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A Comparative Study of Central Corneal Thickness in Normal Tension Glaucoma, Primary Open Angle Glaucoma and Ocular Hypertension

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Abstract

Introduction: Measurement of accurate IOP is important not only for classification but for clinical management of glaucoma patients. In individuals with thick cornea, IOP measurement by GAT may show falsely high readings. The present study was undertaken to compare the CCT in patients with Normal Tension Glaucoma (NTG), Primary Open Angle Glaucoma (POAG), Ocular Hypertension (OHT) and normal subjects and its effect on the clinical management.

Methods: The patients were grouped as NTG, POAG, and OHT. Intraocular pressure was recorded using applanation tonometry. Gonioscopy was done and the optic nerve head was examined. Central corneal thickness was measured using ultrasonic pachymeter. All the results were tabulated and statistically analysed with p less than 0.05 to be significant.

Results: A total of 99 patients were included. The mean IOP in patients of NTG was 16.70 ± 1.90 mm Hg, in patients of POAG was 29.61 ± 8.55 mm Hg, patients of OHT was 24.5 ± 1.51 mm Hg. The mean CCT of NTG was 503.91 ± 11.31 microns and 504.36 ± 11.07 microns in right and left eye respectively, in POAG patients was 525.25± 23.59 microns and 526.38 ± 21.98 microns in right and left eye respectively, OHT was 572.25 ± 22.71 microns and 572.67 ± 22.20 microns in right and left eye respectively and difference was statistically significant.

Conclusion: This study confirms that central corneal thickness is significantly lower in normal tension glaucoma patients compared to controls and primary open angle glaucoma patients whereas ocular hypertension patients have significantly higher central corneal thickness than controls and primary open angle glaucoma patients. No significant difference is found between primary open angle patients and controls.

Keywords: Central corneal thickness; Glaucoma;

Introduction

Glaucoma is a chronic progressive optic neuropathy with characteristic optic nerve head changes and visual field defects for which increased IOP is an important risk factor. Although factors other than IOP are involved in glaucoma, IOP is important because it is the only risk factor which can be pharma co modulated to date. Cartwright and Anderson in their study on patients with NTG with asymmetric IOP showed that glaucomatous damage was greater in the eye with higher IOP [1].Visual field loss of patients whose IOP is lowered pharmacologically is usually slowed [2]. Most glaucoma patients appear to have abnormal sensitivity to IOP that may be offset if IOP is lowered to mid normal or low normal range and perhaps 90% or more may benefit from sufficiently low IOP. Measurement of accurate IOP is important not only for classification but for clinical management of glaucoma patients. It is important therefore to ensure that IOP readings are taken using highly accurate method. Goldman Applanation Tonometry (GAT) has been considered to be the gold standard for measurement of IOP. Ehlers et al have shown that central corneal thickness affects the accuracy of applanation tonometry. Reduced corneal thickness of 0.45mm causes an underestimation of IOP by up to 4.7mmHg, whereas an increased CCT of 0.59mm could cause an overestimation of 5.2mmHg [3]. Therefore in individuals with thick cornea, IOP measurement by GAT may show falsely high readings and for thin cornea low readings.

Central Corneal Thickness (CCT) is an important factor to be evaluated when assessing target IOP levels for the management of glaucoma and also during follow up. Shih CY et al concluded that central corneal thickness has significant effect on the clinical management of patients with glaucoma and glaucoma suspects [4].

Copt RP, Thomas R, Mermoud and several other authors in their studies have shown that CCT in patients with normal tension glaucoma is lower and ocular hypertension is higher compared to corneas of healthy individuals [5]. The present study was undertaken to compare the CCT in patients with Normal Tension Glaucoma (NTG) with that of Primary Open Angle Glaucoma (POAG), Ocular Hypertension (OHT) and normal subjects and its effect on the clinical management of patients of glaucoma.

