EFFECT OF SUCCESSFUL GLAUCOMA SURGERY ON RETINAL NERVE FIBER LAYER THICKNESS AND OPTIC NERVE HEAD PARAMETERS ASSESSED BY FUNDUS PHOTOGRAPHY, HEIDELBERG RETINAL TOMOGRAPHY AND OPTICAL COHERENCE TOMOGRAPHY

DISSERTATION SUBMITTED AS PART OF FULFILMENT FOR THE MS BRANCH III (OPHTHALMOLOGY) EXAMINATION DEGREE EXAMINATION OF THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY, TO BE HELD IN APRIL 2014

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled "Effect of successful glaucoma surgery on retinal nerve fiber layer thickness and optic nerve head parameters assessed by Fundus Photography, Heidelberg Retinal Tomography and Optical Coherence Tomography" done towards fulfillment of the requirements of the Tamil Nadu Dr. MGR Medical University, Chennai, for the MS Branch III (Ophthalmology) examination to be conducted in April 2014, is a bona fide work of Dr. David J. Mathew, postgraduate student in the Department of Ophthalmology, Christian Medical College, Vellore.

Dr.Thomas Kuriakose; DO, DNB

Professor, Head of the Department

Department of Ophthalmology,

Christian Medical College,

Vellore- 632001

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Dr.Lekha Mary Abraham; DO, DNB

Professor,

Department of Ophthalmology,

Christian Medical College,

Vellore- 632001

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Introduction The term 'glaucoma' alludes to a large number of diseases. The common features are progressive optic neuropathy and visual field loss. Various risk factors contribute to these two standard features. Retinal ganglion cells are the cells that are damaged in glaucoma.(1) The field loss caused by the disease process is considered to be irreversible and can lead to blindness if appropriate treatment is not instituted. Clinical evaluation of the optic nerve head and the retinal nerve fiber layer, combined with visual field testing is the gold standard for diagnosing glaucoma. (2) Progressive damage to the optic nerve head causing increased cup-to-disc ratio is referred to as worsening...

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Introduction

The term ‘glaucoma’ alludes to a large number of diseases. The common features are progressive optic neuropathy and visual field loss. Various risk factors contribute to these two standard features. Retinal ganglion cells are the cells that are damaged in glaucoma.(1) The field loss caused by the disease process is considered to be irreversible and can lead to blindness if appropriate treatment is not instituted. Clinical evaluation of the optic nerve head and the retinal nerve fiber layer, combined with visual field testing is the gold standard for diagnosing glaucoma. (2)

Progressive damage to the optic nerve head causing increased cup-to-disc ratio is referred to as worsening of “cupping”. Likewise, “reversal of cupping” alludes to restoration of the optic nerve head appearance. In children, there is a known reversal of glaucomatous cupping following reduction in intra-ocular pressure which is believed to be due to a decrease in the stretching of the scleral rim of the optic nerve head. In adults, however, the sclera loses its ability to stretch and the optic disc size remains relatively constant. In spite of these factors, reversal of cupping has been noted in adult patients following intraocular pressure reduction by the way of medical management or surgery. The mechanism of this reversal of cupping in adults is yet unexplained.

Does this reversal of cupping translate to improvement in visual fields? There is no conclusive well established answer, but there may be an improvement in visual fields in patients who demonstrate reversal of cupping.(3) Are these changes in the optic nerve head transient or permanent? Existing literature shows conflicting results. Topouzis et al (4) demonstrated reversal of cupping till 4 months after surgery and that the changes were not maintained at 8 months after surgery. On the other hand, Kotecha et al (5) demonstrated reversal of cupping only at 2 years after surgery. The question of whether reversal of cupping is seen more frequently after surgical

or medical management has no established answers. However, reduction of intraocular pressure is thought to be the main contributing factor to reversal of cupping.

Studies have been done in the past which have demonstrated reversal of cupping in adults following reduction of intraocular pressure (5–7) as well as no significant improvement in the optic disc parameters after IOP reduction. (8) However, there is no similar published study done on Indian eyes till date.

This prospective observational study aims to explore the change in ONH parameters and RNFL thickness by adequate reduction in IOP after successful glaucoma surgeries on Indian eyes. The baseline evaluation includes visual acuity, intraocular pressure, optic disc photograph, HRT and Stratus OCT for all adult patients posted for trabeculectomy and combined trabeculectomy and cataract surgery. The aforementioned tests will be repeated at 1, 3 and 6 months in those who have undergone successful trabeculectomy to determine if a significant reduction in IOP results in any change in measureable parameters of the ONH and RNFL. Given the increasing cost of anti glaucoma medications, and increasing life expectancy among our patients, this may help us to modify our line of management towards early surgical intervention.

Aims and Objectives

AIM:

To study the effect of successful glaucoma surgery on retinal nerve fiber layer (RNFL) thickness and optic nerve head (ONH) parameters using clinical examination, Heidelberg Retinal Tomography II (HRT) and Stratus Optical Coherence Tomography (OCT).

OBJECTIVES:

- To document optic disc parameters using clinical examination, HRT and OCT pre-operatively and post-operatively in all patients undergoing glaucoma surgery
- To determine the change in RNFL thickness following successful trabeculectomy using OCT and HRT and correlate this change in thickness with the change in IOP
- To determine the change in the cup:disc ratio and other neuro-retinal rim parameters following successful trabeculectomy using clinical examination, HRT and OCT and correlate this with the change in IOP
- To assess the correlation between HRT and OCT for similar parameters

Literature Review

Glaucoma is a chronic optic neuropathy characterized by progressive deleterious changes of the Optic Nerve Head (ONH) and Retinal Nerve Fiber Layer (RNFL) for which intraocular pressure (IOP) is a modifiable risk factor. The typical structural damage in the optic disc, noted in glaucoma, is usually with corresponding functional changes in the visual field. It should be noted that high intraocular pressure (IOP) is a risk factor for glaucoma which is established to be causal. It is the only risk factor that can be treated. However, it is neither sufficient nor absolutely necessary for the diagnosis of glaucoma.(9–11)

