Original Article

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Comparison of Optic Nerve Head and Retinal Nerve Fibre Layer Thickness Analysis by Spectral Domain OCT

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Abstract

Purpose: The aim of the study was to compare optic nerve head (ONH) and Retinal nerve fibre layer (RNFL) thickness tomographic parameters measured by Spectral Domain (SD) OCT and to identify which measurements are best able to differentiate between normal and glaucomatous eyes in Indian population. *Design*: Cross sectional prospective diagnostic study. *Methods*: Participants were recruited from a university-based clinic. 30 age matched normal and 30 Open angle glaucomatous eyes who full filled the inclusion criteria were selected. All cases were subjected for optic nerve head (ONH) and Retinal nerve fibre layer (RNFL) thickness evaluation with the SD OCT (Carl Zeiss). All parameters were compared with normal eyes. The areas under the receiver operating curves AROC were calculated for each single parameter and then compared. *Results*: Comparative analysis of SD-OCT parameters revealed statistically significant difference in all five RNFL parameters between both the groups. Most of the ONH parameters demonstrated statistically significant difference in glaucoma group when compared with control group. The inferior quadrant (0.976) and average RNFL thickness (0.970) obtained the highest AROC values in open angle glaucoma group. The rim area had the best diagnostic accuracy among the ONH parameters (AROC = 0.951). *Conclusion:* In the present study, RNFL parameters presented with better discriminatory abilities than ONH parameters in the normal and glaucomatous group. Out of all the RNFL and ONH parameters inferior quadrant RNFL thickness, average RNFL thickness and rim area had the best ability to discriminate between glaucomatous and normal eyes.

Keywords: Optical Coherence Tomography; Retinal Nerve Fiber Layer Thickness; Optic Nerve Head Analysis; Spectral Domain.

Introduction

Optical coherence tomography (OCT) was first described by Huaug et al. in 1991. It is a noninvasive technique for in vivo non-sectional imaging of ocular structures such as retina, RNFL and optic nerve head [1]. The most significant leap forward occurred when the moving reference mirror used during the collection of time-domain (TD) OCT data was abandoned in favor of Fourier analysis of collected data. As a result, the current spectral-domain (SD) OCT technology collects up to 55,000 A-scans per second with an axial resolution of 5 μm [2].

The clinical utility of SD-OCT in glaucoma has primarily focused on the evaluation of RNFL parameters because it enables a comprehensive assessment of all the RGC axons as they approach the ONH but this may not be reliable in cases of coexisting pathology. The SD-OCT is also able to provide topographical measurements of the ONH, including optic disc area, neuroretinal rim area and volume, as well as cup area and volume. The previous versions of OCT technology were also able to provide such measurements but they were less reproducible

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and accurate as a large amount of data interpretation was required [3,4]. However, the utility of the ONH parameters by SD-OCT for diagnosing glaucoma has not been well established. Some studies like by Mwanza et al have shown that ONH parameters are able to discriminate between glaucomatous age matched healthy controls similar RNFL thickness [5]. Other studies have reported that ONH parameters are inferior to RNFL measurements for glaucoma diagnosis [6]. So in our study we have compared the various ONH parameters with RNFL thickness parameters of SD-OCT to find out which are the most sensitive and specific parameters.

Methods

Study Participants and Examination

This study included 30 normal and 30 Glaucomatous eyes, recruited prospectively from the outpatient department of Ophthalmology at DY Patil Medical college Nerul, Navimumbai in a period from October 2015 to September 2016. This study was approved by the Ethics committee of the University. Informed consent was obtained from all participants.