Materials and Methods

The study was a prospective study conducted in the department of Ophthalmology at a tertiary care centre in South India. Ethical committee clearance was obtained from the study. A written informed consent was obtained from all the patients. The study was conducted from January to August 2017. A total of 99 patients diagnosed with glaucoma attending the Ophthalmology

OPD were included in the study. The patients were grouped as Normal tension glaucoma, Primary open angle glaucoma, Ocular hypertension. Patients with IOP of 21mmHg or lower at initial visit, open, normal angles, glaucomatous optic disc and glaucomatous visual field defects were diagnosed as NTG, patients with IOP greater than 21mmHg, open, normal angles, glaucomatous optic disc and glaucomatous visual field defects were labelled as POAG, patients with IOP greater than 21mmHg, open, normal angles, normal optic disc, normal visual fields were diagnosed as ocular hypertensive's. Age and gender matched controls were selected from patients attending the OPD for other complaints. Eyes with corneal pathology, eyes with previous intra ocular, eyes with secondary glaucoma were excluded. Detailed ophthalmic and systemic history was obtained from all the patients. All patients underwent a thorough ophthalmic examination including visual acuity, Slit lamp bio microscopy of anterior segment. Intraocular pressure was recorded using GAT. Multiple measurements were taken during office hours to rule out diurnal variations in NTG patients. Patient cornea was anaesthetized with 4% xylocaine and stained with fluorescein strips. Necessary adjustments were made so that flattened area with 2 semi circles of equal size are seen in the middle of view. The pressure on the eye was increased by turning the measuring drum until the inner borders of the two fluorescein rings just touch each other. Reading on the measuring drum is multiplied by 10 to get IOP in mmHg. Three readings were taken and average was calculated. Gonioscopy was done using Goldman three mirror lens to know the status of the angle. The pupils were dilated using tropic amide eye drops and the optic nerve head was examined using 90D lens .Detailed drawings of ONH was done that included area of cupping and pallor in all quadrants, position of kinking of vessels, splinter hemorrhages, peripapillary changes. Indirect ophthalmoscopy was done to look for any peripheral retinal pathology. Visual fields were assessed using automated static perimetry of Octopus 500. Central corneal thickness was measured using ultrasonic pachymeter on the next follow up visit. After applying a drop of 4% xylocaine for local anaesthesia, the pachymeter tip was placed perpendicularly on the cornea and centered over an undilated pupil and readings were taken. From each eye 3 readings were taken and average was calculated. The measured IOP were corrected using linear correction formula. Ehlers and Hansen calculated an error evoked by a thinner or thicker cornea to be 0.7mmHg per 10 µ deviation from the normal value of 520 µ. Doughty and Zaman Meta analysis study has showed that a 10% difference in CCT would result in a 3. 4 +/- 0.9 mm Hg difference in IOP (P </= 0.001, r = 0.419) [2]. Shih CY, Graff Zivin JS et al in their study used a linear correction formula based on extensive literature review and 2.5 mmHg is added or subtracted for every 50 µ deviation in CCT from the reference value. A correction factor (CF) of 2.5 mmHg was used [4].

In our study we used the same linear correction scale of 2.5 mmHg addition or subtraction for every 50 µ deviation.

Corrected IOP = Measured IOP – (CCT – Reference CCT) * 2.5

The population based Baltimore Eye survey [6] observed 50% and Early manifest Glaucoma Trial [7] 30% reduction in the risk for every 3.0mmHg decrease in the initial IOP. Leske MC et al in Early manifest Glaucoma Trial reported 'each higher (or lower) mm of Hg of IOP on follow-up was associated with an approximate 10% increased (or decreased) risk of progression. In regard to CCT adjusted IOP values, Shih CY et al defined measurement-significant outcomes as IOP correction of 1.5mmHg or greater (in either direction) and out-comes significant results as an IOP adjustments of 3.0mmHg or greater [4]. In our study, we opted the same cut off value and modification in the glaucoma treatment plan was then noted for patients with measurement and outcomes significant IOP adjustments. The changes in therapy included addition or discontinuation of anti glaucoma medications and recommendation or deferment of glaucoma incisional surgery. All the results were tabulated and statistically analysed with p values less than 0.05 to be significant.

