elevated IOP. Glaucoma is the second leading cause of blindness worldwide, disproportionately affecting Asians. There were 60.5 million people with OAG and ACG in 2010, increasing to 79.6 million by 2020, and 74% will have OAG. Asians will represent 47% of those with glaucoma. So precise IOP measurement is the key to diagnose and manage Glaucoma. Currently GAT is still the most common gold standard method for tonometry. CCT is known to affect the accuracy of intraocular pressure measurements by GAT. Underestimation of IOP in patients with POAG with thin corneas may lead to a misdiagnosis of NTG while overestimation may lead to a misdiagnosis of OHT. Therefore we aimed to compare the CCT of the NTG, POAG and OHT groups to controls to check whether there was a difference in our population and to evaluate the effect of CCT on the diagnosis different types of glaucoma patients because of its effect on IOP measurement.

Methods: In study, out of 61 patients, 4 groups were made, POAG, NTG, OHT and Control. In all participants, CCT by OCT was measured along with IOP measurement by GAT after all systemic and ophthalmological assessment including Gonioscopy, Perimetry. Resultant corrected IOP based on CCT was compared to original IOP. Study data were analysed using GraphPad instat to get statistical significance (if P- values < 0.05).

Results: In our study, CCT value of NTG group was significantly lower compared to control group ($p < 0.05$) while OHT group had significantly higher compared to control group ($p < 0.05$). Statistically significant changes in mean IOP were noticed in NTG group only ($p < 0.05$).

Conclusion: CCT measurement is to be made an important parameter to measure along with IOP measurement to get precise IOP values by getting rid of ocular rigidity as a limiting factor for IOP measurement. We recommend CCT measurement along with GAT in glaucoma patients especially POAG, NTG and raised IOP patients of OHT to get precise IOP levels to classify as well as diagnose all considering CCT being a risk factor for Glaucoma and a limitation of GAT.

Keywords: *Primary Open Angle Glaucoma; Normal Tension Glaucoma; Ocular Hypertension; Central Corneal Thickness; Intra Ocular Pressure; Ocular Coherence Tomography*

Abbreviations

POAG: Primary Open Angle Glaucoma; NTG: Normal Tension Glaucoma; OHT: Ocular Hypertension; CCT: Central Corneal Thickness; IOP: Intra Ocular Pressure; OCT: Ocular Coherence Tomography; GAT: Goldmann's Applanation Tonometry; RE: Right Eye; LE: Left Eye; PACG: Primary Angle Closure Glaucoma; VA: Visual Acuity; Nd: YAG Laser: Neodynium doped Yttrium; Aluminum; Garnet Laser

Introduction

Glaucoma is derived from a greek word, "Glaukoma (glaucosis)" by ancient greek 400 BC coined by Hippocrates meaning Clouded or Blue-green hue, most likely describing a person with a swollen cornea or who was rapidly developing a cataract, both of which may be caused by chronic elevated pressure inside the eye. At present, Glaucoma is not a single disease but a group of disorders characterised by a progressive Optic Neuropathy resulting in a characteristic appearance of Optic Disc and a specific pattern of Irreversible Visual field defects in accordance with optic disc changes that are frequently but not invariably with raised IOP. Here, elevated IOP is one of the primary risk factors, but Glaucoma co-exists with or without elevated IOP [1].

It is estimated that there are more than 60 million cases of glaucoma worldwide and it will increase to 80 million by 2020 [2]. The estimated prevalence of glaucoma is 2.65% in people above 40 years of age. Globally, primary open-angle glaucoma (POAG) is more prevalent than primary angle closure glaucoma (PACG) and responsible for around three fourth of all glaucoma cases. Overall glaucoma is the 3rd major cause of blindness after cataract and refractive errors in India [3].

In India, the estimated number of cases of glaucoma is 12 million, around one fifth of the global burden of glaucoma. More importantly it was observed that more than 90% cases of glaucoma were undiagnosed and identified only at the time of survey (98.6% in the Chennai Glaucoma Study and 93% in ACES) [5]. The National Blindness survey 2001 showed that glaucoma is the third major cause of blindness in India and responsible for 5.9% of blindness (VA < 6/60) [6]. There has been a more than threefold increase in proportion of glaucoma blindness compared to that found in the previous National survey in 1986 - 1989 [7]. It is perceived that glaucoma blindness is underestimated in these surveys as the blindness is defined on visual acuity criteria instead of visual fields which are defining criteria for glaucoma [3].