Participants included normal subjects and glaucoma patients. Each study participant underwent complete ophthalmologic examination including a medical history review, best-corrected visual acuity (BCVA), slit-lamp examination, Goldmann Applanation tonometry, Gonioscopy, dilated fundus examination, Visual field testing (SITA 24-2 test of Humphrey visual field analyser 750i, Carl Zeiss Meditec, Dublin) and RNFL thickness with ONH analysis by Spectral domain OCT (Cirrus OCT, Carl Zeiss, Meditec Dublin,)

All of them had to meet the following inclusion criteria: Age more than 18 years, BCVA better than 20/80 (Snellen), refractive error less than-5 D or + 5D of spherical equivalent

The study included only patients with reliable VF testing with acceptable fixation losses as defined by Ocular Hypertension Treatment Study (OHTS) of less than 33% fixation loses [7]. Patients also had to have less than 20% false positives and 20% false negatives. Exclusion criteria included patients with 1) history of any intraocular surgery in normal and glaucoma group (except uncomplicated intraocular surgery), 2) traumatic glaucoma, 3) Diseases affecting vision (Pituitary lesions, demyelinating diseases) 4)Patient suffering from neurological disorder affecting visual field, 5)current use of medications that could affect visual field sensitivity, 6) uncontrolled hypertension and/or diabetes mellitus with retinopathy. Normal eyes were consecutively recruited from patients referred for refraction that underwent routine examination

without abnormal ocular finding except for clinically insignificant senile cataract on Slit lamp examination, intraocular pressure of <22mmhg on all occasions and normal Visual field test results that were defined as a pattern standard deviation (PSD) > 5% and glaucoma hemifield test (GHT) within normal limits [8]. Glaucoma patient included those with 1) Elevated intraocular pressure >21mmhg at two occasions, 2) Wide and Open angles on gonioscopy 3) Typical glaucomatous optic disc damage, 4) Eyes with Glaucomatous visual field defect showing GHT outside 99% of normal age specific limits, a PSD with p-value < 5%, or a cluster of 3 or more points in the pattern deviation plot in a single hemifield with p-values <5%, one of which must have a p-value < 1% [8]. When both eyes fulfilled the inclusion criteria, only one eye per subject was randomly selected.

Ciirus HD-Oct Measurements

The qualifying eye of each participant was dilated with tropicamide 1% and phenylephrine 2.5% eyedrops 10-15 min prior to scanning. All scans were acquired with a Cirrus HD-OCT (version 7.0.1.290) using the Optic Disc Cube 200 x 200 protocol.

OCT scans for ONH, RNFL of a signal strength of 6/10 and above without any discontinuity, blinking or involuntary saccades artifacts were only accepted. Blinking was indicated by a straight horizontal black line across the fundus OCT image whereas involuntary saccade artifacts present as breaks in the vessels within 1.73 mm radius around the ONH.

Statistical Analysis

Mann-Whitney U test and one-way ANOVA was used for comparison amongst the two groups. ROC curves were constructed to compare the diagnostic ability of parameters assessed by SD-OCT in discriminating glaucomatous and normal eyes for each parameter. The ROC curve provides the trade off between the sensitivity and 1- specificity.

All data was evaluated using statistical software Minitab13. Demographic and ocular characteristics of the normal and glaucoma groups were compared using chi-square and non-paired 2 tailed Student's t tests for categorical and continuous variables respectively. Mean values of peripheral RNFL thickness and ONH parameters were compared between normal and glaucomatous eyes using One-way analysis of variance (ANOVA) test. Receiver operating characteristics (ROC) curves were used to describe the ability of each parameter to differentiate between normal and glaucomatous eyes. P-values <0.05 were considered statistically significant. The ROC curve plots the proportion of the false positives (1-specificity) against the proportion of true positives (sensitivity). It is useful way of showing the tradeoff between sensitivity and specificity of a given test or measure. The diagnostic performance of the test is then judged by its closeness to the upper left corner of the graph or the left-hand and the top border of the ROC space, which is assessed quantitatively by reporting the areas under receiver operating characteristic (AUCs). The AUC measures a test diagnostic ability, that is, its power to correctly classify those with and without the disease. An AUC of 1 (100% sensitivity and 100% specificity) represents a perfect test, while an AUC = 0.5 indicates a completely worthless test. The AUC was used to summarize the diagnostic accuracy of all the parameters.

Accuracy = (sensitivity + specificity) / 2.