Results

A total of 99 patients were included in the study. Out of 99 patients in the study, 64 (64.65%) were males and 35 were (35.35%) females and the difference was not statistically significant ($p > 0.05$). The patients were divided into four groups- 28 patients (21 males, 7 females) of POAG, 22 patients (11 males, 11 females) of NTG, 12 patients of OHT (8 males, 4 females) , 37 controls (males 24,females 13). All the subjects were studied in terms of age, IOP, CCT, corrected IOP. Although the observations were made in both eyes of all the subjects, the right eye of each subject was included for statistical analysis.

The mean age of females in the study was 55.80 ± 6.45 years with a range from 40 years to 70 years. The mean age of males was 56.38 ± 8.58 years ranging from 40 years to79 years. There was no statistically significant difference in mean age among males and females ($P > 0.05$).

The mean age of NTG patients was 57.45 ± 8.51 years ranging from 40 years to79 years, POAG patients was 57.50 ± 7.45 years ranging from 45 years to79 years, OHT patients was 50.58 ± 4.25 years ranging from 44 years to 58 years. The difference observed in mean age among the different groups was not statistically significant ($P > 0.05$).

The mean IOP value in the study population was 21.36 ± 7.50 mm Hg in right eye and 19.56 ± 5.47 mm Hg in left eye. The RE Mean IOP in the right eye among males was 22.297 ± 5.45 mm Hg ranging from 12 to 40 mm Hg and among females the mean IOP was 19.657 ± 4.53 mm Hg ranging from 12 to 28 mm Hg. There was no statistically significant difference in mean IOP values between males and females ($P > 0.05$). The mean IOP values in the left eye among males was 20.063 ± 5.45 mm Hg ranging from 12 to 54 mm Hg and among females the mean IOP was 18.914 ± 5.49 mm Hg ranging from 20 to 30 mm Hg. There was no statistically significant difference observed in mean IOP values between male and females ($P > 0.05$). The mean IOP clinically was lower in females compared to males but was not statistically significant.

The mean IOP in patients of normal tension glaucoma was 16.70 ± 1.90 mm Hg ranging from 12 to 20 mm Hg, in patients of POAG was 29.61 ± 8.55 mm Hg ranging from 16 to 54 mm Hg, patients of OHT was 24.5 ± 1.51 mm Hg ranging from 16 to 54 mm Hg. There was a statistically significant difference in the mean IOP values among the three groups. The further subgroup comparison of mean IOP between the groups revealed that the NTG patients had statistically significant lower IOP than POAG and OHT patients ($p < 0.05$). The OHT patients had statistically significant higher IOP than NTG patients and statistically significant lower IOP than POAG patients table 1.

Table 1: Mean IOP in study groups

Study groups	n	Mean	SD	Min	Max	F value	P value
Normal	37	16.70	1.90	12	20	45.26	<.0001
NTG	22	17.00	2.60	12	20		
POAG	28	29.61	8.55	16	54		
OHT	12	24.5	1.51	22	26		

The mean CCT of the study population was 527.13 ± 28.09 microns ranging from 481 to 610 microns in the right eye and 528.02 ± 27.85 microns ranging from 480 to 610 microns in the left eye. The mean CCT in the RE among males was 530.09 ± 29.193 microns ranging from 481 to 610 microns and among females the mean CCT was 521.71 ± 29.193 microns ranging from 482 to 602 microns. There was no statistically significant difference in the mean CCT between males and females ($P > 0.05$). The mean CCT in the left eye among males was 531.02 ± 28.664 microns ranging from 485 to 610 microns and in females the mean CCT was 522.71 ± 25.91microns ranging from 480 to 600 microns. The difference observed in mean CCT between males and females was not statistically significant ($P > 0.05$). Even though the mean CCT was not statistically significant between the males and females with respect to left and right eyes, CCT in females was lower than the males' tables 2 and 3.