IOP is measured by one of the methods that is GAT [8]. CCT is efficiently measured by OCT that is accurate, non-contact, reliable, easy, quick, consistent, reproducible method compared to conventional Ultrasonographic Pachymetry which is a contact method requiring topical anaesthetic agents [9]. OCT is a method which uses optical back scattering of light to image various tissues of eye from cornea to retina and optic nerve head and provides cross-sectional and 3D images of them so that individual tissues can be identified along with their thickness and abnormalities.

Ehlers., *et al.* study has shown that Cornea is thicker towards periphery and the CCT is 500 - 540 micrometer and 0.7 mm-Hg variation in IOP following change of 10 micrometer CCT. CCT is a key determinant of the IOP. People having Lesser CCT are at increased risk of having Glaucoma [10].

If the cornea is thinner, an underestimation of IOP is likely to result, and if thicker, an overestimation. Corneas tend to be thicker than average individuals with ocular hypertension, and thinner in both but more in NTG than in patients having POAG [11]. Here in, our study is carried out to find the important relationship of CCT that is to be considered every time taking IOP by GAT.

Materials and Methods

After getting ethical approval, study was carried out with enrolment of total 122 eyes of 61 subjects including 20 normal control subjects of age 20 - 60 years. The trial was prospectively registered under Clinical Trial Registry of India.

Ethical consideration

Informed written consent from each participant was taken. The identity of every participant during study period and also during analysis and after publication of the study will be kept confidential in future.

Inclusion criteria

- Patients of 20 - 60 years of age of both gender giving written and informed consent.
- Subjects having Primary Open Angle Glaucoma (POAG) characterized by IOP > 21 mm-Hg (considering diurnal measurement of IOP), Glaucomatous optic nerve damage, an open anterior chamber angle, characteristic visual field loss consistent in pattern with nerve appearance, absence of signs of secondary glaucoma.
- Subjects having Normal-Tension Glaucoma (NTG) characterized by IOP <= 21 mm-Hg (considering diurnal measurement of IOP), signs of optic nerve damage in a characteristic glaucomatous pattern, an open anterior chamber angle, Visual field loss consistent in pattern with nerve appearance, absence of signs of secondary glaucoma.
- Subjects having Ocular Hypertension (OHT) characterized by IOP > 21 mm-Hg(considering diurnal measurement of IOP) without detectable glaucomatous damage.
- The controls had an IOP of 21 mmHg or lower (considering diurnal measurement of IOP), with a normal optic nerve head and normal visual fields.

Exclusion criteria

- Secondary Glaucoma
- Angle closure Glaucoma
- Pre-existing retinopathy, visual field defects, Non- glaucomatous optic atrophy
- Any corneal pathology including corneal opacity, corneal scars and corneal oedema
- History of previous Intraocular surgery
- History of previous Intraocular Laser treatment like Nd:YAG Laser PI
- Any Drugs or treatment affecting IOP like Steroid treatment, long term use of Oral Contraceptive pills, oral beta-blockers
- Any Drugs causing corneal dryness which interfere with Central Corneal Thickness like anti-histaminics and decongestants, Non-steroidal anti-inflammatory drugs, antidepressants like sertraline, etc.
- Allergy to Mydriatic agents, Topical Anaesthetic drops or Fluorescein dye.

Method

- Detailed clinical record was prepared on a pre-diagnosed proforma and all patient were subjected to detailed history including Chief Complaints, Past History, Personal History, Family History, Drug History followed by general examination and vitals monitoring.
- We divided the patients into 4 groups including POAG, NTG, OHT and Controls were created by level of IOP in each eye, Perimetry results, Gonioscopy and Optic disc and fundus evaluation.
- Best corrected visual acuity (BCVA) was taken using Snellen's chart.
- Subjects were examined by slit lamp for anterior segment of eyes to rule out exclusion factors of study as mentioned above.
- IOP measurement in each was done using Hagg-Sterit GAT with Fluorescein stain.
- Diurnal variations in IOP were measured in each patient every 2 hours for total of 12 hours in a day.