Glaucoma is usually asymptomatic until the late stages of the disease, when the prognosis is poor. End-stage glaucoma can be diagnosed easily, even with a direct ophthalmoscope. It is however best to detect the disease at an early stage where the diagnosis is easily possible. Even at this stage, appropriate intervention can change the course of the disease and alter the prognosis. Diagnosis in the pre perimetric stage is ideal. However, such a diagnosis is not as critical as compared to the diagnosis of an established disease. "Labeling" and life-long treatment and their implication to the patient go hand in hand with a diagnosis of glaucoma.(12,13)

Glaucoma is a disease characterized by insult to the retinal ganglion cells causing progressive damage to the optic nerve head and retinal nerve fiber layer.(14) Damage to the retinal ganglion cells is believed to be irreversible as it is caused by apoptosis.(15,16) This structural damage has been shown to precede functional (visual field) loss.(17,18) The evaluation of glaucomatous damage is largely clinical by measuring the changes in the neuro-retinal rim, optic disc cupping and identifying retinal nerve fiber layer loss on

indirect ophthalmoscopy using a slit lamp and high power condensing lens for appropriate magnification. However, these are subjective (19,20) and newer imaging modalities give a quantitative measurement of these same parameters.

Epidemiology

According to the World Health Organization (2010), glaucoma was responsible for 8% of global blindness and 2% of visual impairment.(21) Disability adjusted life years (DALY) due to glaucoma increase more than two fold between the years 1990 and 2010 with the increase in life expectancy.(22) Glaucoma is the third leading cause of blindness.(23) Estimates as per 2010 indicate that about 60.5 million people were suffering from glaucoma and about 8.4 million were blind as a consequence of glaucoma.(24) Primary open angle glaucoma patients numbering approximately 44.7 million cases worldwide are thought to be more common than primary angle closure glaucoma patients who number about 15.7 million. However, primary angle closure glaucoma is more likely to cause blindness among affected persons(24), thereby accounting for about half of total glaucomatous vision loss. The projections for 2020 reveal that nearly 80 million people will have glaucoma.(24) Over a time period of 12 to 20 years, the risk of going blind due to POAG is about 14.5% to 27% and 7% to 9% for unilateral and bilateral involvement respectively.(25,26)

Detection of the established glaucoma is the first step in the recommended strategy for prevention of blindness.(9,12) The patient in a developing country like India does not present with a diagnosis of glaucoma for further evaluation. Despite the presenting

complaints, if the treating Ophthalmologist is serious about prevention of blindness, all potentially serious ocular disease, including glaucoma, should be ruled out in all patients. A diagnosis of glaucoma is best confirmed by a specialist using his/her experience as well as other tools.

Normal appearance of the disc

The optic nerve head shows a high inter-individual variability within the normal population.(27) A study done by Jonas et al (28) used 107 freshly enucleated human donor eyes. The retina and choroid were mechanically removed and a millimeter scale placed against the inner scleral canal (or optic nerve head) showed a minimal disk diameter of 1.67 ± 0.72 mm and a maximal diameter of 1.92 ± 0.32 mm. The optic disc is vertically ovoid in shape usually with the lesser diameter horizontally and the larger diameter vertically. The disc area in the study ranged from 0.68 mm^2 to 4.42 mm^2, the mean disc area being 2.59 ± 0.72 mm^2.

In normal eyes, the areas of the optic disc and optic cup are correlated with each other: the larger the optic disc, the larger the optic cup. In normal eyes, the shape of the optic cup is horizontally oval; the horizontal diameter is about 8% longer than the vertical diameter. In normal eyes, the optic cup depth depends on the cup area and, indirectly, on the disc size: the larger the optic cup, the deeper it is. Because of the vertically oval optic disc and the horizontally oval optic cup, the CDR in normal eyes is significantly larger horizontally than vertically.

Optic cup measurements also show variability in the normal population with differences between different populations. The mean vertical cup diameter in the Vellore eye study was 1.06 ± 0.23 mm(29,30), 0.75 ± 0.29 mm in American eyes (31) and 1.53 mm (standard error 0.0004) from the Beaver Dam Eye Study.(32) Optic cup area ranges between 0.53 mm^2 and 1.40 mm^2.(33,34) Post-fixation shrinkage occurs in histologically fixed specimen (35,36) and in vivo studies in turn should be adjusted for ocular and camera magnification.(37) Thus, no absolute measurement for optic nerve head parameters is available. Until a way of assessment which accounts for these shortcomings is developed, ONH parameters measurement are at best an estimate and hence must be used with caution.(38)

Nevertheless, cup-disc ratios are not altered by either ocular or camera magnification, since magnification equally alters disc and cup parameters. Just like the disc and cup parameters vary greatly between normal individuals, the cup-disc ratio also varies likewise. Mean vertical cup-disk diameter ratios vary from 0.3 to 0.56(29–32,39,40)and mean cup-to-disk area ratios vary from 0.14 to 0.37.(29,30,40,41)

Another parameter to describe the optic nerve head is the ratio of the horizontal-to-vertical cup-to-disc diameter ratio. The horizontal cup-disc diameter ratio is usually higher than the vertical cup-to-disc diameter ratio in normal eyes (as per the shape of the neuroretinal rim according to the ISNT-rule in most patients(42). The resultant value of the horizontal-to-vertical cup-to-disc ratios is usually more than 1.0. If the neuroretinal rim shape changes, the quotient of the horizontal-to-vertical cup-to-disc ratios decreases to values lower than 1.0 as the vertical cup-to-disc ratio increases more when compared

to the horizontal cup-to-disc ratio. An advantage of using horizontal-to-vertical cup-to-disc ratio is that it is not dependent on the size of the optic cup and disc. Moreover, it is independent of the magnification due to the optical media.(38)

Assessment of the disc

A magnified and stereoscopic examination of the optic disc is possible using a 60, 78 or 90 diopter (D) lens. A contact lens along with the slit lamp can also be used for examining these structures.(43) Examination of the retina needs an indirect ophthalmoscope. The indirect ophthalmoscopy using a 20D lens is not adequate to comment on the optic disc. Though direct ophthalmoscope can identify advanced glaucomatous discs it is not ideal for the diagnosis and follow up of glaucoma.

