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Original Article

Frequency doubling technology and standard automated perimetry in detection of glaucoma among glaucoma suspects

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ABSTRACT

Background: Frequency Doubling perimetry (FDT) has been found to precede visual loss detected by standard automated perimetry (SAP) by as much as four years and the initial development of glaucomatous visual field loss as measured by SAP was found to occur in regions that had previously demonstrated abnormalities on FDT testing.

Methods: A study on 55 glaucoma suspects (determined as per American Academy Guidelines, Preferred Practice Pattern, Oct 2010), was compared to 50 healthy participants (HP). Both glaucoma suspects and HP underwent SAP and FDT in random order. Only reliable fields were compared.

Results: Mean deviation of FDT Matrix was significantly lower than SAP SITA in suspect and healthy group; two devices showed significant correlation amongst both groups (suspects $p = 0.002$, healthy $p = 0.011$). Significant difference was found in PSD of SAP SITA and FDT Matrix ($p = 0.001$) in the glaucoma suspect group, PSD of FDT Matrix was significantly higher than PSD of SAP SITA in the healthy group ($p < 0.001$). PSD of SAP SITA significantly correlated with FDT Matrix PSD in glaucoma group ($r = 0.579$; $p = 0.001$) but no significant correlation found in healthy group ($r = 0.153$; $p = 0.290$). Percentages of normal test locations significantly higher in FDT Matrix compared to SAP SITA in glaucoma suspects and healthy participants.

Conclusion: FDT correlates well with SAP and may be used for patients who are unable to perform well and reliably with SAP but does not show any features of earlier glaucoma changes in this study.

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Introduction

Glaucoma is a major irreversible cause of blindness in the world, accounting for 15% of all causes of blindness.¹ It is a progressive disease in which visual impairment occurs due to retinal ganglion cells (RGC) death.²

As per American Academy Guidelines, Preferred Practice Pattern, “a glaucoma suspect is an individual with clinical findings and/or a constellation of risk factors that indicate an increased likelihood of developing Primary Open Angle Glaucoma (POAG)”. Clinical findings that make a person suspect for primary open angle glaucoma, depend on one of the following clinical findings in, at least, one eye of the suspect, with an open angle of the anterior chamber on gonioscopy. These findings are: Appearance of the optic disc or retinal nerve fiber layer that is suspicious for glaucomatous damage, enlarged cup-disc ratio, asymmetric cup-disc ratio, notching or narrowing of the neuroretinal rim, disc hemorrhage, nerve fiber layer defect, visual field suspicious for glaucomatous damage in the absence of clinical signs of other optic neuropathies, arcuate bundle defect, nasal step, paracentral scotoma, altitudinal defect, larger mean pattern standard deviation, consistently elevated intraocular pressure (IOP) associated with normal appearance of the optic disc and retinal nerve fiber layer and with normal visual field test results. Family history is a definite risk factor for glaucoma.³

Frequency doubling perimetry (FDP) is a relatively new psychophysical test that has good potential in screening for early glaucomatous damage.⁴ It has advantages being easy to administer and interpret, liked by most patients, not greatly affected by refractive error and cataract, has high test-retest reliability, offers rapid screening tests, and has different full threshold programs. Maddess et al. reported that the frequency doubling illusion could be useful in detecting glaucomatous field loss.⁴ The frequency doubling technology (FDT) stimulus predominately stimulates the magnocellular ganglion cell pathway, which is primarily involved in motion detection and flicker detection. It is believed that the neurophysiological substrate for the frequency doubling illusion in humans lies in a subgroup of M cells, the proposed My cells, which show nonlinear characteristics to contrast and are thought to be preferentially lost in early glaucoma.⁵ Standard automated perimetry (SAP) is considered the gold standard method of measuring the visual field.

A study was done to correlate frequency doubling perimetry (FDP) results with glaucomatous visual field defects, as assessed by standard automated perimetry (SAP), in a glaucoma suspect population. In a study by Kelly DH, the analysis of the FDT examinations during follow up revealed that in 59% of converters, the FDT abnormalities preceded SAP visual loss by as much as 4 years and the initial development of glaucomatous visual field loss as measured by SAP occurred in regions that had previously demonstrated abnormalities on FDT testing.⁶ Landers et al, also conducted a study to evaluate if FDT predicted future visual field loss with SAP just as it may be predicted with short wavelength automated perimetry and found that both short wavelength automated perimetry (SWAP) and FDT detected field loss earlier than SAP.⁷ With paucity in literature about the ability of FDT to detect field loss

in glaucoma suspects, a study was conducted to correlate results of frequency doubling technology to SAP and to study if FDT could detect field loss earlier in comparison to SAP in glaucoma suspects in a subject population where such a study had never been conducted earlier.

