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Original Article

Ophthalmology Section

Echographic Optic Nerve Evaluation: A Novel Diagnostic Modality in Glaucoma

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ABSTRACT

Introduction: Primary Open-Angle Glaucoma (POAG) is considered a leading cause of blindness among all others. Different technologies such as Scanning Laser Polarimetry (SLP) and Optical Coherence Tomography (OCT) closely correlate in measuring structural parameters of the Retinal Nerve Fiber Layer (RNFL) and Optic Nerve Head (ONH). Visual impairment related to glaucomatous damage is attributed to the RNFL. Earlier studies have shown that retro-bulbar optic nerve thickness is reduced in glaucoma and have suggested that this is also the result of RNFL destruction.

Aim: To investigate the correlation between the orbital and intraocular portions of the optic nerve among POAG patients.

Materials and Methods: This was a hospital-based cross-sectional study done in a tertiary care ophthalmic institute from October 2019 to February 2021. One eye of 32 volunteers with newly diagnosed POAG underwent optic disc analysis using OCT and echographic measurements of the retrobulbar optic nerve. For statistical calculations, Statistical Package for Social Sciences (SPSS) Statistics version 20.0 software (IBM Corp., Armonk, NY, USA) was used. Spearman's rho (rs) was used as the index of correlation between retrobulbar optic nerve dimensions and ONH topographical data. A correlation between OCT-based RNFL and optic disc parameters was compared with retrobulbar optic nerve dimensions measured with the help of Ultrasonography- Brightness (USG B) Scan.

Results: Orbital Optic Nerve Diameter (OND) and Optic Nerve Cross-sectional Area (ONCSA) significantly and positively correlated with Neuro-retinal Rim (NR) area (OND: p-value=0.00001; ONCSA: p-value=0.00001) and average nerve fiber layer thickness (OND: p-value=0.0001; ONCSA: p-value=0.00002). The Retrobulbar ONCSA-to-disc area ratio (ONCSA/D) was found to have a statistically demonstrable positive correlation with Neuro-retinal Rim Area/Disc area ratio (NR/D) (p=0.00003).

Conclusion: This study showed that retrobulbar optic nerve dimensions correlate well with SD-OCT-based ONH parameters. Echographic measurements of the retrobulbar optic nerve add a new biomarker in the diagnosis of glaucoma.

Keywords: Primary open angle glaucoma, Optical coherence tomography, Retinal nerve fibre layer, Ultrasound

INTRODUCTION

Optic neuropathies, as an entity, constitute the second most common cause of legal blindness in the world [1]. Inflammation, ischaemia, and compression are among the different causes of optic neuropathies, with POAG remaining the leading cause. Axonal loss, combined with changes in the extracellular matrix of the lamina cribrosa, results in a characteristic form of optic neuropathy. Concerning POAG, as estimated in 2010, results in thinning of the RNFL and cupping of the ONH, ultimately leads to Visual Field (VF) defects and significant blindness in an estimated 9.4 million people worldwide [2].

The role of structure-function relationships is widely evaluated for POAG, [3-8], and in ischemic [9,10] and compressive [11] optic neuropathy. Technologies such as SLP and OCT closely correlate in measuring structural parameters of RNFL and ONH [5,7,12-14]. Comparing these methods with Standard Automated Perimetry (SAP) as the main procedure for assessing visual function has established that measurable structural changes precede measurable functional deficits in POAG [4,5]. Since axonal loss is irreversible and POAG progression can be decelerated by eye-pressure-lowering treatments, early identification of patients at risk is crucial [15], especially for future clinical trials aimed at neuro-protection.

As retinal ganglion cell axons ultimately propagate to the VF cortex via the optic nerve, retrobulbar optic nerve parameters may be considered a suitable surrogate marker for detecting optic atrophy. Histologic evidence has shown that optic atrophy does lead to a thinning of the retrobulbar optic nerve [16], suggesting that OND may correlate with the extent of optic atrophy. Visual impairment related to glaucomatous damage is attributed to the RNFL. Previous literature has indicated a scant number of studies regarding the correlation of retrobulbar optic nerve thickness with the population of the RNFL [17,18]. This correlation is extremely beneficial in cases with a doubtful appearance of ONH or due to the non-visualisation of ONH due to any media opacity. This study was conducted to investigate the relationship between orbital optic nerve dimensions and ONH topographical measurements.