There are many structural changes in the optic disc due to glaucoma .(27) Most commonly encountered is an increase in the cup to disc ratio (CDR). A CDR of 0.7:1 with a vertically oval cup is more suspicious of glaucoma. . However, it should be kept in mind that the CDR if used in isolation can be a source of error. The reason for this is as follows: about 1.2 million axons of the retinal ganglion cells (RGC) leave the eye through the optic nerve head, forming the “neuro-retinal” rim (NRR) of the optic disc. The cup can be imagined as the space that is left over after these axons have filled the optic nerve head. The size of the optic disc varies in the population and the “cupping” varies with the size of the disc. Hence, a small disc may not have any cupping and a large disc is can have a very large cup, even beyond the 0.7:1 cut-off. Thus, the CDR should be taken into consideration only in the light of the disc size. The size of the disc can be measured on

the slit lamp using a 60 D lens. The magnification factors for the lenses are as follows: 1 for 60 D, 1.13 for 78 D and 1.3 or 1.41 for 90 D (44,45). The height of the slit beam is adjusted vertically till it just encompasses the margins of the optic disc.

The average vertical diameter of the optic disc in Indian eyes is approximately 2.0 mm.(27) It is not as important to get an actual measurement as it is to get a general understanding whether a disc is of small, medium or large size. However, this comes with experience and is possible only after seeing, examining and measuring a large number of optic discs. While examining any disc, the examiner should assess if the disc in question is "allowed" to have the existing cup. A vertical CDR of 0.3, usually considered to be normal, may not be physiological if the disc is small. On the other hand, a large cup may be physiological in large discs.

If the CDR differs by more than 0.2 between the eyes (after ruling out or accounting for a difference in size of the two discs), glaucomatous damage should be suspected. A loss of the disc rim or in other words, increase in CDR over time is typical of glaucoma. However, it should be kept in mind that CDR is just a surrogate measure for the entity that we really want to examine, which is the neuroretinal rim (NRR), the part occupied by the axons. Changes in the NRR thus derived suggest pathology.

Another parameter that can be taken into consideration is the rim to disc ratio in different areas of the disc. Rim to disc ratio in the superior, superotemporal, nasal, inferotemporal and inferior areas of the disc are usually considered. A rim to disc ratio of less than 0.1:1

should be indicate glaucomatous change until otherwise proved. Rim to disc ratio also allows better monitoring of the progression of glaucoma.(46,47)

Disc Photography

In addition to clinical evaluation of the optic disc, optic disc photography is commonly used in clinical practice. The advantages of stereophotography include permanent recording of the status of the optic disc. These pictures can be used for serial evaluation of discs, good visualization of the peripapillary region and a relatively faster examination of the optic disc without pupillary dilatation (if non-mydriatic fundus cameras are used). The limitations include the need for clear media, good pupil dilatation (if non-mydriatic camera is not available), a trained photographer and the delay involved. Retinal nerve fiber layer (RNFL) photography is based on the fact that green light is absorbed by melanin in the retinal nerve fiber layer. However, in comparison to scanning laser equipments, this device is not as convenient and needs dilated pupils (not required with the newer non-mydriatic camera devices) and high competence levels of the technical personnel. Moreover, the examination with RNFL photographs needs considerable learning and experience. The advantage of RNFL photography is that it picks up glaucomatous damage before visual field defects emerge.(48)

Heidelberg Retina Tomography (HRT)

The Heidelberg Retina Tomograph is based on the principle of confocal laser scanning system designed for procuring and analyzing three-dimensional images of the posterior

segment of the eye. It also enables quantitative assessment of the topography of ocular structures as well as the precise follow-up of changes in the topography.

In a laser scanning system, the light source used is a laser. The laser beam is focused on a point of the object to be examined. The reflected light traces its path back and is subsequently separated from the incident beam. This separated reflected beam is deflected to a detector. This point imaging is extended to a two-dimensional level by using scanning mirrors. A small diaphragm is placed in front of the detector at a place that is optically conjugated to illuminating system's focal plane (general principle of a confocal system). This confocal pinhole effectively allows only light that is reflected from the object at the focal plane. Thus, most of the light reflected from layers of the three-dimensional object below or above the focal plane is screened out. This mechanism effectively suppresses out-of-focus light. This is how an optical section of a three-dimensional object is obtained. In order to extend this mechanism to three-dimensional levels, the focal plane can be moved. By this technique, we can acquire images at different depths. The series of optical section images obtained can be used to construct a layer-by-layer three-dimensional image of the examined three-dimensional object.

A series of images thus obtained by using HRT consists of 16 images per 1mm depth. This is subject to a maximum of 64 images when imaging a depth of 4mm. The field of view is 15° by 15°. The time taken for acquisition of two-dimensional optical section images is about 32 milliseconds. The repetition rate is 20 Hz. The images are subsequently digitized in frames of 256 x 256 picture elements (pixels). The light source used by HRT is a diode laser with a wavelength of 670 nm. Pupil dilation is not necessary

to acquire the images. Even a pupillary diameter of 1 mm is sufficient to acquire high quality images. Topography images are then computed from the acquired images, consisting of 256 x 256 individual height measurements which are scaled for the individual eye. They also have a reproducibility of the height measurements of approximately 10 to 20 microns.

The Heidelberg Retina Tomograph software defines a reference plane for each individual eye. The reference plane is located 50 microns below the retinal surface at the area of the papillo-macular bundle and parallel to the peripapillary retinal surface. This definition derives its reason from the fact that the nerve fibers at the papillo-macular bundle remain intact longest during the development of neuronal damage due to glaucoma. The nerve fiber layer thickness at this location is approximately 50 microns. All structures located below this reference plane are considered to be the "cup". All structures located above the reference plane but within the contour line are considered to be "rim".

The HRT is used to measure the patient's disc topography regionally and globally. Variable disc sector analyses can also be obtained using HRT. The six standard HRT regions are defined as temporal/superior, nasal/superior, nasal, nasal/inferior, temporal/inferior, and temporal.

The HRT II is designed to image the optic nerve head only and is specifically used for evaluation and monitoring glaucoma patients. This instrument has the advantage of smaller size as well as simplified user requirements when compared to HRT. In addition, a new diagnostic parameter, the Moorefield's Regression Analysis (MRA), has been

added in HRT II. It is used to classify eyes as either glaucomatous or healthy. It uses linear regression between the disc area and the logarithm of rim area. This value is compared to that in healthy eyes and values in each of the six standard regions. A red X denotes “outside normal limits” (outside 99.9% prediction interval), a yellow exclamation mark denotes “borderline” (between 95% and 99.9% prediction interval) and a green check denotes “within normal limits” (within 95% prediction interval).

