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CLINICAL INVESTIGATION

Spectral-Domain Optical Coherence Tomography and Scanning Laser Polarimetry in Glaucoma Diagnosis

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Abstract

Purpose: To evaluate glaucoma diagnostic capability of the retinal nerve fiber layer (RNFL) imaging by spectral-domain optical coherence tomography (Cirrus OCT) and scanning laser polarimetry (GDx VCC).

Methods: We imaged 88 glaucomatous and 77 healthy eyes using both devices. Areas under the receiver–operating characteristic curves (area under the curves, AUCs) and sensitivities at fixed specificities of average, superior, and inferior RNFL thickness were compared. Likelihood ratios (LRs) and diagnostic agreement based on normative classifications yielded by both devices were determined.

Results: The best performing parameter was the nerve fiber indicator (NFI) in GDx VCC and inferior RNFL thickness in Cirrus OCT (AUC = 0.912, 0.961, $P = 0.045$). The AUCs of the Cirrus OCT were significantly higher than those of GDx VCC in all parameters. Most of the parameters in Cirrus OCT were more sensitive than GDx VCC in the detection of glaucoma at fixed specificity values. Cirrus OCT had an infinite LR with abnormal classification results in both average and superior RNFL thickness. There was good agreement between the two instruments with respect to abnormal classifications (kappa, 0.611–0.766)

Conclusion: Both Cirrus OCT and GDx VCC RNFL measurements showed good glaucoma diagnostic capabilities. Cirrus OCT showed higher sensitivities than GDx VCC. **Jpn J Ophthalmol** 2010;54:544–549 © Japanese Ophthalmological Society 2010

Keywords: glaucoma, scanning laser polarimetry, spectral domain OCT

Introduction

Glaucoma is an optic neuropathy characterized by progressive loss of retinal ganglion cells (RGCs) and their axons. Visual field (VF) testing, which evaluates functional defects, is considered the gold standard for the detection of glaucoma. However, structural damage may precede functional loss diagnosed by VF testing.[1,2] Therefore, it is crucial to objectively and accurately assess structural damage before irreversible functional impairment occurs.

Scanning laser polarimetry (SLP) and optical coherence tomography (OCT) measure the thickness of the peripapillary retinal nerve fiber layer (RNFL). The GDx variable corneal compensator (VCC; Carl Zeiss Meditec, Dublin, CA, USA) is currently the commercially available version of SLP. This device equipped with a VCC measures the peripapillary RNFL thickness from the birefringence properties of RGC axon microtubules.[3,4]

OCT uses a scanning interferometer to obtain a cross section of the retina and calculates RNFL thickness from the two segmentation lines of the inner and outer boundaries of the RNFL.[5] Recently, spectral-domain (SD) OCT has been developed from time-domain (TD) OCT, and the SD

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Cirrus OCT instrument (Carl Zeiss Meditec) has become available. This technology has higher axial resolution and scan speeds than the conventional TD Stratus OCT.[6]

Several comparative studies have shown that GDx VCC and TD Stratus OCT are highly effective and have similar capabilities in the diagnosis of glaucoma.[7–11] However, to the best of our knowledge, no study has yet compared the glaucoma diagnostic capability of GDx VCC with that of the newly introduced SD Cirrus OCT in the same subjects. In the present study, we compared the diagnostic capability of these two devices in the same study population using similar inclusion and exclusion criteria.

Subjects and Methods

Subjects

Healthy and glaucomatous subjects who met the eligibility criteria were recruited prospectively at our glaucoma clinic and were examined between March 2008 and March 2009 at the Asan Medical Center (Seoul, Korea). All subjects underwent a complete ophthalmic examination, which included tests for best-corrected visual acuity (BCVA), slit-lamp examination, Goldmann applanation tonometry, gonioscopy, Humphrey field analyzer (HFA) using the Swedish Interactive Threshold Algorithm version 24-2 (Carl Zeiss Meditec), stereoscopic optic nerve photography, SLP with the GDx VCC and SD Cirrus OCT. One eye per subject was randomly selected if both eyes were eligible. Inclusion criteria for both glaucoma and healthy subjects were BCVA ≥20/30; spherical equivalent within ±5 diopters (D), and a cylinder correction within +3 D; presence of a normal anterior chamber and open angle on slit-lamp and gonioscopic examination; reliable HFA results with false-positive error <15%, false-negative error <15%, and fixation loss <20%; absence of ocular pathologies other than glaucoma; and no history of diabetes mellitus.