Results

Table 1 shows the clinical characteristics of the study sample which comprised of 60 subjects in total. The normal group comprised 30 cases, 18 male and 12 female, and their average age was 57.0 ± 10.5 years. The glaucoma group comprised 30 cases, 20 male and 10 female, and the mean age was 59.2 ± 8.5 years. There was no significant difference between the normal and glaucoma group in terms of age, sex and refractive error. There was statistically significant difference between the normal and glaucoma groups in VF mean deviation (MD)(P < 0.001) and pattern standard deviation (PSD) (P<0.001).

Table 1: Patient Characteristics

Patient Characteristics	Normal Group Mean	SD	Glaucoma Group Mean	SD	P values
Age	57	10.5	59.2	8.5	0.152
Sex	18.12		20:10		0.961
Refractive error	-1.43	20.5	-1.05	2.20	0.325
VF mean deviation in dB	-1.31	1.62	-10.03	6.56	<0.001
VF pattern standard deviation in dB	1.41	0.3	6.05	3.8	<0.001

VF- visual field , SD-Standard deviation dB- decibels

In regard to the RNFL thickness in the normal & glaucoma group the results are as shown in (Table-2) In the normal group the Inferior quadrant (126.2 ± 15.1) was the thickest, followed in order by the superior, nasal and temporal quadrants.

In Glaucoma group the Average RNFL thicknesses was 66.4±15.3 μm, Superior 84.5±21.8 μm, Inferior 79.8±27.3 μm, Nasal 58.7±15.6 μm, and Temporal 52.7±12.9 μm . There was a significant reduction (p value >0.001 [S]) detected in all areas when compared to normal group.

Table 2: RNFL thickness (μm) of Normal and Glaucoma subjects

RNFL Parameters	Normal Group Mean	SD	Glaucoma Group Mean	SD	P Value
Average RNFL	102.3	9.3	66.4	15.3	<0.001
Superior	113.7	8.98	84.5	21.8	<0.001
Inferior	126.2	15.1	79.8	27.3	<0.001
Nasal	75.5	9.54	58.7	15.6	<0.002
Temporal	62.1	7.06	52.7	12.9	<0.003

Table 3 shows the ONH parameters of normal and glaucoma group. Disc area measured with Cirrus HD-OCT did not differ between the two groups (p=0.16). There was statistically significant difference between the rim area, average C/D ratio, Vertical C/D ratio and cup volume (p< 0.001) between the normal and glaucoma group.

Table 4 shows that the area under the AUC curve for inferior RNFL thickness was 0.976 with 93.6% specificity and 91.4% sensitivity. For average RNFL thickness, the AUC curve was 0.970 with 92.3% specificity and 87.7% sensitivity. The AUC curve for superior RNFL was 0.940 with a sensitivity of 86.7% and specificity of 85.6%. We found that the inferior RNFL thickness followed by the average and superior RNFL thickness had the highest power to discriminate between glaucoma and normal eyes, with an area under the ROC of 0.976, 0.970 and 0.940 respectively.

In our study the best ONH parameters with high area under the ROC curve were Rim area with 0.951 AUC with 92.3% specificity and 87.0% sensitivity. For vertical C/D ratio the AUC was 0.930 with 91.6% specificity and 83% sensitivity. The AUC for Average C/D ratio was 0.901 with 90.1% specificity and 76.7% sensitivity.

Table 3: Optic Nerve Head Topographic Parameters of Normal and Glaucoma Subjects

ONH Parameters	Normal Mean	Normal SD	Glaucoma patients Mean	Glaucoma patients SD	P value
Disc Area (mm²)	2.10	0.29	2.24	0.45	0.160[ns]
Rim Area (mm²)	1.37	0.19	0.75	0.26	<0.001
Average C/D ratio	0.43	0.13	0.73	0.11	<0.004
Vertical C/D ratio	0.47	0.12	0.71	0.09	<0.002
Cup volume (mm²)	0.23	0.14	0.567	0.33	<0.001

Table 4: Values of areas under AUC curve for ONH, RNFL OCT parameters.