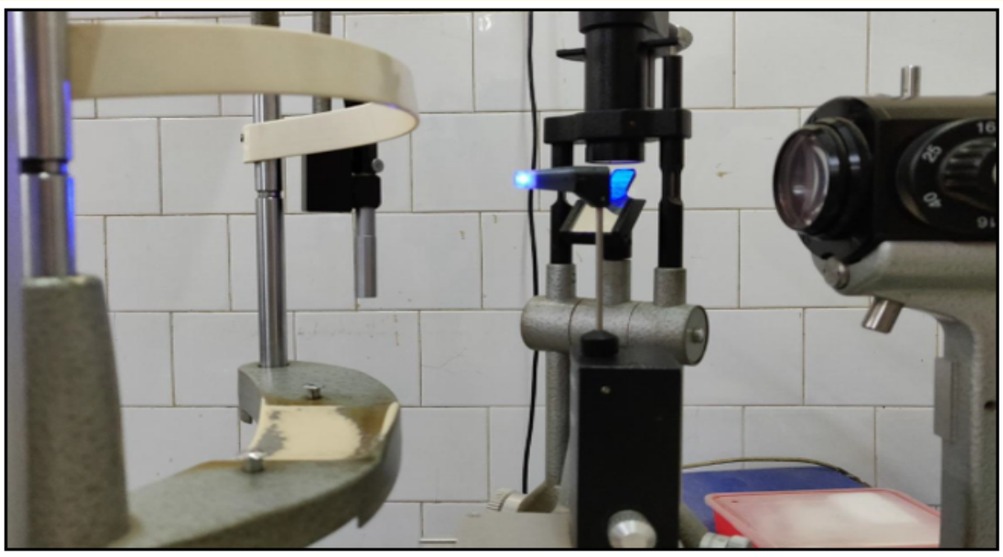

Figure 1: *Slit lamp mounted GAT illuminated with cobalt blue light.*

Gonioscopy

Anterior chamber angle assessment was done using Volk 4-mirror Gonioscopy lens with prior sterilisation. Gonioscopy is performed in both eyes in turn. Shaffer's method was used for grading of angle closure.

Perimetry

Visual field analysis was done using OCTOPUS 900 AUTOMATED STATIC PERIMETER. Here "white-on-white" perimetry with TOP (Tendency Oriented Perimetry) strategy was used. VFs were analyzed according to following octopus criteria for visual field defects (VFDs): MD (mean deviation) > 2 dB, loss of variance (LV) > 6 dB, and at least seven points with sensitivity decreased > 5 dB, three of them being contiguous [24].