A sensitivity of 84.3% and specificity of 96.3% exists for distinguishing normal eyes from eyes with early changes of glaucoma, if considering the relation between the disc size and the cup disc area ratio or the rim area(49). The same author has demonstrated that HRT analysis of the optic nerve head was more sensitive than stereoscopic disc photographs for detection of early glaucoma (84.3% vs 70.6%)(50). The reproducibility and repeatability of HRT is known to be very good.(51–54)

Studies comparing OCT with confocal scanning laser ophthalmoscopy and scanning laser polarimetry have shown good correlation in distinguishing between non-glaucomatous and glaucomatous eyes. Zangwill et al.(55) found no significant difference between OCT, GDx and HRT in differentiating normal eyes from glaucomatous eyes. The best parameters for each instrument were considered in this study: inferior RNFL thickness for OCT, mean height contour in the inferior nasal position in HRT and linear discriminant function in GDx. A study done by Garcia-Sanchez et al.(56) revealed that for OCT, sensitivity and specificity for picking up early to moderate glaucoma ranged from 76 to 79% and 68 to 81%, respectively.

A disadvantage of HRT II is that the normative data used in MRA consists of subjects with European ancestry only with a limited range of disc area. (57) Another disadvantage is that a trained operator is needed to identify and delineate the border of the optic disc. This introduces subjectivity to the analysis of topographic measurements. These disadvantages were addressed in the newer version of the HRT software (HRT III) which includes an expanded normative database including 215 healthy African–American eyes and 733 healthy Caucasian eyes. A further database of approximately 100 Indian (South Asian) eyes is now available and collection of Hispanic and Asian databases is currently in progress. (58)The HRT III also includes an automated, operator-independent classifying procedure of the optic disc, the glaucoma probability score (GPS) classification.(57) Also, there is a scaling error in the HRT II software, in which horizontal measurements are enlarged by 4% which has been corrected in the HRT III.(58)

Optic disc topography depends on factors like cardiac pulsation(59) and intraocular pressure. Variations in optic disc topography can be brought about by post-operative(3,6) or diurnal(60) changes in IOP and can make diagnosis of glaucoma progression difficult. Also, confocal scanning techniques fail to pick up vessel shift, pallor of disc and disc hemorrhage, which could be indicators of glaucoma progression. The other factors that can impede good image acquisition include corneal edema, anterior uveitis, posterior subcapsular cataract, peripapillary atrophy, vitreous opacities, high axial myopia and posterior staphylomas(61).

Optical Coherence Tomography

The Optical Coherence Tomography (OCT) imaging is analogous to B-scan ultrasonography, except that OCT measures light rather than acoustic waves from the tissue boundaries. The STRATUS OCT 3 has an axial resolution of 10 microns. This high resolution enables the original concept of OCT technology of a non-contact, non-invasive, non-excisional 'optical biopsy', without the need to remove and process specimens, as in conventional excisional biopsy or histopathology.

The OCT is based on an optical technique known as Michelson low coherence interferometry, which measures the echo delay and intensity of back reflected or back scattered infrared light (approximately 800 nm) from internal tissue microstructure, to achieve cross-sectional tomographic images of optical reflectivity.

The OCT includes a software package that facilitates image acquisition, storage, retrieval and quantitative analysis. Being the anterior most layer of the retina, the RNFL is one of the layers with the greatest reflectance. This property is attributed to the structure of the fibers, which are perpendicular to the direction of the light beam. This allows it to be automatically segmented and measured accurately by computer algorithms. Average RNFL thickness is displayed for each quadrant (superior, temporal, nasal, and inferior), for each clock hour, and for the entire cylindrical section (mean average). The normative database is obtained by evaluating the RNFL thickness measurements in an ethnically wide variety of 328 subjects.

Another feature of the Stratus OCT is the ability to obtain quantitative measurements of optic disc topography by a series of radial line scans across the disc. The instrument objectively finds the margin of the disc, using a signal from the end of the retinal pigment epithelium. Disc parameters that are measured include cup volume, cup and rim area, and CDR.

Clinical changes in glaucoma

The relationship between the cup disc ratio and the disc size has already been discussed above.

Neuroretinal rim: The neuroretinal rim width is the distance between the border of the optic disc limited by the scleral ring and the position of vessel bending. The NRR exhibits a characteristic configuration in normal eyes based on a vertical oval shape of the disc and the horizontally oval shape of the cup. The rim shape follows the 'ISNT rule' (Inferior rim > Superior rim > Nasal rim> Temporal rim). When the ISNT rule is not obeyed, glaucoma must be suspected. In a study done on normal and glaucomatous eyes using disc photographs and confocal scanning laser ophthalmoscopy, the ISNT rule was intact in 52 (79%) of 66 normal eyes and 12 (28%) of 43 glaucomatous eyes. (62) However other results have shown that the inferior sector of the optic disc may not show thickest rim in 37.8% of normal eyes. (45) Hence, the rule must not be used in isolation, but with other disc findings. In glaucoma, NRR is lost in all sectors of the optic disc with regional preferences, depending on the stage of the disease. In eyes with initial glaucomatous damage, rim loss is found predominantly at the infero-temporal and

supero-temporal disc regions followed by temporal rim; the nasal rim being the last to be affected. (I→S→T→N).(63) Focal atrophy begins as a 'polar notch' which gradually extends till it reaches the disc margin to produce a 'sharpened rim'. There may be concentric atrophy in which the loss of NRR begins temporally and progresses circumferentially ('temporal unfolding') with the retention of the round appearance of the cup. This is often difficult to differentiate from a large physiological cup.(63)

The color of the rim is equally important. Pallor of the rim increases the likelihood of a non glaucomatous optic neuropathy, especially when pallor is out of proportion to the size of the cup. One analysis of optic disc morphology concluded that pallor of the NRR was 94% specific for non glaucomatous atrophy, whereas focal or diffuse obliteration of the NRR with preservation of color of any remaining rim tissue was 87% specific for glaucoma.(45) One major exception to this rule is the eye with angle closure glaucoma, following a large and rapid rise in IOP. The disc often appears pale without dramatic cupping.(64)

Cup:disc ratio (CDR): In glaucoma, the optic cup depth depends on the type of glaucoma and the level of IOP. The deepest optic cups can be found in glaucomatous eyes with high values of IOP, such as juvenile-onset open angle glaucoma and secondary open angle glaucoma caused by traumatic recession of the anterior chamber angle.