RNFL Parameters	AUC (95 % CI)	Specificity	Sensitivity	Accuracy
Average RNFL thickness	0.970 (0.939 - 0.991)	92.3%	87.7%	90 %
Superior quadrant	0.940 (0.883 – 0.962)	85.6%	86.7%	86.1 %
Inferior quadrant	0.976 (0.947 – 0.998)	93.6%	91.4%	92.5 %
Nasal quadrant	0.820 (0.824 – 0.932)	88 %	65.3 %	76.6 %
Temporal quadrant	0.735 (0.801 – 0.899)	77.3 %	61 %	69.1 %
ONH Parameters				
Rim area (mm²)	0.951 (0.917 – 0.987)	92.3 %	87.0 %	89.65%
Average C/D ratio	0.901 (0.860 – 0.955)	90.1 %	76.7 %	83.4%
Vertical C/D ratio	0.930 (0.889 – 0.972)	91.6 %	83. %	87.3%
Cup volume (mm³)	0.862 (0.802 – 0.920)	86.4 %	79.3 %	82.8 %

Discussion

The present study was an attempt to evaluate the usefulness of OCT in detecting structural damage in Mild and moderate glaucomatous eyes. We compared RNFL and ONH OCT parameters in normal and glaucomatous eyes. We tried to identify parameters best able to discriminate between both the groups.

In regard to our study of RNFL analysis, there was significant reduction (P<0.001) in average and mean RNFL thickness in all quadrants compared to normal subjects .Our study had comparable results with a study by Mansoori et al [9]. In this study, the normal eyes had thickest RNFLT in inferior quadrant followed by superior, nasal and temporal quadrant. Statistically significant differences in RNFLT measurements were found for most of the parameters except temporal quadrant between glaucoma and normal eyes.

We found that the inferior RNFL thickness followed by the average and superior RNFL thickness had the highest power to discriminate between glaucoma and normal eyes, with an area under the ROC of 0.976, 0.970 and 0.940 respectively.

Our observations were comparable to the findings seen by Budenz et al [10] in a study which included 18 mild, 21 moderate and 24 severe glaucoma subjects based on visual field damage. They reported that the RNFL thickness of the inferior quadrant, average RNFL thickness, and RNFL thickness of the superior quadrant had the highest AUCs of 0.97, 0.97 and 0.95, respectively. This study had more of severe glaucoma patients as compared to our study. In a recent study by Yüksel et al [11] that included 81 healthy eyes, 68 eyes with mild, 72 eyes with moderate and 73 eyes with severe glaucoma, RNFL thickness of the inferior quadrant (AUC = 0.74) and average RNFL thickness (AUC = 0.74) were the best parameters and performed equally in discriminating between normal eyes and those with mild glaucoma, followed by the RNFL thickness of the superior quadrant (AUC = 0.68).

Kanamori et al [12] showed an AROC of 0.93 with inferior RNFL as the best parameter for such a differentiation. Chen et al [13] showed that average RNFL was the best parameter for differentiating early glaucoma from normal eyes with AROC curve area of 0.793. However in this study a significant difference was not detected in the other quadrants, possibly because of the difference of the sensitivity of measuring equipment's, the size of the study population, and the subjects. Manassakorn et al [14] compared the RNFL thickness and ONH parameters by Stratus OCT in 42 healthy and 65 glaucomatous eyes including 44 with early disease. They found that RNFL thickness at clock-hour 7 and 6 , inferior quadrant, and average RNFL were best at discriminating between normal and the glaucomatous group.

Park et al [15] compared stratus OCT and spectral domain Cirrus HD OCT in 72 normal subjects and 52 early glaucoma patients based on SAP results. They observed that Cirrus OCT showed better diagnostic capability (AROC of 0.94 for inferior quadrant and 0.937 for average RNFLT) than Stratus OCT (AROC of 0.898 for inferior quadrant and 0.896 for average RNFLT). This was explained by difference in measurement techniques , higher scan resolution and more accurate data registration by Cirrus HD OCT. Study by Mansoori T [9] in Indian eyes showed a largest AROC for 12 O clock hour (0.98), average RNFLT (0.96) and superior quadrant RNFLthickness (0.9). Here Superior thining of RNFLT faired better than inferior. This study was done by spectral domain OCT in early glaucoma patients only. This study showed loss mostly in superior quadrant probably due to selection of patient with RNFL loss in superior hemifield as explained by author.