MATERIALS AND METHODS

It was a cross-sectional study that included the final diagnosis of POAG in patients attending the Ophthalmology department at a Tertiary care ophthalmic institution. The hospital-based study was performed from October 2019 to February 2021. Institutional Ethics Committee (IEC) clearance was obtained prior to the recruitment of the patients (Government of India, Institutional Ethics Committee Midnapore Medical College, Reference Number: IEC/2019/05).

Inclusion criteria: Those patients who were atleast 18 years of age with clear optical media, characteristic Glaucomatous Optic disc findings, and a raised Intraocular Pressure (IOP) >21 mmHg and those patients who could perform automated perimetry under acceptable recorded reliability indices were included in the study.

Exclusion criteria: Patients with any associated retinal pathology, presence of other varieties of glaucomatous changes, significant

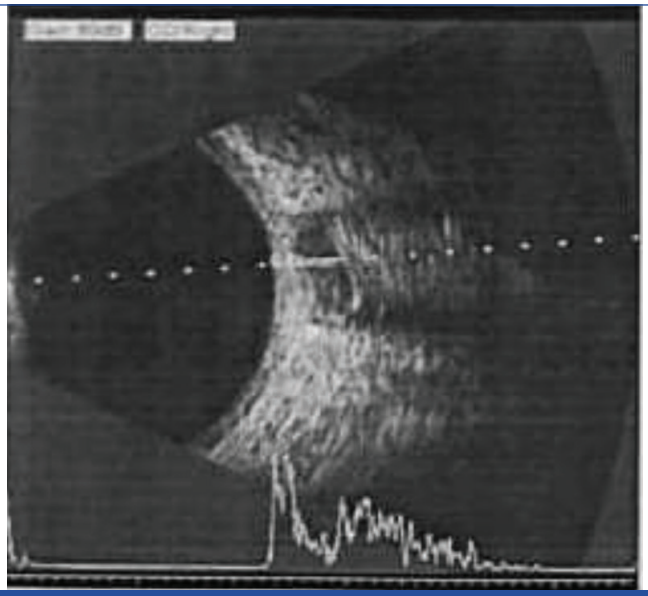
media opacity, Best Corrected Visual Acuity (BCVA) below 3/60 in Snellen's chart, and those unable to cooperate during investigations were excluded from the study.

Sample size calculation: The sample size was determined based on the prevalence of POAG patients attending the ophthalmology Outpatient Department (OPD) in the same institute during the study period. After that, patients who agreed to take part in the study were taken for calculations. A total of 32 subjects were included.

Procedure

The criteria for VF abnormalities included a corrected pattern standard deviation with $p<0.05$ or a glaucoma hemifield test outside normal limits, obtained with atleast two reliable and reproducible VF examinations using the Humphrey Field Analyser (HFA) 24-2 protocol. Patients with advanced glaucomatous changes and poor vision were diagnosed based solely on optic disc changes, raised IOP, and RNFL changes measured with Spectral Domain-OCT (SD-OCT). All the patients underwent SD-OCT-based ONH calculations, including cup area, rim area, vertical cup-disc ratio, cup volume, rim volume, and average RNFL thickness. Additionally, all the patients under observation underwent 2 mm retrobulbar optic nerve dimensions measurements with the help of the USG B-scan. The dimensions of the retrobulbar optic nerve considered were OND and ONCSA. For all measurements, five repeated readings were taken, and the mean was calculated. All the procedures were performed by a single experienced operator in a masked fashion to eliminate operator bias on the same instrument every time.

SD-OCT related calculations were accepted as the computer-generated automated reporting produced by the machine algorithm itself. In the case of USG B-scan retrobulbar optic nerve dimensions, measurements were taken in conjunction with A-scan echography. There is ambiguity about optic nerve thickness along the course of the intra-orbital region among investigators [19,20]. So, in the present study, the ultrasound probe was focused on the region of 2-4 mm of the retrobulbar region, resulting in greater resolution of orbital structures and minimising inter-subject variability. Within the depth of focus, the probe achieves a lateral resolution of <0.8 mm, and at the focal plane, it achieves lateral and axial resolutions of 0.3 mm and 0.12 mm, respectively [21]. The technique used by us was previously described in the literature. Briefly, the patients were asked to move their eyes in all four gaze positions for three minutes to induce a redistribution of subarachnoid fluid [Table/Fig-1].