The horizontal CDR is smaller than the vertical one in less than 7% of normal eyes. This is important for the diagnosis of glaucoma, in which, in early to medium advanced stages, the vertical CDR ratio increases faster than the horizontal one, leading to an increase of the quotient of horizontal to vertical CDR to values lower than 1.0. The high inter-

individual variability of the optic disc and cup diameters explain why the CDR ranges from 0.0 to almost 0.9 in a normal population making it inconclusive in the diagnosis of glaucoma.(27)

Retinal nerve fiber layer: Qualitative examination of RNFL is performed with slit lamp biomicroscopy using a high power magnification lens and red-free green light. In normal eyes, bright striations are visible and the retina glistens in the regions where the RNFL is thickest: supero-temporal and infero-temporal from the disc. The vessels are buried within the nerve fiber layer and look blurred. RNFL loss can occur in a diffuse, localized or mixed pattern. With diffuse loss, there is general reduction of the RNFL brightness. The comparison of superior and inferior fibers helps to identify qualitative differences in the amount of visible RNFL. When the RNFL is lost, vessel borders become clearer. Localized RNFL loss occurs in about 20% or more of all glaucomatous eyes.(27) It appears as wedge-shaped dark areas emanating from the optic disc. These defects follow an arcuate pattern. Inexperienced examiners tend to overestimate localized defects and underestimate diffuse loss.(63) Localized RNFL loss should not be confused with grooves that frequently can be seen within a healthy nerve fiber layer. These slit like defects are narrower than the vessels and do not reach the disc margin.(27)

Disc hemorrhages: Splinter hemorrhages usually occur near the margin of the ONH. Although they typically cross the disc margin, the papillary portion disappears first, leaving the appearance of an extra-papillary hemorrhage. They precede or occur with notching of the NRR or RNFL defects. They are transient and usually visible for 1–6 months and are indicative of progression.(27) While more common in normal tension

glaucoma, they can be present in all types and indicate that the disease is not stable and needs further evaluation and treatment.(27)

Other signs: These include saucerization, laminar dot sign, baring of circumlinear vessels, bayoneting of vessels, bean-pot cupping and overpass sign. Also an asymmetry of the cup–disc ratio greater than 0.2 between eyes should be viewed with suspicion. This comparison is only valid, however, when optic discs have similar size and shape.

Changes in disc photographs

Evaluation of disc photographs, usually stereophotographs, can be a useful tool to document as well as assess progression of the disease. Zeyen et al(65) looked at the reproducibility of optic disc changes in patients with glaucoma using stereophotographs. The intraobserver reproducibility (95% confidence interval) in the evaluation of change ranged between 0.79 (CI: 0.45-1.14) and 1.00 (CI: 0.69-1.31). The interobserver reproducibility (95% confidence interval) for evaluation of change ranged between 0.45 (CI: 0.15-0.75) and 0.75 (CI: 0.44-1.06). The assignment reproducibility (first consensus versus second consensus for evaluation of change) between the senior readers came to 0.94 (CI: 0.63-1.25). When another experienced ophthalmologist replaced one of the readers, the assignment reproducibility was 0.94 (CI: 0.63-1.25).

HRT: changes in glaucoma

HRT assesses numerous parameters during a single optic nerve head examination. Of these parameters, many have been studied as indicators for glaucoma. The diagnostic ability of HRT is summarized in Table 1.

Table 1: Diagnostic ability of HRT

Study	Parameter(s)	Sensitivity	Specificity	Area under ROC curve	Comments
Pueyo et al(66)	MRA FSM RB	85% 73% 66%	95.5% 95.5% 95.5%	0.902 0.899 0.877	Gold standard: Only disc and field changes
Leon-Ortega et al(57)	HRT II MRA HRT II VCDR	62% 44.9%	92% 95%	- 0.843	VF MD = 3.3 – 3.6 dB
Uchida et al(67)	Global area ratio Cup shape measure All measurements	77% 83% 81%	93% 86% 81%	0.89 0.93 0.90	Early Glaucoma VFMD = -4.8dB Not accurately randomized: difference in the optic disc size
Wollstein et al (49)	Linear regression between disc area and log of NRR area Regression between disc area and cup:disc area ratio	84.3% 74.5%	96.3% 97.5%	- -	Early Glaucoma VFMD= -3.6 dB
Wollstein et al (50)	Linear regression techniques	84.3%	95.8%	-	Early Glaucoma VFMD = -3.6dB
Zangwill et al (55)	Mean-height contour Linear Discriminant function Temp–Inf Rim disc ratio	- - -	- - -	0.86 0.85 0.84	Only IOP and fields were used as gold standard
Mederios et al(68)	Linear discriminant function	-	-	0.86	
Greaney et al (69)	Rim area	84%	90%	0.92	
Thomas et al (70)	MRA (POAG) MRA (PACG) FSM (POAG) FSM (PACG) Cup-shape measure(POAG) CSM (PACG)	83.3% 75.9% 74.3% 58.3% 62.9% 33.3%			All participants were early POAG or PACG

OCT changes in glaucoma

It has been demonstrated that among different OCT parameters, peripapillary RNFL and ONH measurements possess greater discriminating ability in detecting glaucomatous damage when compared to macular thickness and volume parameters. However, it has been suggested that study of the macular region may provide a quantitative measure for monitoring progression of glaucoma. (71) RNFL thickness measured using OCT has been shown to grade the severity of glaucoma and also accurately identify normal from glaucomatous eyes, even in the early stages.(72) The sensitivity and specificity of RNFL measurements using OCT for perimetric glaucoma is very high. The RNFL is thinner in patients with preperimetric glaucoma and ocular hypertensive glaucoma suspects with a central corneal thickness of less than 555 μ. (73)

Amongst the studies done on Indian eyes, Sony et al. (74) found that the difference between inferior and superior quadrants was not statistically significant. Parikh et al (75) and Ramakrishnan et al (76), have shown that RNFL thickness is more in the superior than inferior quadrants. These studies suggest that the ISNT rule does not apply to RNFL in Indian eyes. However, studies by Subbiah et al (77) and Gyatsho et al (78) showed otherwise.