Materials and methods

The study was conducted in the outpatient department of ophthalmology at a tertiary eye care center from July 2009 to July 2012 and Cases of Primary Open Angle Glaucoma (POAG) suspects were studied. Glaucoma suspects were those with a family history of glaucoma i.e. mother, father or sibling with glaucoma, Optic nerve heads suggestive of glaucoma i.e. vertically elongated optic cups, notching, disc hemorrhage, asymmetry of discs, intraocular pressure taken by applanation tonometry to be high on more than two occasions.

As no such study has till date been conducted in our setting, a pilot study with 55 cases (glaucoma suspects) was conducted. Additionally, 50 non cases (no family h/o glaucoma, optic nerve head normal, and IOP within normal limits on two readings) were also examined to assess validity of both the techniques. Institutional ethical clearance was obtained for the conduct of the study and written informed consent was obtained from all the participants.

The inclusion criteria for glaucoma suspects were those glaucoma suspects who were not suffering from any ocular or systemic diseases and BCVA minimum 6/9. The exclusion criteria were patients suffering from any other ocular/systemic disease which could have caused optic disc changes and/or ametropia more than ± 5 Dsph and ± 3 Dcyl.

All patients underwent a comprehensive ocular examination consisting of: Best corrected visual acuity, Slit lamp examination, IOP was measured using applanation tonometer (AT) using the Haag Streit slit lamp attachment, Gonioscopy with single mirror gonioscope, dilated fundus examination done with Slit lamp biomicroscopy with +90 D lens to evaluate the optic nerve head. Fundus camera was used to document optic nerve head. Pachymetry for central corneal thickness done with ultrasound pachymeter Pachette 2 (model DGH-550). SAP was done with Humphrey Visual Field Analyzer (Carl Zeiss Meditec, Dublin, CA), using 24-2 SITA Standard. FDT perimetry was done with the Humphrey Matrix (Carl Zeiss Meditec) using 24-2 full threshold using ZEST strategy. SAP and FDT were performed randomly on the same day with a gap of at least 15–20 min given to reduce fatigue related errors. All the subjects were made to wear appropriate refractive corrections for both the tests and the pupils had a diameter of at least 3 mm. Only the reliable (fixation losses <20%, false-positives and false-negatives <33%) visual fields were included in the study. In case of unreliable fields, the test was repeated after few days. If both eyes were eligible for the study, the eye with more reliable field was selected for analytical purposes. All visual field threshold data of the left eye were transposed for the right eye orientation. For comparative analysis, the blind spot thresholds were not used. The two locations above and below the blind spot were excluded, leaving 52 points for analysis in the SAP as well as in FDT Matrix.

Table 1 – Mean test duration (in seconds).

	Mean test duration in SAP	Mean test duration in FDT	p value*
Glaucoma suspects	334.3 ± 66.2	321.4 ± 16.9	0.133
Healthy	319.22 ± 59.70	317.26 ± 17.98	0.811
*t test.			

Visual fields were considered to be abnormal according to Hodapp-Parrish-Anderson criteria. A glaucomatous field loss on white-on-white perimetry was defined as a cluster of 3 or more points depressed at the 5% level on the pattern deviation plot with one of the points depressed at the 1% level in either hemisphere. The clinically significant visual field defect on FDP was defined as presence of 2 adjacent points at $p < 5\%$, and one of these $p < 1\%$ deviation in the pattern deviation plot in either hemisphere. p value (probability value): all abnormal global indices are presented with a probability value ($p < x\%$), indicating that less than $x\%$ of normal populations has figures as obtained in the field test or in other words there is an $x\%$ chance that this index may be normal. When the p value is lower than given any global index it has higher chances of being abnormal.

DEFECT SIZE: The size of the glaucomatous defects was determined by counting the number of abnormal points in the pattern deviation plot as per Anderson's criteria one. **DEFECT DEPTH:** The depth of the defect was assessed by averaging the threshold values of the abnormal points in the pattern deviation plot.