Study by Rao et al (2014) [16] in preperimetric glaucoma by SD-OCT but by RTV machine showed all RNFL parameters to be be significantly thinner in glaucoma group compared to control group. In this study average RNFL thickness (0.786), temporal (0.762) and inferior (0.752) RNFL thickness parameters had the best AUCs. It is one of the few studies which has reported temporal thining & comparable AUC to average & inferior RNFL thickness.

According to our study, a significant difference was detected in the comparison of the parameters of the optic nerve disc between the normal and glaucoma groups, except the diameter of the optic nerve disc and the disc area. Our study had similar results compared to study by Mwanza et al [5] which showed that regardless of disease stage, the best parameters by Cirrus OCT were vertical rim thickness (VRT) , (0.963) rim area (0.962) vertical cup-to-disc ratio (VCDR) (0.951) average cup disc ratio (CDR) (0.930) and horizontal rim thickness (HRT) (0.883).

The largest AUCs obtained with Cirrus OCT in the study by Calvo P et al [17] were observed for vertical C/D ratio (0.980) and rim area (0.966). Here 156 glaucomatous eyes with perimetric glaucoma were evaluated. They evaluated only ONH parameters. Our observations were comparable to the findings seen in the study by Leung et al [18] examined the diagnostic accuracy of ONH parameters to detect mild glaucoma using Stratus OCT in a study comprising 41 normal and 30 eyes with early glaucoma. VRT (AUC = 0.968), VCDR (AUC = 0.962), and CDR (AUC = 0.960) had the highest ability to distinguish the two groups of eyes.

A Study was done by Garas A et al [19] in Caucasian population which showed that most RNFL thickness and GCC (Macular) Measurements had high specificity (94.6-100%) but it was low (72.0-76.3%)for optic disc parameters. Our study shows better accuracy of ONH as compared to this study. Probably because this study included half OHT and preperimetric glaucoma and perimetric glucomas, where as our study had only perimetric glaucoma. So Optic disc parameters fares better in perimetric glaucoma.

Using visual field defects as reference standard, Rao et al [20] evaluated the accuracies of the RNFL, ONH, and macular thickness scanning protocols obtained by SD-OCT to differentiate normal eyes from eyes with glaucomatous field defects and found that the RNFL and inner retinal macular thickness measurements had good diagnostic accuracy, with ROC curve areas of 0.88 and 0.87, respectively. The RNFL and macular parameters performed significantly better than the best ONH parameter, which had an ROC curve area of 0.81. This was a study in 140 perimetrically proven glaucomatous eyes but RTVue OCT was used. This was comparable to our study which showed that inferior RNFL thickness with AUC of 0.976 performed better than the ONH rim area parameter with AUC of 0.951 .This shows that results of various machine with spectral domain technology are comparable.

Another study with glaucoma, preperimetric glaucoma and healthy subjects demonstrated that RNFL thickness was better than any tested ONH parameter.This study had more of preperimetric patients (405)as compared to perimetric glaucoma (229). Lisboa et al [21] demonstrated that RNFL parameters performed significantly better than ONH for detecting preperimetric glaucoma in their observational study with RTVue SD-OCT.

Conclusions

Out of all the RNFL parameters compared our study shows that the inferior RNFL thickness followed by average and superior quadrant as the best parameters in the differentiation of glaucoma from healthy eyes. Among ONH OCT parameters Rim area was the best parameter to differentiate between glaucoma and normal subjects. However, in our study, RNFL thickness parameters had higher sensitivity and specificity for the detection of glaucoma compared to ONH. Although each parameter alone can successfully discriminate between eyes with glaucoma and healthy eyes, combining parameters from various scanned region can improve diagnostic performance of OCT.

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