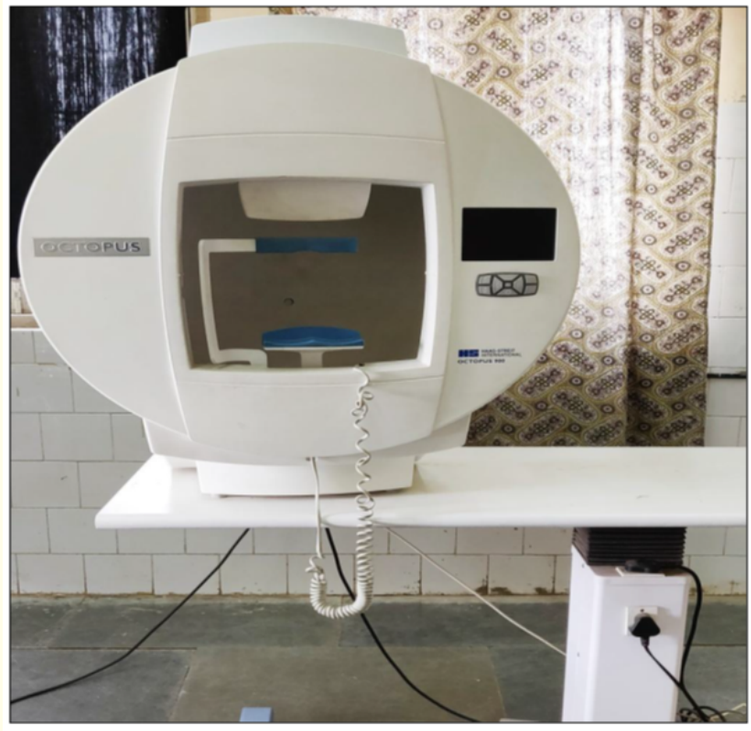

Figure 2: *Octopus Perimeter.*

Optic disc and fundus evaluation

Dilated posterior segment fundus evaluation was done using Heine Direct Beta 200 Ophthalmoscope then 90D slit lamp biomicroscopy including Optic disc for the area of cupping and pallor in all the quadrants, the position of kinking of the vessels, splinter haemorrhages and peripapillary changes [17]. Besides Optic disc, Media including cornea, cataract grade, any vitreous opacities is to be noted then Macula is assessed for its foveal reflex whether present, absent or dull then assessment of retinal vessels with retinal background is done.

Central corneal thickness

CCT was measured using AS-OCT in TOPCON 3D OCT Maestro Machine.

Figure 3: *TOPCON OCT.*

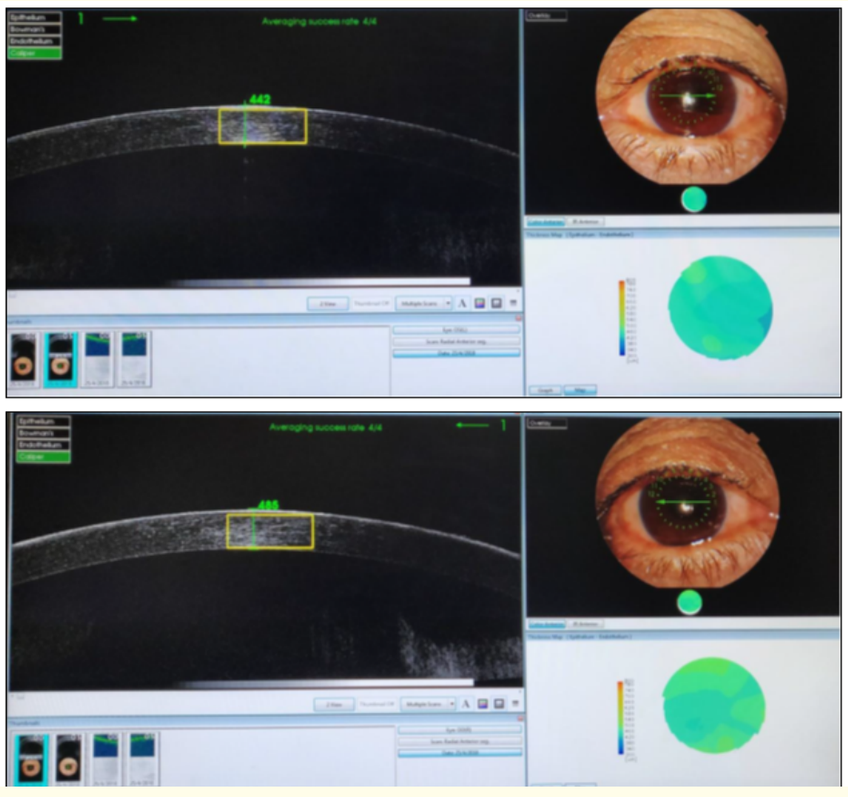

Figure 4: *AS - OCT Scans.*

IOP correction factor as per obtained CCT was done using following linear formula: "IOP correction factor (mm-Hg) = [(CCT - 545) * 2.5]/50"

Here, 545 microns is the reference CCT for GAT [13].

The correction factor that is obtained by the above mentioned formula is subtracted from the measured IOP reading and final IOP result is documented. So, Corrected IOP = Measured IOP - [(CCT - 545) * 2.5]/50.

These revised corrected IOP values were taken into considerations and appropriated adjustments in anti- glaucoma treatments were made [21].

Statistical analysis

- All data were collected and tabulated in Microsoft Excel sheet.
- Computerized analysis was performed in GraphPad instat software (version 3.06).
- Kolmogorov Smirnov normality test was used in GraphPad instat software to decide distribution of data.
- As per available database and details of participant, data are summarized as Mean Standard Deviation (SD) and as percentage wherever required.
- Inter-group comparison of qualitative data was done using Kruskal-Wallis test (Nonparametric distribution) and One-way Anova test (Parametric distribution) and Unpaired t-test.
- P - value < 0.05 is taken statistically significant.