[Table/Fig-1]: Ultrasonography (USG) B scan image showing retrobulbar optic nerve area with simultaneous A-scan. The hypoechoic interpial distance is calculated as Optic Nerve Diameter (OND).

The USG probe was then placed on the temporal bulbar conjunctiva with the eye in the primary position. On the echographic screen, a transverse B-scan of the intra-orbital part of the optic nerve could be noticed and confirmed by the presence of dural echoes on a simultaneous A-scan. OND was calculated as the maximal inter-pial distance in the horizontal plane. The perimeter of the nerve was then calculated with a marker, and the area within was taken as the ONCSA.

STATISTICAL ANALYSIS

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) Statistics version 20.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were expressed in terms of numbers and percentages, while quantitative variables were expressed as mean±standard deviation. Spearman's rho (rs) was used as the index of correlation between ONH topographical data and retrobulbar optic nerve dimensions. Orbital optic nerve fiber count shows considerable interpersonal variability, and hence this coefficient plays a vital role in eliminating ambiguity [21]. The average of the five ultrasound-based measurements of the OND and cross-sectional area were standardised for calculation. A p-value less than 0.05 was considered statistically significant.

RESULTS

Thirty-two patients diagnosed with POAG of different grades were enrolled in the study. The average age of the study population was 50.53±10.19 years. The gender distribution of the study population showed a slight male preponderance (n=18, 56.25%), while the laterality distribution was equal for both eyes. The BCVA on presentation ranged from 6/6 on Snellen's chart to PL positive. On the HFA 24-2 protocol, the variation of field defects ranged from paracentral scotoma to being unable to perform the test properly due to tunnel vision in advanced cases [Table/Fig-2].

Variables	n (%)
Age (years)	50.53±10.19
Gender	
Male	18 (56.25)
Female	14 (43.75%)
Laterality	
RE	16
LE	16
Range of eyesight	
6/6-6/12	19
6/18-6/60	6
<6/60	7
Types of scotoma and vision	
Paracentral scotoma	5
Arcuate scotoma	10
Biarcuate scotoma	9
Central tunnel vision	8
Applanation tonometry	25.607±3.697mmHg

[Table/Fig-2]: The socio-demographic and basic characteristics of the study population.

On SD-OCT, the calculation of optic disc area ranged from 2.07-4.26 mm^2 with a mean±Standard Deviation (SD) of 2.799±0.636 mm^2. The range for Cup-Disc (CD) Ratio was 0.56-0.97. The rest of the topographic dimensions calculated in SD-OCT are given in [Table/Fig-3].

Echographic measurements of orbital OND ranged between 1.44-3.78 mm, with a mean (±SD) of 2.468±0.621 mm. The orbital

Parameters	Mean	SD	Range
Cup-disc ratio	0.75	0.12	0.56-0.97
Disc area (mm^2)	2.799	0.636	2.079-4.263
Cup area (mm^2)	1.997	0.765	0.942-3.536
Rim area(mm^2)	0.821	0.51	0.117-1.54
Cup volume (mm^3)	0.805	0.535	0.213-1.683
Average RNFL thickness (μ)	77.086	18.366	54.234-99.184
Rim volume (mm^3)	0.185	0.151	0.028-0.534

[Table/Fig-3]: Topographic measurements of the Optic Nerve Head (ONH) as measured by the SD-OCT.

OND correlated positively and significantly with ONH dimensions calculated, namely rim area, rim volume, and average RNFL thickness, except with cup area, cup volume, and CD ratio where the correlation was negative and statistically significant ($p<0.05$) [Table/Fig-4].

	Orbital Optic Nerve Diameter (OND) 2.468±0.621mm		Orbital Optic Nerve Cross Sectional Area (ONCSA) 5.316±2.544mm^2	
	Spearman's 'rho'	p-value	Spearman's 'rho'	p-value
Disc Area	-0.045	0.37	-0.094	0.28
Cup area	-0.476	**0.01**	-0.492	**0.008**
Rim area	0.737	**0.00001**	0.736	**0.00001**
Cup disc ratio	-0.711	**0.00002**	-0.686	**0.00006**
Cup volume	-0.518	**0.005**	-0.481	**0.009**
Rim volume	0.7	**0.00003**	0.69	**0.00005**
Average RNFL thickness	0.668	**0.0001**	0.716	**0.00002**

[Table/Fig-4]: Echographic measurements of retrobulbar Optic Nerve Diameter (OND) and cross-sectional area and their correlation with Optic Nerve Head (ONH) topographical area.