Glaucomatous eyes were defined as those with a glaucomatous VF defect confirmed by at least two reliable VF examinations and by the presence of a glaucomatous optic disc either with increased cupping (vertical cup disc ratio >0.7), a difference in vertical cup–disc ratio >0.2 between eyes; or either diffuse or focal neural rim thinning or hemorrhage. Eyes with glaucomatous VF defects were defined as those that had (1) a cluster of three points with a probability of less than 5% on a pattern deviation map in at least one hemifield, including at least one point with a probability of less than 1% or a cluster of two points with a probability of less than 1%; and (2) a glaucoma hemifield test outside 99% of the age-specific normal limits or a pattern standard deviation outside 95% of the normal limit. A normal VF was defined as one not meeting the above-mentioned criteria of glaucomatous VF defects. Healthy subjects with no family history of glaucoma, normal optic disc appearance, normal VF result, and intraocular pressure of less than 22 mmHg were used as controls. Intervals between Cirrus OCT, GDx VCC, and VF examinations were less than 2 weeks. Informed consent was obtained from all participants, and all procedures conformed to the Declaration of Helsinki. The study was approved by the Institutional Review Board of the Asan Medical Center at the University of Ulsan (Seoul, Korea).

GDx VCC

SLP imaging was performed with the GDx VCC. The basic principles and technical characteristics of the GDx VCC are described elsewhere.[12,13] Imaging was performed using a scan circle of 3.2 mm diameter centered on the optic disc, and the mean of three measurements was used for data analysis. We excluded all poor-quality scans, defined as those with a quality score grade of less than 8 and an atypical retardation pattern with a typical scan score of <80.[14] Atypical retardation pattern images included those that did not follow the normal physiological distribution of the RNFL.[14] Temporal-superior-nasal-inferior-temporal average, nerve fiber indicator (NFI), and superior/inferior average RNFL thicknesses were measured. The normative classification consisted of four categories: 5–100 percentile (white color); 2–5 percentile (blue); 1–2 percentile (sky blue); and <1 percentile (yellow). Less than 5% of the normative database was regarded as abnormal in our current analysis. All images were acquired by a single well-trained operator. The pupils were dilated if their diameter was less than 3 mm.

Cirrus OCT

SD OCT imaging was performed with the Cirrus OCT. In the Cirrus OCT, optic disc scans that capture a 6 mm × 6 mm × 2 mm "cube" of data (composed of 200 A-scans from each of 200 B-scans) were used for analysis. After creating an RNFL thickness map from the cube data set, the software automatically determined the center of the disc and then extracted a circumpapillary circle (1.73-mm radius) from the cube data set for RNFL thickness measurement. We excluded images with (1) signal strength less than 6; (2) overt misalignment of the surface detection algorithm on at least 15% of consecutive A-scans or 20% of cumulative A-scans; or (3) overt decentration of the measurement circle location, assessed subjectively. In addition, we excluded images if the subject had an involuntary saccade within a 1.73-mm radius during the scan. The average, superior, and inferior quadrant RNFL thickness values were used for analysis. The Cirrus OCT normative classification consisted of four categories: 95–100 percentile (hypernormal; white color on the thickness map); 5–95 percentile (normal; green); 1–5 percentile (borderline; yellow); and <1 percentile (abnormal; red). As with GDx VCC, less than 5% of the normative database was regarded as abnormal values in our current analysis. All images were acquired by a single, well-trained outside operator. Pupils were dilated if their diameter was less than 3 mm.

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Statistical Analysis

One eye from each subject was used for statistical analysis. One eye was randomly selected for analysis when both eyes of a subject fulfilled both the inclusion and exclusion criteria. The Wilk-Shapiro test was used to test the distribution of numerical data. Depending on the data distribution (Gaussian versus non-Gaussian), either parametric or non-parametric tests were employed to compare variables. For data with a Gaussian distribution, we compared healthy eyes and glaucomatous eyes using the unpaired *t* test; otherwise, we employed the Mann-Whitney test. To compare categorical data, the χ-squared test was used.

To test the diagnostic capability of RNFL thickness in both healthy and glaucomatous eyes, the areas under the receiver–operating characteristics curves (AUCs), including the overall average and the superior and inferior RNFL thickness, were compared. The DeLong method was used to evaluate statistical differences between AUCs, as determined by three imaging devices.[15] Sensitivities at fixed specificities of 80%, 90%, and 95% or higher were also calculated from the receiver–operating characteristic curves. Sensitivities at fixed specificities were compared with McNemar's statistics.