The results were collated, tabulated and statistically analyzed using the non-parametric Wilcoxon signed rank test and the paired t test. Spearman's correlation coefficient was used to correlate the global indices between the two devices. A posteriori power analysis revealed 80% power and thus significance of 5% was used.

Results

The study included 55 glaucoma suspects whose age ranged from 17 to 81 years with mean age of 44.50 ± 13.58 . The age range of the healthy group was between 40 and 73 years with a mean age of 49 ± 8.74 . There were 29 (53%) males and 26 (47%) females among cases and 30 (60%) were males and 20 (40%) females among healthy group. Table 1 shows mean test duration. Mean test duration was significantly shorter with FDT Matrix as compared to SAP SITA. Mean threshold values and comparisons have been depicted in Table 2. Difference in mean threshold values at each testing point between SAP SITA and FDT Matrix are shown in Figs. 1 and 2.

Table 2 – Mean threshold values (dB).

	Mean threshold in SAP	Mean threshold in FDT	p value*	Spearman's correlation coefficient (p value)
Glaucoma suspects	28.61 ± 1.91	24.11 ± 1.96	0.001	0.888 (0.001)
Healthy	29.77 ± 1.94	25.95 ± 1.98	0.001	0.865 (0.001)
*t test.

Fig. 1 – Difference in mean threshold (dB) at each testing point between SAP SITA and FDT Matrix (Mean threshold values of SAP SITA minus FDT Matrix) in the glaucoma suspect group.

Mean deviation of FDT Matrix (Table 3) was significantly lower than SAP SITA in the suspect group as well as in the healthy group but the two devices showed significant correlation amongst both groups (suspects $p = 0.002$, healthy $p = 0.011$). Table 4 shows that there was significant difference in PSD of SAP SITA and FDT Matrix ($p = 0.001$) in the glaucoma suspect group and PSD of FDT Matrix was significantly higher than PSD of SAP SITA in the healthy group ($p < 0.001$). PSD of SAP SITA significantly correlated with FDT Matrix PSD in the glaucoma group ($r = 0.579$; $p = 0.001$) but no significant correlation was found in the healthy group ($r = 0.153$; $p = 0.290$).

The percentages of normal test locations were significantly higher in FDT Matrix as compared to SAP SITA in both glaucoma suspects and healthy participants (Table 5). Table 6 shows Abnormal Test Locations and number of points depressed at level of $p < 1\%$ was significantly higher in SAP SITA as compared to FDT Matrix in the glaucoma suspect group whereas there was no significant difference at level of $p < 5\%$, $p < 2\%$ and $p < 0.5\%$. In the healthy group, number of points depressed at level of $p < 5\%$, $p < 2\%$ and $p < 1\%$ was significantly higher in SAP SITA as compared to FDT Matrix (Table 7). Mean defect size detected by SAP SITA was significantly larger than FDT Matrix in the glaucoma suspect group with strong correlation between the devices. Mean defect size detected by SAP SITA was significantly larger than FDT Matrix in the healthy group but there was no significant correlation between the two devices in this group (Table 8). Mean defect of SAP SITA was significantly higher than FDT Matrix in glaucoma suspect and healthy participants and no significant correlation was found between the devices (Table 9).

		3.3	3.12	2.48	2.78		
	4	4.22	2.82	4.1	4.38	4.18	
	2.22	3.72	4.18	3.46	2.8	4.7	5.68
1.98	2.06	3.54	2.8	3.24	2.42	3.64	5.46
1.96	3.12	3.84	3.82	3	2.4	2.58	6.14
	4.24	4.22	4.68	4.42	3.1	4.64	4.16
		5.06	5.02	5.7	4.38	4.48	4.58
		3.88	4.54	4.66	4.92		

Fig. 2 – Difference in mean threshold (dB) at each testing point between SAP SITA and FDT Matrix (Mean threshold values of SAP SITA minus FDT Matrix) in the control group.

Discussion

Determination of visual field defects is crucial for diagnosing glaucoma and assessing its progression. Numerous perimetric devices have been marketed but even now SAP remains the gold standard. Amongst the more recent devices used to assess visual field damage in glaucoma is frequency doubling perimetry. Two generations of frequency doubling perimeters

have been used, of which the latest one is the Matrix FDP. It is believed that My subset of ganglion cells have not been found in primate retina and studies by Anderson and Johnson have substantiated that FDT tests the contrast sensitivity of magnocellular cells in general and not a specific subset of My cells. FDT is sensitive to glaucomatous visual field losses because it tests a sparse population of retinal ganglion cells (RGC) which comprise approximately 10% only of the entire RGC population. In this study we compared the two perimetric devices between glaucoma suspects and normal healthy population.