In a study done at our hospital, it was found that the mean RNFL thickness in the inferior quadrant (131.50 μm) was thicker than that in the superior quadrant (126.87 μm). (79)

RNFL thickness v/s age: RNFL thickness reduces with increasing age especially in the superior and inferior quadrants. In a study done on Thai eyes by Manassakorn et al (80), average RNFL loss was found to be 2.3 μm per decade, which is similar to the value

reported by Budenz et al. (81)(2 μ per decade)and Sung et al. (82) (2.55μ per decade). However, Parikh et al (75), in their study on Indian eyes showed a decay of 1.6μ/decade which is less than that in other published studies. Age related thinning was significant in superior and temporal quadrants. The insignificant slope of RNFL loss in the inferior quadrant probably suggests that axons of the inferior RNFL are more resistant to age-related changes. This implicates that any amount of RNFL thinning in the inferior quadrant indicates pathology. Sony et al (74), found a significant negative correlation between age and average RNFL thickness. Ramakrishnan et al (76), found no such correlation.

RNFL thickness v/s axial length: Studies have shown that longer and more myopic eyes had thinner RNFL.(81) For every 1mm increase in axial length, mean RNFL measured was thinner by 2.2 microns.(81) In a study by Leung et al (83), the RNFL measurements were significantly lower in the high myopia group (less than -6.0D) compared with those of the low-to-moderate myopia group (-0.5 to -6.0D). A significant proportion (16.5%) of myopic eyes was classified as outside normal limits, with reference to the normative database. Therefore, the values provided by OCT as normal may not be reliable in the analysis of RNFL in myopic eyes. However, Sony et al (74), showed no significant correlation between refractive error and axial length and any of the measured RNFL parameters in Indian eyes.

RNFL v /s optic disc area: Budenz et al (81) showed that for every increase in mm^2 of optic disc area, mean RNFL thickness increased by approximately 3.3μ. However, other studies (84) showed no correlation.

Several studies were done to determine whether the RNFL thickness was significantly different among healthy, ocular hypertensive (OHT) and glaucomatous eyes, and these are summarized in Table 2. Analysis of RNFL thickness in glaucomatous, OHT, and normal eyes separately revealed a characteristic double-hump pattern with RNFL thickness peaks in the superior and inferior quadrants which were depressed in glaucomatous eyes.(84) Average RNFL was significantly thinner in OHT eyes than in normal eyes especially in the inferior and nasal quadrants (by about 15%).(84)

Table 2: RNFL thickness in healthy, ocular hypertensive (OHT) and glaucomatous eyes (SD in brackets)

Study	Normal (N)	OHT	p (N vs OHT)	Glaucomatous (G)	p (N vs G)
Bowd et al (84)	85.8	72.8	<0.001	44.4	< 0.001
Leung et al (85)	106.83 (10.73)	-	-	76.36 (21.14)	< 0.001
Leung et al (86)	106.44 (11.15)	-	-	79.21 (17.06)	< 0.001
Subbiah et al (77)	94.26 (12.36)	82.87 (17.21)	0.008	52.95 (31.10)	< 0.001
Mistlberger et al (87)	90.86 (14.17)	83.69 (16.57)	0.15	56.89 (21.52)	< 0.0001
Bagga et al(88)	140.0 (13.9)	-	-	90.6 (31.0)	< 0.0001
Hong et al (89)	104.83 (14.35)	-	-	83.71 (11.76)	< 0.001
Kim et al (90)	101.7 (10.9)	-	-	93.6 (13.4)	0.002
Kanamori et al (14)	120.8 (12.90)	116.1 (8.9)	<0.01	84.5 (21.2)	(early glaucoma =98.7) < 0.001
Medeiros et al (2)	96.5 (9.9)	-	-	74.2 (13.3)	< 0.001
Gyatsho et al (78)	101.52 (10.13)	93.01 (11.95)	<0.001	60.43 (16.68)	0.022

Cup reversal

Progressive damage to the optic nerve head causing increased cup-to-disc ratio is referred to as worsening of “cupping”. Likewise, “reversal of cupping” alludes to restoration of the optic nerve head appearance.

Glaucomatous damage to the optic nerve head leads to loss of gangion cells and tissue loss at the neuroretinal rim which subsequently results in a larger cup. Since the disc size remains relatively constant, the cup-to-disc ratio also increases. Reversal of cupping, i.e. decrease in the cup disc ratio after control of intraocular pressure by medication or surgery has been reported. This is commonly seen in congenital glaucoma.(91,92)However, it has also been noted before in adult glaucoma patients. (93)

This reversal of cupping can be due to just edema leading to a falsely low cup disc ratio. On the other hand, it can also be due to regeneration of viable neurons. An interesting hypothesis in this context is that before irreversible death occurs in a ganglion cell, there is an intermediate stage of reversible dysfunction secondary to intraocular pressure elevation and other unknown factors. If, however, IOP is a major cause of dysfunction, lowering it should result in recovery of RGC function.(94)

On the other hand, reduction of the intraocular pressure need not result in structural or functional changes. Jindal et al (95) demonstrated in their pilot study that though positive correlations were made out between IOP reduction and changes in HVF, Accumap and HRT measures, these were not statistically significant. Another study by Sehi et al (96) explored the pattern ERG (PERG) changes in eyes treated with Latanoprost to attain a

20% drop in intraocular pressure. There was no improvement in RGC function as measured by PERG.