Positive likelihood ratios (PLRs) and negative likelihood ratios (NLRs) for glaucomatous change detection using a normative RNFL thickness classification were calculated using the formulae: PLR = sensitivity/1 − specificity; and NLR = 1 − sensitivity/specificity. The likelihood ratio (LR) of a given result indicates to what extent that result will either raise or lower disease probability. A value of 1 indicates that the test provides no additional information, and ratios higher or lower than 1 respectively increase or decrease the likelihood of disease. The use of LRs to predict posttest disease probability has been suggested by Jaeschke and colleagues.[16] In their model, LRs higher than 10 or lower than 0.1 are associated with large effects on posttest probabilities, LRs from 5 to 10 or from 0.1 to 0.2 with moderate effects, LRs from 2 to 5 or from 0.2 to 0.5 with small effects, and LRs closer to 1 are insignificant. The 95% confidence intervals (CIs) for LRs were also calculated.

Agreement of normative classifications between the two devices was assessed with kappa statistics. All statistical analysis was performed using SPSS version 15.0 (SPSS, Chicago, IL, USA) and MedCalc version 9.6 (Mariakerke, Belgium).

Results

Initially, we enrolled 100 glaucoma patients and 84 normal healthy subjects, but 19 of the latter were excluded because of poor image quality. Fifteen had poor image quality in the GDx VCC scan, seven in the Cirrus OCT scan, and three in images of both devices. Ultimately, we included 88 glaucomatous subjects (48 men, 40 women) and 77 healthy subjects (39 men, 38 women) in the final analysis. All enrolled subjects were Koreans. Table 1 shows the baseline demographic characteristics of healthy and glaucomatous subjects. Both imaging devices showed a statistically significant difference between healthy eyes and glaucomatous eyes in average, superior, and inferior RNFL thickness. The GDx VCC results showed that the NFI of glaucomatous eyes was higher than that of healthy eyes (Table 2).

AUC and Sensitivity at Similar Level of Fixed Specificities

Both the GDx VCC and Cirrus OCT showed excellent glaucoma diagnostic capability. The "best" parameter of each device was NFI measured by the GDx VCC (AUC = 0.912), and the inferior RNFL thickness assessed by Cirrus OCT (AUC = 0.961, Table 3). The AUC of the GDx VCC NFI was significantly lower than that of the inferior RNFL thickness yielded by Cirrus OCT ($P = 0.045$). The Cirrus OCT showed significantly higher AUCs in discrimination of glaucoma and healthy subjects than GDx VCC in all parameters (average, superior, and inferior RNFL thickness). The Cirrus OCT showed significantly higher sensitivity than the GDx VCC for most of the parameters at a similar level of specificity (≥95%, ≥90%, and ≥80%, respectively, Table 4).

PLRs and NLRs

Table 5 shows the PLRs and NLRs for glaucoma detection using GDx VCC and Cirrus OCT. Average and superior RNFL thickness classification by Cirrus OCT showed an infinite PLR, while PLR of GDx VCC ranged from 17.1 to 37.6. NLR ranged from 0.33 to 0.48 in Cirrus OCT and from 0.52 to 0.57 in GDx VCC.

Table 1. Demographics and baseline characteristics of study participants

	Healthy ($n = 77$)	Glaucoma ($n = 88$)	*P* value
Age, mean ± SD (years)	51.7 ± 11.4	53.7 ± 10.8	0.065
Male/female	39/38	48/40	0.642
Intraocular pressure, mean ± SD (mmHg)	15.6 ± 3.4	15.9 ± 2.6	0.664
Spherical equivalent, mean ± SD (diopters)	–1.75 ± 2.87	–1.25 ± 2.12	0.751
VF MD, mean ± SD (decibels)	–1.06 ± 1.63	–6.33 ± 4.79	<0.001
VF PSD, mean ± SD (decibels)	1.6 ± 0.38	6.7 ± 4.12	<0.001

MD, mean deviation; PSD, pattern standard deviation; SD, standard deviation; VF, visual field.