Echographic measurements of orbital ONCSA ranged between 1.63-11.22 mm^2, with a mean (±SD) of 5.316±2.544 mm^2. Similar to OND, the orbital ONCSA correlated positively and significantly with all ONH dimensions calculated, namely rim area, rim volume, and average RNFL thickness, except with cup area, cup volume, and CD ratio where the correlation was significantly negative [Table/Fig-4].

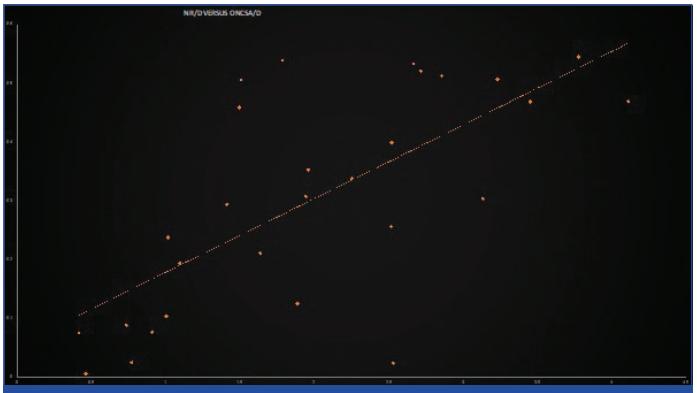
The calculation of NR/D ranged between 0.005-0.544, while the orbital ONCSA/disc area ratio (ONCSA/D) ranged from 0.415 to 4.109. The NR/D significantly correlated with average RNFL thickness (rs=0.69414, p=0.00004). The ONCSA/D was negatively correlated with disc area (rs=-0.34397, p=0.07) and significantly correlated with average RNFL thickness (rs=0.668, p=0.0001) [Table/Fig-5]. Finally, correlating NR/D with ONCSA/D resulted in a significant positive result (rs=0.704, p=0.00003) [Table/Fig-6].

Parameters	NR/D Range 0.005-0.544		ONCSA/D Range 0.415 to 4.109	
	Correlation	p-value	Correlation	p-value
Disc Area	-0.165	0.402	-0.344	0.07
Average RNFL Thickness	0.694	**0.00004**	0.668	**0.0001**
ONCSA/D	0.704	**0.00003**	-	-

[Table/Fig-5]: Correlation of combinations of echographic and OCT based dimensional ratios with disc area and average RNFL thickness and also their mutual correlation and statistical significance.

DISCUSSION

In this study, the authors included 32 perimetry-proven glaucomatous patients with insignificant gender and laterality distribution to compare the SD-OCT-measured ONH measurements with the USG B-scan-measured retrobulbar optic nerve dimensions. The authors showed that OND and ONCSA positively correlate statistically



[Table/Fig-6]: Simple regression scattergram of the orbital Optic Nerve Cross-sectional Area/disc area ratio (ONCSA/D) versus Neuroretinal rim area/disc area ratio (NR/D).

significantly with rim area, rim volume, and average RNFL thickness while negatively correlating with cup area, cup volume, and cup-disc ratio with statistical significance.

In the current settings, the diagnosis of POAG solely depends on the results of ONH evaluation, tonometry, and VF testing [22]. Although it is a well-proven fact that raised IOP neither concludes a patient as glaucomatous nor does a normal IOP discards the chance of a patient being a case of normotensive glaucoma [22], nowadays IOP has lost its importance as a hallmark for diagnosing POAG.

In the case of ONH evaluation, OCT RNFL has brought a revolutionary change in order to objectify the subjective glaucomatous disc changes and is a brilliant tool to pick-up pre-perimetric glaucomatous disc changes. However, in the presence of dense media opacities, such as dense cataracts, central leucomatous corneal opacity, vitreous haemorrhage, etc., and in cases of ONH anatomical variations like tilted disc, myelinated nerve fiber, etc., it becomes very difficult to observe glaucomatous ONH changes. VF testing is a crucial component in diagnosing glaucomatous changes and is also a good tool to measure disease progression and Visual Field Index (VFI). However, it is seen that in cases of advanced glaucomatous changes with decreased visual acuity and in cases of physical and mental limitations, patients are usually unable to perform VF testing satisfactorily, hampering the reliability indices [2-8].