Reversal of cupping in congenital glaucoma

The optic nerve changes seen in primary congenital glaucoma are different from those seen in adults with glaucoma. Optic nerve head cupping may occur rapidly and quite early in infants.(97–101) In addition, optic nerve head cupping may be reversible with reduction or normalization of intraocular pressure.(91,92) However, this is uncommon in adults with glaucoma induced optic nerve head damage. (97)

Several hypotheses have been propounded to elucidate the pathogenesis optic nerve head cupping in infants. Firstly, it has been suggested that loss of astroglial cells may be induced by elevated intraocular pressure.(99) Secondly, extracellular fluid shifts within the optic nerve head may cause changes in the cup at different levels of intraocular pressure.(102) Thirdly, the lamina cribrosa can be posteriorly displaced and the scleral canal may be enlarged. This may lead to changes in the cup size with fluctuation of IOP during infancy. (97,103) The last explanation seems most reasonable nowadays, based on the fact that the connective tissue of the lamina cribrosa is not mature during early neonatal life.(97) Reversibility of cupping in congenital glaucoma is thought to be due to incomplete development of connective tissue in the lamina cribrosa. This allows posterior movement of the optic disc tissue in consequence to elevated intraocular pressure, with an elastic return to normal when the IOP is lowered.(97) A recent study by Mochizuki et al (104) also supports this view. When reversal of cupping is apparent clinically after successful IOP-lowering surgical intervention for congenital glaucoma, the scleral canal is found to shrink in area. On the other hand, when reversal of cupping is not seen, the scleral ring continues to enlarge in size,

indicating ongoing stress on the optic nerve. Clinically obvious reversal of cupping is less frequently observed in case of adults after surgery. This may be due to lower elasticity of the scleral ring in adults in comparison to children. Recently, cerebrospinal fluid pressure has also been proposed to have a role in reversal of cupping.(105)

In some cases, the disc does not show any reversal or shows only partial reversal after normalization of IOP. In such cases, either a portion of the stretching induced due to high IOP is permanent with remolding of the connective tissue, or there has been a permanent loss of glia and axons.(97) Reversal of cupping following a reduction in IOP in congenital glaucoma is a common occurrence. (106,107) However, it does not occur in all cases of treated congenital glaucoma. (108)

Recently, Spectral Domain OCT (SD-OCT) has been used to quantify reversal of cupping after surgical reduction of IOP. (109) Swinnen et al (110) reported two cases of reversal of cupping following trabeculectomy with mitomycin-C in young adult patients diagnosed with secondary glaucoma. The decreased CDR remained unchanged for 6 and 36 months respectively for the two cases. An improvement of the visual field as well as the optic disc parameters on HRT was also noted.

Reversal of cupping in adults

Till two decades ago, reversal of cupping in adults after instituting treatment for glaucoma was underestimated, with a dearth of studies on the subject.(111) Over the last two decades, this deficiency in literature is slowly being filled. Studies have been done using HRT for assessment of optic disc changes(3,4,6,7,93,112–114) and OCT for assessment of peripapillary retinal nerve fibre layer changes(115,116) following IOP lowering. A few studies have also been done using Rodenstock Optic Nerve Head Analyzer. (117,118)

A study by Irak et al(6) utilized HRT to explore the relationship between intraocular pressure and optic disc topography prior to and after trabeculectomy. 49 eyes were studied, with the preoperative images obtained approximately 2 months prior to surgery and postoperative test done at 3 months or later. The results revealed an association between the decrease in IOP and decrease in cup area and volume, cup disc area ratio. There was also an association between the decrease in IOP and increase in rim area and volume, mean height contour, height in contour and retinal cross-section area. Both these associations were significant ($p<0.01$). The disc topography changes were more strongly linked with the percent decrease in IOP than the mean change in IOP.

Chang et al(116) used OCT to assess change in RNFL thickness with decrease in IOP. In this study 21 eyes were taken into consideration and IOP reduction was by the way of medical or surgical intervention. OCT was done before and after initiation of treatment or surgery. An IOP reduction of more than 30% was achieved in 20 out of 21 eyes. However, the quadrant analysis on OCT RNFL did not show a significant change in any quadrant.

In a study conducted by Aydin et al(115), OCT was used to assess RNFL thickness change after glaucoma filtration surgery. In this study 38 eyes of 31 glaucoma patients were considered. The surgical intervention was either a trabeculectomy or a trabeculectomy combined with cataract surgery. OCT testing was done 1 week to 6 months prior to surgery and 6 to 12 months after surgery. In this study, visual fields were also considered in addition to RNFL thickness and intraocular pressure. The results revealed an increase in the mean RNFL thickness and thickness in all four quadrants after

surgery, which was statistically significant. However, there was no correlation between the change in NFL thickness and visual field indices.

Topouzis et al(4) in their study on 25 eyes of 25 patients evaluated changes in disc topography after trabeculectomy using HRT. In this study, imaging was done preoperatively as well as 2 weeks, 4 months and 8 months after the surgical intervention. 2 weeks postoperatively, there was a decrease in the cup volume as well as the mean cup depth along with increase in height variation contour and increased negativity of cup shape parameter. 4 months postoperatively, only the cup shape measure showed a statistically different change. 8 months postoperatively, there was no statistically significant variation in the disc parameters with respect to the preoperative baseline.

Kotecha et al(93) used HRT to evaluate optic disc changes after trabeculectomy. Imaging was done preoperatively and at 3 months, 1 year and 2 years. Out of the 95 patients enrolled, analysis of 70 patients was done. An increase was noted in the rim area and rim volume postoperatively. However, statistical significance was noted only 2 years after surgery. The rim volume change on segmental analysis revealed most change in the superotemporal, superonasal, inferonasal and nasal areas at 2 years postoperatively. The analysis also revealed that the reduction in IOP was the single most important factor in causing reversal of cupping.

A Japanese study by Yoshikawa et al(7) evaluated the change in disc parameters using HRT and their association with reduction in IOP following trabeculectomy in 22 patients . The analysis revealed that all parameters except the cup volume showed change which

was statistically significant. Increase in rim volume was the most marked of all the changes noticed and it was more obvious in the cases that had an IOP of less than 15 mm Hg after surgery.

Lesk et al(3) used HRT to measure the optic nerve head changes in 21 patients after glaucoma surgery. Visual field assessment by automated perimetry was also carried out. Those having reduction in IOP of more than 40% had improvement and those with less than 25% IOP reduction had worsening of the optic disc parameters. High correlation was observed between the percent IOP reduction and changes in the disc parameters. Improvement of the cup disc ratio correlated well with the visual field improvement.