Results and Discussion

In our study, we enrolled total 61 patients including 4 groups depending on IOP levels, perimetry and gonioscopy into POAG, NTG, OHT and controls to establish the relationship of GAT and CCT. Among 61 subjects, 22 (36%) of POAG, 10 (16.38%) of NTG, 9 (14.74%) of OHT and 20 (32.79%) of Normal subjects (Figure 5).

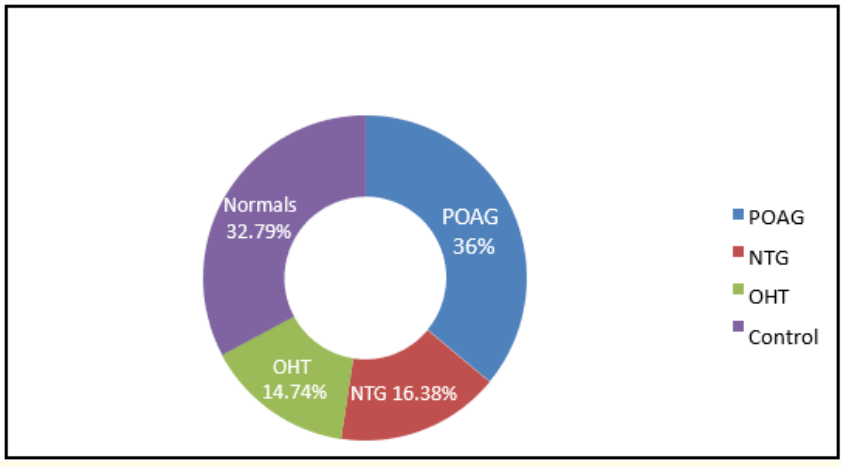

Figure 5: *Percentage (%) distribution subjects of POAG, NTG, OHT and normals.*

Mean IOP values of both eyes of POAG and OHT groups compared to control group were found to be statistically significant ($p < 0.05$) while NTG group values were not found significant ($p > 0.05$) (Table 1).

	Control	POAG	NTG	OHT
Right Eye	17 (+/-3)	25 (+/-2)	17 (+/-2)	26 (+/-3)
Left Eye	18 (+/-2)	25 (+/-3)	17 (+/-2)	26 (+/-3)

Table 1: *Mean IOP (in mm-Hg) of all groups.*
Data are here represented as mean (Standard deviation). P value < 0.05 is considered significant.

CCT values of the NTG group, RE 504 (+/-16) micro meter and LE 498 (+-/29) micro meter were significantly lower than that of Control group. POAG group had CCT, RE, 544 (+/-16) micro meter and LE 544 (+/-25) micro meter while the OHT group, RE 568 (+/-15) micro meter and LE 571 (+/-13) micro meter had significantly higher central corneal thicknesses than those of the control group. Control group had CCT values, RE 541 (+/-18) micro meter and LE 543 (+/-17) micro meter which was not statistically significant compared to POAG group (Table 2).

	Control	POAG	NTG	OHT
Right Eye	541 (+/-18)	544 (+/-16)	504 (+/-16)	568 (+/-15)
Left Eye	543 (+/-17)	544 (+/-25)	498 (+-/29)	571 (+/-13)

Table 2: *Mean CCT (in micrometer) of all groups.*
Data are here represented as mean with standard deviation. Here, P value < 0.05 is considered significant. Here, P-value is < 0.0001 (Extremely significant) and is calculated using Kruskal Wallis test for RE and LE.

Now after applying IOP CF into calculated mean IOP levels, mean IOP levels before and calculated corrected mean IOP based on CCT values in POAG and Control groups remain similar and the corrected mean IOP levels in NTG group is significantly higher compared to previous mean IOP levels and the corrected mean IOP levels in OHT group is lower compared to previous mean IOP (Table 3 and Figure 6).