Table 2. Comparison of RNFL thickness measured by scanning laser polarimetry (GDx VCC) and spectral-domain OCT (Cirrus OCT) in healthy and glaucomatous eyes

	GDx VCC			Cirrus OCT		
Parameter	Healthy (n = 77)	Glaucoma (n = 88)	P value	Healthy (n = 77)	Glaucoma (n = 88)	P value
Average[a] (mean ± SD)	59.3 ± 6.6	46.5 ± 7.8	*<0.001	97.6 ± 8.6	72.7 ± 12.1	<0.001
Superior quadrants[a] (mean ± SD)	72.6 ± 8.0	56.5 ± 12.7	*<0.001	124.6 ± 13.3	89.7 ± 20.7	<0.001
Inferior quadrants[a] (mean ± SD)	69.0 ± 8.7	51.4 ± 11.2	*<0.001	126.3 ± 13.4	81.4 ± 21.4	<0.001
NFI,[b] median (range)	13.7 (8.1)	43.6 (23.2)	*<0.001			

VCC, variable corneal compensator; NFI, nerve fiber indicator; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.
[a]Unpaired t test.
[b]Mann-Whitney test, χ-squared test.

Table 3. AUCs (95% confidence interval) of RNFL thickness and NFI measured by GDx VCC and Cirrus OCT

Parameter	GDx VCC	Cirrus OCT	P value
Average	0.911 (0.856–0.949)	0.952 (0.907–0.979)	0.041
Superior	0.856 (0.793–0.905)	0.923 (0.871–0.958)	0.017
Inferior	0.899 (0.843–0.941)	0.961 (0.920–0.985)	0.007
NFI[a]	0.912 (0.858–0.950)		0.045

AUC, area under the receiver–operating characteristic curve.
[a]Comparison between best-performing parameters (GDx VCC, NFI; Cirrus OCT, inferior RNFL thickness).

Diagnostic Agreement of Normative Classification

We tested for agreement of diagnostic categorization with each imaging device. The GDx VCC and Cirrus OCT abnormal classifications in average RNFL thickness agreed in 86% of cases, with a substantial chance-corrected agreement (kappa = 0.662). The kappa value of superior and inferior RNFL thickness was 0.766 and 0.611, respectively.

Discussion

OCT and SLP are different RNFL imaging modalities widely used for the diagnosis of glaucoma. Although the Cirrus OCT and GDx VCC (SLP) employ different technologies, both noninvasively measure peripapillary RNFL thickness. Previous studies have confirmed that both Stratus OCT and GDx VCC have good measurement reproducibility.[17–25] GDx VCC and Stratus OCT are reported to have similar diagnostic performance with respect to discrimination between healthy and glaucomatous eyes.[7–11]

Recently, OCT technology has evolved from TD OCT (Stratus) to the SD OCT. SD OCT has a theoretical advantage over conventional TD OCT because of enhanced axial resolution and faster scan speed, and may thus provide higher quality images and more accurate measurements.[26]

Recent publications have shown that the Cirrus OCT used in our current study has good measurement reproducibility.[27,28] According to our analysis, all parameters of both Cirrus OCT and GDx VCC showed excellent glaucoma diagnostic capability. NFI was the best performing parameter of the GDx VCC, whereas inferior RNFL thickness had the highest AUC for Cirrus OCT, similar to what has been reported previously.[7,10,13,29]

However, when we compared the glaucoma diagnostic performance of the Cirrus OCT and the GDx VCC, the Cirrus OCT had significantly higher AUCs than did the GDx VCC in average, superior, and inferior RNFL thickness. More Cirrus OCT parameters displayed significantly higher sensitivities at fixed specificities of ≥95%, ≥90%, and ≥80% than did GDx VCC measurements. Because for clinical diagnosis glaucoma screening devices with high sensitivity and specificity are required, Cirrus OCT may have better glaucoma diagnostic and screening capabilities than the GDx VCC.

It is difficult to explain why Cirrus OCT appears to have better glaucoma diagnostic capability than the GDx VCC, because these two devices employ totally different technologies. Inherent differences of working principles or other factors, such as the influence of image quality on measurement accuracy, and software-related issues, might lead to differences in measurement quality, but we have limited access to the relevant technical information.

Cirrus OCT showed higher PLRs for abnormal results and lower NLRs for within-normal-limits data in the normative classification for all measurements than did the GDx VCC. Thus, we believe that, compared with the GDx VCC, Cirrus OCT has a better glaucoma diagnostic capability in terms of normative classification. However, the NLRs for within-normal-limits data in the normative classification were in the range 0.33–0.57 for both devices, indicating that the within-normal-limits information in the normative classification are of limited use for the exclusion of glaucoma.