In this scenario, it is of utmost necessity to innovate a surrogate diagnostic protocol that can replace the current diagnostic criteria in challenging situations. Loss of retinal nerve fibers has been demonstrated in glaucoma [23,24], and the disturbances in RNFL correlate well with the extent of pathological optic disc cupping [25-28]. Since the RNFL contains retinal ganglion cells and is part of the optic nerve, a reduction in the size of the retrobulbar optic nerve might be expected in glaucoma. This study, along with previous studies [16,17], has confirmed this fact. However, the relationship between optic nerve dimensions and the SD-OCT-measured ONH dimensions is the unique criteria in this article.

The present study results are in sync with the study by Beatty S et al., [17]. In their study, they also showed a significant correlation between OND and ONCSA with rim volume positively and with CDR negatively [17]. But on the contrary, they showed no statistical correlation with other disc parameters mentioned in this study. The present findings are consistent with the study by Dichtl A and Jonas JB, who also demonstrated decreasing optic nerve thickness with decreasing NR [18]. However, they used an older version of USG B-scan without A-scan tracing and morphometric disc dimension calculation for their study.

A study by Queiroz WS et al., showed, in thirty eyes of 15 glaucomatous patients with any CD ratio, a strong correlation between CD ratio results obtained by fundus Biomicroscopy (BIO) and the measurements of Cup-OND (C/OND) (ultrasound) (r=0.788,

p<0.0001), and with C/D obtained by OCT (r=0.8529, p<0.0001) [29]. However, the comparison of CD ratio results obtained with OCT to those obtained with C/OND (Ultrasound) showed only a moderate correlation (r=0.6727, p<0.0001). Bland-Altman analysis did not show good agreement between CD ratio (BIO) and C/OND (ultrasound). They concluded that B-mode ultrasound examination with a 20 MHz probe can be a good additional method for the evaluation of the CD ratio in glaucomatous patients and may be considered as an alternative gross tool in glaucomatous patients with optic media opacities.

According to the literature, although optic nerve fiber count shows a significant and positive correlation with the orbital ONCSA, the role of measurements of the retrobulbar optic nerve in glaucoma assessment may be limited because of the considerable inter-individual variability in its dimensions [19]. Furthermore, several investigators have shown that larger, non-glaucomatous discs have larger CD ratios [30,31], and that glaucomatous optic neuropathy is more difficult to detect in small discs [32,33]. In order to adjust for the inter-individual variability in the pattern and behaviour of different optic discs, the authors incorporated the orbital optic nerve cross-sectional area into a ratio with its corresponding ONH area and named this the ONCSA/D ratio. If the retrobulbar optic nerve does reflect the NR area, it will have a demonstrable significant and positive correlation with the NR/D and a significantly negative correlation with the CD ratio. Also, ONCSA/D and NR/D should be considered even more sensitive indicators for axonal loss, as each ratio is an indicator for present optic nerve fiber count as a fraction of the baseline count for that individual eye.

Limitation(s)

The small sample size, making it challenging to draw generalised opinion regarding the effect of glaucomatous optic neuropathy on retrobulbar optic nerve dimensions. On the other hand, this study could only establish the fact of decreased optic nerve dimensions in the setting of different stages of progression of glaucomatous optic nerve fiber loss. However, this study fails to offer any objective cut-off or algorithm to calculate the amount of glaucomatous optic nerve damage by measuring retrobulbar optic nerve dimensions.

CONCLUSION(S)

This study concluded that with accurate choice of optic nerve dimensions in the retrobulbar region, they correlate significantly with NR, Cup-Disc Ratio, and average retinal nerve fiber layer thickness. A statistically significant correlation has been established between NR/D and orbital ONCSA/D. This indicates that USG B-scan-measured retrobulbar optic nerve dimensions correlate well with SD-OCT-based ONH parameters. Hence, echographic retrobulbar optic nerve thickness measurement can be a useful tool for detecting glaucoma suspects when traditional parameters of tonometry, optic disc morphometry, and VF assessment fail to detect glaucomatous changes. The authors hope this article will prove to be a cornerstone in the future development of a specific algorithm for the diagnosis of POAG based on echographic measurements of retrobulbar optic nerve dimensions.

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