	POAG		NTG	
	Right Eye	**Left Eye**	**Right Eye**	**Left Eye**
Mean IOP (mm-Hg)	24.5 (+/-2)	25 (+/-3)	16.9 (+/-1.9)	16.6 (+/-1.7)
Mean Corrected IOP(mm-Hg)	24.6 (+/-2.08)	25.07 (+/-3.2)	18.9 (+/-1.8)	18.9 (+/-2.4)
P- value	> 0.05	> 0.05	< 0.05	< 0.05
Statistically significant	Not significant		Significant	
	OHT		Control	
	Right Eye	**Left Eye**	**Right Eye**	**Left Eye**
Mean IOP (mm-Hg)	25.6 (+/-3.0)	26 (+/-3.3)	16.8 (+/-3)	17.7 (+/-1.9)
Mean Corrected IOP(mm-Hg)	24.5 (+/-2.9)	24.7 (+/-3.6)	17.03 (+/-3.1)	17.8 (+/-2.1)
P- value	> 0.05	> 0.05	> 0.05	> 0.05
Statistically significant	Not significant		Not significant	

Table 3: *Comparison of mean IOP levels vs mean corrected IOP.*
Data are here represented as mean with standard deviation. Here, P value < 0.05 is considered significant. Unpaired t-test is applied for comparison of mean IOP.

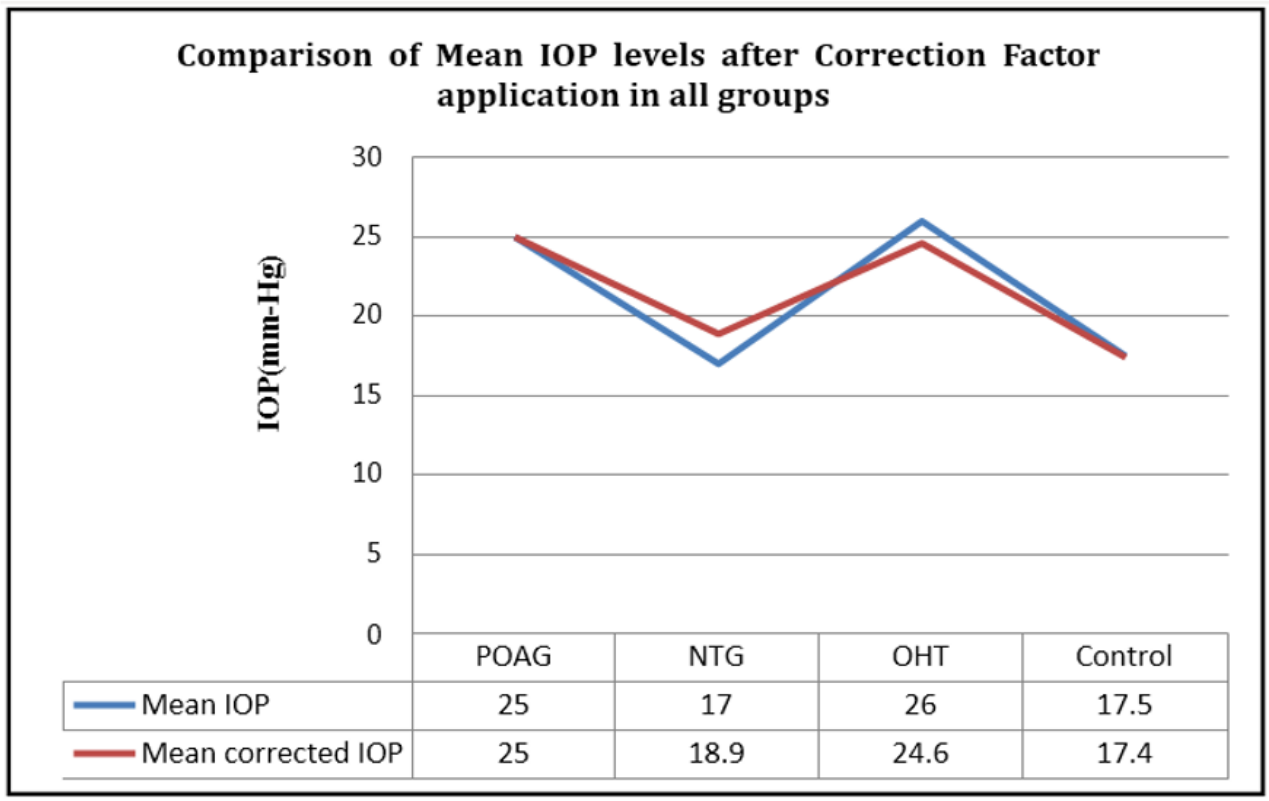

Figure 6: *Comparison of Mean IOP levels in different groups in the study after correction factor application.*

But here, no any reclassification of groups was applicable in study as per revised corrected IOP. So CCT is an important risk factor for Glaucoma and also makes a limitation for GAT for accurate IOP calculation.