When we assessed agreement between abnormal results yielded by normative classification of average RNFL thickness by the two devices, the variation-corrected parameter (kappa) ranged from 0.611 to 0.766, indicating good between-instrument agreement.

Assessment of the diagnostic capabilities, including AUC values, sensitivity, and specificity, in case–control studies that use new techniques (such as SD Cirrus OCT) requires

Table 4. Sensitivities of the GDx VCC and Cirrus OCT in the detection of glaucoma at three different specificities

	Specificity ≥ 95%			Specificity ≥ 90%			Specificity ≥ 80%		
	GDx VCC	Cirrus OCT	*P* value	GDx VCC	Cirrus OCT	*P* value	GDx VCC	Cirrus OCT	*P* value
Average	68(96)	75(96)	*0.031	82(91)	85(91)	0.25	85(81)	88(82)	0.50
Superior	56(96)	75(95)	*<0.001	67(91)	84(91)	*<0.001	75(81)	88(81)	0.001
Inferior	53(96)	83(95)	*<0.001	68(91)	88(91)	*<0.001	81(81)	94(81)	<0.001

Table 5. PLR and NLR of normative classification in detection of glaucoma from GDx VCC and Cirrus OCT RNFL thickness measurements

Parameter	GDx VCC		Cirrus OCT	
	PLR	NLR	PLR	NLR
Average	17.5 (4.4–70.0)	0.56 (0.46–0.68)	I (N–I)	0.4 (0.31–0.51)
Superior	17.1 (4.3–68.4)	0.57 (0.47–0.69)	I (N–I)	0.48 (0.38–0.59)
Inferior	37.6 (5.3–266.8)	0.52 (0.42–0.64)	51.6 (7.3–363.8)	0.33 (0.25–0.45)

PLR, positive likelihood ratio; NLR, negative likelihood ratio; I, infinite; N, not applicable.

careful consideration of the patients being studied. Currently, there is no gold standard for diagnosing glaucoma. Visualization of changes on optic disc photographs, which may take years to occur, or VF defects detected by achromatic automated perimetry, which may not appear until many retinal nerve fibers are lost, are commonly employed to diagnose glaucoma. In the current study, we did not include so-called preperimetric glaucoma patients or glaucoma suspects (patients suspected of having lost nerve fibers but with no VF changes). A study of such patients will be very challenging because observation of glaucoma suspects over a long period of time will be required. Therefore, it is important to keep in mind that our estimates of the diagnostic capabilities of these two devices are probably higher than what would be observed in clinical practice.

The current study had several limitations. First, our study population was racially homogeneous (Asian). The percentages of Asian eyes in the normative databases of the two devices are different, and databases with varying percentages of different races might compromise comparisons of RNFL thickness data. Notably, more Asian control eyes are included in the Cirrus OCT database than in the GDx VCC database. Moreover, assessment of a normal population of a single race, followed by comparisons with multiracial normative databases, may skew specificity data. Second, we cannot exclude the possible effect of a selection bias, in that most of our glaucomatous subjects had early-to-moderate glaucoma. The ability of a new device to diagnose glaucoma in patients with relatively advanced glaucoma (as in our study) may erroneously inflate diagnostic sensitivity. In clinical practice, where ophthalmologists attempt to discriminate glaucoma from suspected or early glaucoma, accuracy may be lower than reported here. Imaging comparisons on early glaucomatous eyes or on those suspected of having subtle structural changes might yield different outcomes in terms of RNFL thickness, sensitivity, and specificity.

The value of a diagnostic test is influenced by the proportions of study patients with very high (>10) or very low (<0.1) LRs, thus strongly influencing the probability of disease detection. In our study population, no parameter of any device had a very low NLR. Therefore, selection of other cutoff values or measurement parameters may produce different results. Studies with larger sample sizes may provide more robust estimations of LRs.

In conclusion, RNFL measurements provided by both Cirrus OCT and the GDx VCC, exhibited good glaucoma diagnostic capability. The Cirrus OCT measurements were of higher sensitivity than were the GDx VCC measurements. However, our results apply specifically to Asians and should not be generalized to other populations. Further work is needed to assess the diagnostic capability of Cirrus OCT and GDx VCC for early diagnosis of glaucoma and in monitoring the progression of glaucoma in other ethnic groups.

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