Our study result of variability in FDT Matrix test duration as reflected by the standard deviation is markedly lower than SAP SITA. This difference reflects the different mode of testing used by the devices. FDT Matrix used the maximum likelihood estimation (ZEST) procedure where each point is tested 4 times in various thresholds according to the patient response. Because of the fixed number of tests at each point, the duration of the test is shortened and nearly constant with a narrow standard deviation. SAP uses multiple stimulations at each point with a gradual increase in the threshold level until the stimulus is observed. Shorter test duration has the potential of improving the reliability parameters arising due to patient fatigue, thereby providing reliable results.

Direct comparison of target thresholds between the two techniques is not possible due to variability in the dB units. The FDT uses a proprietary method to compute sensitivity; a 1 dB change in FDT is approximately equal to 0.05 log unit change in Michelson contrast. In SAP the threshold sensitivity

Table 3 – Mean deviation (dB).

	Mean deviation in SAP	Mean deviation in FDT	Wilcoxon signed ranks test	p value	Spearman's correlation coefficient (p value)
Glaucoma suspects	-2.1 ± 2.16	-3.6 ± 3.75	3.22	0.002	0.432 (0.001)
Healthy	-0.746 ± 0.980	-1.715 ± 2.618	2.544	0.011	0.171 (0.234)

Table 4 – Pattern standard deviation (dB).

	PSD in SAP	PSD in FDT	Wilcoxon signed ranks test	p value	Spearman's correlation coefficient
Glaucoma suspects	2.0 ± 0.67	3.2 ± 0.80	8.934	0.001	0.139 (0.310)
Healthy	1.914 ± 0.732	2.867 ± 0.760	5.015	0.001	0.153 (0.290)

Table 5 – Normal test locations.

	Normal test locations in SAP 2860 (%)	Normal test locations in FDT 2860 (%)	Wilcoxon signed ranks test	p value
Glaucoma suspects	2475 (86.5)	2560 (89.5)	2.422	0.015
Controls	2320 (89.23)	2436 (93.69)	3.104	0.002

Table 6 – Abnormal test locations in glaucoma suspects.

Points depressed in PDP	SAP (%)	FDT (%)	Wilcoxon signed ranks test	p value	Spearman's correlation coefficient
$p < 0.5\%$	52 (1.8)	75 (2.6)	1.511	0.131 NS	0.237 (0.082) NS
$p < 1\%$	56 (2.0)	40 (1.4)	1.907	0.057 NS	0.464 (0.001) HS
$p < 2\%$	93 (3.3)	48 (1.7)	2.917	0.004 Sig	0.057 (0.677) NS
$p < 5\%$	184 (6.4)	137 (4.8)	2.226	0.026 Sig	0.24 (0.078) NS

Table 7 – Abnormal test locations in healthy.

Points depressed in PDP	SAP (%)	FDT (%)	Wilcoxon signed ranks test	p value	Spearman's correlation coefficient
$p < 0.5\%$	27 (1.04)	38 (1.46)	1.572	0.116 NS	0.060 (0.680) NS
$p < 1\%$	43 (1.65)	11 (0.42)	2.927	0.003 Sig	0.184 (0.200) NS
$p < 2\%$	68 (2.62)	25 (0.96)	3.065	0.002 Sig	0.048 (0.738) NS
$p < 5\%$	142 (5.46)	90 (3.46)	2.737	0.006 Sig	0.173 (0.229) NS

Table 8 – Mean defect size.

	Mean defect size in SAP	Mean defect size in FDT	p value	Spearman's correlation coefficient (p value)
Glaucoma suspects	7.0 ± 4.35	5.4 ± 4.43	0.016	0.451 (0.001)
Healthy	5.60 ± 4.36	3.28 ± 2.98	0.002	0.086 (0.555)
*t test.				

Table 9 – Mean defect depth.