Ocular Hypertension Treatment Study (OHTS) showed that baseline age, vertical and horizontal cup-disc ratio, pattern standard deviation and intraocular pressure were good predictors for the onset of POAG in the OHTS. CCT was found to be a powerful predictor for the development of POAG. Topical ocular hypotensive medication was effective in delaying or preventing the onset of POAG in individuals with elevated IOP. Although this does not imply that all patients with borderline or elevated IOP should receive medication, clinicians should consider initiating treatment for individuals with ocular hypertension who are at moderate or high risk for developing POAG [19,20].

Anupama C Shetgar, Mariyappa B Mulimani., *et al.* study confirmed that the central corneal thickness was significantly lower in the normal tension glaucoma patients as compared to those in the controls and in the primary open angle glaucoma patients, whereas the ocular hypertension patients had significantly higher central corneal thicknesses than the controls and the primary open angle glaucoma patients. No significant difference was found between the primary open angle patients and the controls [18].

Copt RP, Thomas R., *et al.* study showed NTG patients have a thinner CCT than do patients with POAG or controls. Underestimation of the IOP in patients with POAG who have thin corneas may lead to a misdiagnosis of NTG, while overestimation of the IOP in normal subjects who have thick corneas may lead to a misdiagnosis of OHT [11].

Barun K Nayak, Quresh B Maskati and Rajul Parikh., *et al.* showed in our country around 90% of glaucoma patients remain undiagnosed. On the one hand nearly 50 - 90% of true glaucoma patients remain undiagnosed; on the other hand, nearly half of the "glaucoma patients" using ocular hypotensive medication do not need the medications or are over-treated. With the above figures it is obvious that underdiagnosis and over-treatment are quite common. The issue gets more complex due to the high percentage of non-compliant patients. The effects of under-diagnosis are obvious but the implications of over-treatment are far more deleterious as it increases the cost of treatment, affects the quality of life and subjects patients to the risks of side-effects without much gain [26]. Recently, new factors other than CCT which influence IOP include especially biomechanical properties such as viscoelastics and for that Dynamic contour tonometer (DCT) is a contact available method of measuring the IOP. And this is based on the principle that by surrounding and matching the contour of the cornea, the pressure on the outside matches the pressure on the inside. IOP measured by GAT on an average has been noted to be lower than that measured by the DCT as it is considered to be less affected by corneal biomechanical properties and maintains the natural shape of the cornea during measurement. And another method is ocular response analyzer (ORA) that is a noncontact method of measuring the IOP in addition to biomechanical properties of the cornea using a dynamic bi-directional applanation process. It uses a rapid pulse of air to applanate the cornea and an advanced electrooptical system to monitor its deformation. More studies are needed to evaluate the effect of different individual corneal properties and their clinical relevance on the IOP measurement [29]. As we saw the effect of CCT on the measurement of the IOP by using an applanation tonometer, which is the main parameter in the diagnosis and the follow up of the glaucoma patients, many POAG patients may be misdiagnosed as NTG patients and the normals misdiagnosed as OHT patients so the management differs a lot. CCT measurement is an aid for an ophthalmologist in making a correct diagnosis and in a better management of glaucoma patients, especially when their corneal thickness differs markedly from the normal thickness. And CCT measurement by OCT makes this more easy, non- contact and repeatable than by Pachymeter.

Conclusion

Our study concluded CCT value of NTG group was significantly lower compared to Control group ($p < 0.05$) while OHT group had significantly higher compared to control group ($p < 0.05$) while POAG group had CCT values comparable to Control group ($p > 0.05$). Changes in mean IOP of all groups occur based on CCT values as per the formula but statistically significant changes in mean IOP was noticed in NTG group only ($p < 0.05$). So we recommend CCT measurement along with GAT in glaucoma patients especially POAG, NTG and raised IOP patients of OHT to get precise IOP levels to classify as well as diagnose for effective management considering CCT being a risk factor for Glaucoma and a limitation of GAT. Limitations of our study include limited sample size due to less prevalence of NTG and OHT among population [22,23].

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Conflict of Interest

No conflict of interest.

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