Table 2: Mean CCT of the Entire study sample

Sex(n)	RE CCT (µ)				LE CCT (µ)			
	Mean	SD	Min	Max	Mean	SD	Min	Max
Female(35)	521.71	25.463	482	602	522.71	25.91	480	600
Male(64)	530.09	29.193	481	610	531.02	28.664	485	610
Total(99)	527.13	28.09	481	610	528.02	27.85	480	610
't' value	-1.43				-1.42			
'p' value	0.1569				0.1597			

Table 3: Mean Central Corneal Thickness (CCT) according to age group

		Right eye-CCT				Left eye-CCT			
Age Group	**N**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
40-49	16	544.69	35.99	482.0	595.0	544.13	36.04	480.0	595.00
50-59	55	526.42	26.30	482.0	610.0	527.76	25.83	485.0	610.00
60-69	19	520.11	24.34	483.0	558.0	520.06	25.16	480.0	563.00
>=70	9	515.11	18.28	481.0	538.0	516.89	17.52	485.0	540.00
'F' value		3.25							
'p' value		0.0252							

The mean CCT in right eye in 40 - 49 year group was 544.69 microns, 50 - 59age group was 526.42 microns, 60 - 69 age group was 520.11 microns and greater than 70 age group was 515.11 microns suggesting that mean CCT decreased with advancing age. Although the CCT decreased clinically with increasing age, there was no statistically significant difference in the CCT between different age groups.

The mean CCT of controls was 527.65± 21.90 microns ranging from 481 to 562 microns and 528.76 ± 22.42 microns ranging from 480 to 565 microns in right and left eye respectively. The mean CCT of NTG was 503.91 ± 11.31 microns ranging from 482 to 521 microns and 504.36 ± 11.07 microns ranging from 480.0 to 523.0 microns in right and left eye respectively. The mean CCT of POAG patients was 525.25 ± 23.59 microns ranging from 482 to 590 microns and 526.38 ± 21.98 microns ranging from 485.0

to 590.0 microns in right and left eye respectively. The mean CCT of OHT was 572.25 ± 22.71 microns ranging from 540 to 610 microns and 572.67 ± 22.20 microns ranging from 540 to 610 microns in right and left eye respectively. There was a statistically significant difference in mean CCT among the groups ($P < 0.05$).

The further analysis of comparison of mean CCT between the groups revealed that CCT in NTG patients was statistically significantly lower than the controls, POAG and OHT. The central corneal thickness in OHT patients was statistically significantly higher than the controls, POAG and NTG whereas no difference was found between POAG and controls IOP was corrected after measuring CCT. It was observed 32.258% of total glaucoma patients had significant changes after correcting for CCT. 27.3 %(6 out of 22) in NTG, 66.7 % (8 out of 12) in OHT and 21.4 % (6 out of 28) in POAG group had measurement significant change. The difference observed was statistically significant ($p < 0.05$).

Discussion

Our study showed no significant difference in age between NTG and POAG similar to that found in Morad Y study group [8]. OHT patients were significantly younger than POAG, NTG. This was in accordance with the study done by Copt RP et al. No significant age difference in NTG, POAG and Controls were found in our study.

Copt RP et al in their study found no significant difference in CCT between controls (552 +/- 35 microns) and patients with POAG (543 +/- 35 microns), but the CCT in the group with NTG (521 +/- 31 microns) was significantly lower than that in the control group or the group with POAG ($P < .001$), and the CCT in the group with OHT (583 +/- 34 microns) was significantly higher than in controls or patients with POAG ($P < .001$) and concluded that underestimation of 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 [5].

Thomas R and associates in their study of effect of CCT on applanation reported that there was a statistically significant difference in the mean CCT of the ocular hypertensive's (0.574 +/- 0.033 mm) as compared to the glaucoma (0.534 +/- 0.030 mm) and normal's (0.537 +/- 0.034 mm). Measurement of central corneal thickness is advisable when the clinical findings do not correlate with the applanation IOP [9].

Ventura et al measured CCT in NTG, POAG, OHT and pseudoexfoliatives using optical low coherence reflectometry which is a more precise method than ultrasound pachymeter and confirmed that a significant number of patients with OHT have normal IOP after appropriate adjustments [10].

Mean IOP in study groups ranged from 13.06 to 27.13mmHg. Mean IOP of NTG and controls was significantly lower than POAG and OHT patients. No significant difference was seen between NTG and controls. The mean IOP in patients of OHT was less than POAG, where as in other studies the mean IOP in POAG patients was lower than patients of OHT.