	Mean depth in SAP	Mean depth in FDT	p value	Spearman's correlation coefficient (p value)
Glaucoma suspects	23.90 ± 4.83	15.53 ± 7.10	0.001	0.208 (0.128)
Controls	25.08 ± 6.14	15.84 ± 12.97	0.001	0.033 (0.818)
*t test.				

is reported in terms of log ratio between the maximum stimulus and the threshold stimulus, with 1 dB equal to 0.10 log unit changes in Weber contrast.⁸ Humphrey SITA standard and FDT both use different testing strategies to detect threshold, they also measure different psychophysical attributes. Another study⁹ explains that these findings are due to the suboptimal use of the normative database by FDT Matrix or that FDT Matrix is not suitable to detect early visual field defects before their appearance in SAP SITA. Alternatively, it might be that SAP SITA showed a high number of false positive responses and Matrix results were closer to reality.

MD is an index of average severity of field loss and is affected by degree of loss and number of affected locations. Lower the MD, greater is the severity of field loss. Our study has shown significantly lower MD of FDT Matrix than SAP SITA in the suspect group as well as in the healthy group but the two devices showed significant correlation amongst both groups. PSD indicates the degree to which the numbers in the total deviation plot are not similar to one another and is an index of unequalness in the amount of field loss. A larger PSD indicates a greater loss of field. PSD was raised in FDT compared to SAP in glaucoma suspects. Significant difference was found in PSD of SAP SITA and FDT Matrix in the glaucoma suspect group and healthy group. Significant correlation of PSD of SAP SITA with FDT Matrix PSD was found in the glaucoma group but no such correlation was found in the healthy group. This could be because the selection of patients with perimetrically established glaucoma in our study could have accounted for better correlation of MD and PSD between the two instruments in the glaucoma group as the patients were perimetrically experienced and could perform the tests reliably. Therefore the visual field defects were reproducible. On the other hand, the healthy participants were not perimetrically experienced, although they could perform the tests reliably.

Artes et al compared the results of Humphrey Matrix perimetry with SAP and reported a strong correlation for MD and PSD of FDT Matrix 24-2 program and SAP SITA standard 24-2 test in glaucoma patients with early to moderate visual field loss ($r > 0.8$, $p < 0.001$). This was expected as the normative population used to create the normal database showed high retinal sensitivity to any stimulus used for testing and cases with pathology would present with abnormal threshold points and corresponding positive correlation.¹⁰

Previous studies have shown that the PSD on the FDT Full threshold N30 test and the SITA Standard have poor correlation, while the MD had good similarity with SAP.^{11,12} In contrast to this, in our study the FDT Matrix showed good correlation with SAP SITA with regard to MD and PSD in the glaucoma suspect group possibly because the test patterns in SAP and FDT were similar in our study. We found that there was no significant difference in PSD between SAP SITA and FDT Matrix, with strong correlation between the devices in the glaucoma group. Consistent with the findings reported by Patel et al our results indicate that FDT Matrix delineated smaller and deeper defects than those shown by SAP SITA.⁹ It is possible that this finding was secondary to the larger size of the FDT Matrix stimulus or because of less than optimal performance of the normative database. The majority of the subjects in this subgroup had previous experience with SITA, but not with FDT; therefore, this disproportionate experience with one of the technologies could have biased the findings.

Finally, SAP SITA could detect greater number and larger defects than FDT Matrix. FDT and SAP measure different visual functions. SAP is nonspecific, in that most RGC subtypes can respond to the stimulus whereas FDT is a visual function specific test, in that the low-spatial-frequency, high-temporal-frequency stimulus is thought to target a subset of RGCs, the magnocellular cells.⁶ The mean defect size detected by

SAP SITA was also significantly larger than FDT Matrix in the glaucoma suspects group but there was no significant correlation between the two devices when mean defect size and mean defect depth were measured.

Since a single moderately deep scotoma may show an abnormal PSD and an abnormal MD is known to be affected by degree of loss and by number of affected locations, a single one time, though reliable field, may not indicate a field defect especially because other parameters considered in the study such as defect size and defect depth which are actually measuring the defects, do not show a larger field defect in FDT. Also, the number of normal locations is larger in FDT in comparison to SAP indicating that perhaps the results of mean deviation and PSD have been affected by some single higher numbers in the fields. Therefore, considering all parameters, in this study FDT does not indicate ability to field defects earlier than SAP.

In conclusion, therefore, FDT correlates well with SAP and may be used for patients who are unable to perform well and reliably with SAP but does not show any features suggestive of earlier glaucomatous changes in this study.

Conflicts of interest

All authors have none to declare.

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