In our study, CCT of NTG patients was significantly lower than POAG patients and controls as has been found in Morad Y et al, Emara BY et al, Copt RP et al and Dave et al studies while OHT patients had significantly higher central corneal thickness than controls. Emara BY et al studied CCT in NTG patients and found significantly lower CCT in NTG compared to POAG leading to underestimation of IOP. Corneal thickness should be taken into account when managing these patients to avoid under treatment [11].

Shah S, Chatterji A, Mathai M et al found corneal thickness as a confounding factor in classification of glaucoma patients and reported that patients with thick corneas and high IOP's may not be followed as Glaucoma suspects [12]. Shah S, Spedding C et al assessed the diurnal variations in CCT of Glaucoma suspects and found no significant variation in CCT and concluded that a single measurement of CCT is sufficient when assessing patients with suspected glaucoma [13]. Singh RP and associates measured a CCT of 538 ± 51 microns in NTG patients, 570 ± 32 microns in OHT patients, 547 ± 34 microns in POAG patients and 554 ± 32 microns in normal's showing a significant difference and when CCT is markedly different from normal, the clinician may need to consider this in the diagnosis and management [14].

Chen HC et al studied CCT in normal tension glaucoma and non glaucoma patients and observed a mean (+/- SD) CCT in the healthy subjects and NTG patients to be 554.1 (+/- 36.3) microns and 547.2 (+/- 31.4) microns, respectively with no significant differences in CCT between NTG patients and healthy subjects [15].

Dave and associates measured CCT in glaucoma patients and found CCT in patients with OHT was significantly greater, and in patients with NTG significantly lower, compared to controls and stated that in defining the desired IOP in glaucoma patients, CCT measurements are to be considered along with IOP measurement and visual field analysis [16]. No significant difference in CCT was found between controls and POAG patients similar to that found Morad et al, Shah S et al, Wu L et al [17] and Dave et al.

The relationship between GAT and CCT was investigated in several studies in the past and was found that CCT affects the accuracy of GAT. Different formulas have since then been developed to correct the IOP for CCT. In our study linear regression formula was used where 2.5mmHg is added or subtracted for every 50 microns deviation from reference value of 527.6 microns. Corrected IOP values for all subjects were calculated and measurement outcome and significant changes in treatment outcomes were reported.

6(27.27%) NTG patients showed measurement significant changes with no NTG patients having significant changes in outcomes. 6(21.43%) POAG patients showed a measurement significant changes with 1(3.57%) patient showing significant changes in outcomes. 8(66.67%) OHT patients showed measurement significant changes with 3(25.0%) patients showing significant changes in outcomes. In our study maximum changes are seen in OHT patients followed by NTG and POAG patients.

Early Manifest Glaucoma Trial has concluded that each higher (lower) mmHg of IOP on follow up is associated with an approximately 10% increased (or decreased) risk of progression. Considering that in our study, 8.06% of glaucoma patients have been recommended change in the medical therapy and 3.22% have been asked to discontinue their medication, 1.61% was advised surgery. In Shih et al study 8.5% had a change in medication, 2.1% had deferment or addition of laser and 3.2% had a change in whether they would receive glaucoma surgery.

Reclassification of glaucoma patients was done after correction of measured IOP for CCT. 5 (22.7%) of NTG patients were reclassified as POAG patients and 3(25%) of OHT patients were reclassified as Normal. Nearly one fourth of NTG and OHT were misdiagnosed where as in a study by Copt RP et al, 31% of NTG was reclassified as POAG and 56% of OHT as normal. Limitation of the present study is that no long term follow up was done to support the clinical implications of these changes made in the management based on CCT corrected IOP.

Conclusion

This study confirms that central corneal thickness is significantly lower in normal tension glaucoma patients compared to controls and primary open angle glaucoma patients whereas ocular hypertension patients have significantly higher central corneal thickness than controls and primary open angle glaucoma patients. No significant difference is found between primary open angle patients and controls.

Due to the effect of CCT on measurement of IOP with applanation tonometer, which is the main parameter in the diagnosis and follows up of glaucoma patients, many POAG patients are misdiagnosed as NTG patients and normal's are misdiagnosed as OHT patients and improperly managed. Measurement of central corneal thickness aid the ophthalmologist in correct diagnosis and better management of glaucoma and glaucoma suspects especially when their corneal thickness differs markedly from normal.

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