An Italian study by Figus et al(112) which was done recently to study the optic nerve topography and field changes after surgical reduction of IOP. 56 eyes of 56 patients were enrolled who underwent trabeculectomy. HRT was done prior to surgery and at 3 and 6 months post-operatively. The association between decrease in IOP and optic nerve topography and visual field changes was determined using linear regression. The increase in mean RNFL thickness after trabeculectomy as seen in this study was statistically significant.

Table 3: Studies which used HRT for evaluation of optic nerve head topography

Title /author	Sample size	Population	Study type	Intervention	Result
Irak et al(6)	49	US	Prospective	Trabeculectomy	Improvement in disc topography parameters, associated with percentage decrease in IOP
Topouzis et al(4)	25	US	Prospective	Trabeculectomy	Improvement of HRT disc parameters at 2 weeks and 4 months but not maintained at 8 months post-operatively
Kotecha et al(93)	250	UK	Prospective	Trabeculectomy	Reversal of cupping seen only at 2 years postoperatively
Yoshikawa et al(7)	22	Japan	Prospective	Trabeculectomy	Reversal of cupping present, rim volume change being the most marked of all parameters
Lesk et al(3)	21	US	Prospective	Trabeculectomy	Reversal of cupping related to reduction in IOP and age of the patient. Visual field changes correlated well with the reversal of cupping.
Figus et al(112)	56	Italy	Prospective	Trabeculectomy	Significant increase in mean RNFL thickness
Park et al(113)	13	South Korea	Prospective	Trabeculectomy	Reversal of cupping seen, related to decrease in IOP
Raitta et al(114)	10	Finland	Prospective	Filtering surgery	Decrease in cupping related to drop in IOP

Table 4: Studies using OCT to study ONH or RNFL change after glaucoma surgery

Author	Investigation	Sample size	Population	Parameters	Intervention	Result
Chang et al(116)	Stratus OCT	21	US	Peripapillary RNFL thickness	Medical and surgical treatment	No significant change in RNFL thickness(post op measurement 32-74 days only)
Aydin et al(115)	OCT	38	US	Peripapillary RNFL thickness	Trab + combined	Significant increase in mean NFL thickness
Raghu et al(119)	Stratus OCT	17	India	RNFL thickness and ONH	Trabeculectomy only	RNFL thickness increase at 1 week, reverted to baseline by 3 months

In this study, three imaging modalities were used, which are Heidelberg Retinal Tomography (HRT), Optical Coherence Tomography (OCT) and Fundus Photography.

Materials and Methods

Study design

Prospective cohort study (on South Indian eyes/hospital based study)

Sample Size Calculation

This was an observational study and hence sample size calculation was not critical. Taking the mean pre-operative and 6 months post-operative vertical CDR, the sample size was calculated. With an Alpha error of 5% and power of 90%, and pre-operative mean of 0.80 ± 0.16 and post-operative mean of 0.70 ± 0.21, a sample size of 42 was calculated.

Patient selection

All patients admitted to the Department of Ophthalmology, Christian Medical College, Vellore for glaucoma surgery from February 2012 to April 2013 were recruited for the study provided that they fulfilled the inclusion and exclusion criteria listed below and consented to participate in the study.

Inclusion Criteria:

1. All patients with glaucoma (as diagnosed by optic disc and visual field changes) above 40 years of age who are due to undergo either trabeculectomy or a combined (glaucoma and cataract) procedure as decided by their managing glaucoma consultant.
2. Patient fulfils the criteria for a successful trabeculectomy, i.e. a drop in IOP of 30% or more at 6 months.

3. Subject willing to comply with postoperative follow-up requirements.
4. Subject willing to give informed consent.

Exclusion criteria

1. Patients who have media opacities which precludes preoperative fundus assessment and imaging.
2. Eyes with pre-existing retinopathy due to causes other than glaucoma (diabetic/ hypertensive retinopathy)
3. Eyes which develop post-operative retinopathy (cystoid macular edema)
4. Patients with less than 30% drop in IOP at 6 months when compared to the pre-operative IOP.
5. Patients with IOP less than 6mm of Hg at 3 and 6 months post-operatively.
6. Patients with known neuro-ophthalmological diseases
7. Patients with congenital disc anomalies (tilted disc, optic disc pit, etc)
8. OCT signal strength less than 6 or with any scan message

Surgical intervention

Patients underwent one of the following procedures:

1. Phacoemulsification, intraocular lens implantation and trabeculectomy
2. Manual small incision catatact surgery, intraocular lens implantation and trabeculectomy
3. Trabeculectomy only

4. Extracapsular lens extraction with or without intraocular lens implantation and trabeculectomy

The Blumenthal technique was used for manual small incision cataract surgery. 0.04% mitomycin C was applied subconjunctivally for 90 seconds after a conjuctival peritomy and cauterization of episcleral vessels. All patients received 2-5 injections of 5 Fluorouracil post operatively.

Informed consent was obtained from all the participants using a consent form that was approved by the Institutional review board and in compliance with the 1964 Declaration of Helsinki. Follow up was done at 1, 3 and 6 months after surgery in the glaucoma clinic, which runs on once a week basis in the department. Those patients who missed their appointments were contacted by phone and examined within a week. The examination done at each visit included:

a. **Best corrected visual acuity (BCVA):** BCVA was determined by doing an objective retinoscopy and subjective refraction using a Snellen chart at 6 meters.
b. **Slit lamp biomicroscopy:** All patients underwent a complete ophthalmic examination using a slit lamp biomicroscope which included a detailed evaluation of the filtering bleb.
c. **Intra-ocular pressure was** determined using Goldmann applanation tonometry attached to either a Zeiss / Haag streit slit lamp.
d. **Clinical evaluation of the ONH:** A detailed evaluation of the ONH was performed by one of the consultants specialised in glaucoma using a 78D lens and a Haag Streit slit lamp BM 900.

e. **Vertical disc diameter:** Disc size was estimated using a 78D lens and the adjustable beam height on the slit lamp. The slit beam was placed co-axial with the observation axis and a narrow beam was adjusted to the vertical diameter of the optic disc (till it touched the inner margin of the white Elschnig's ring). The length of the beam was read on the scale of the slit lamp. This value was modified by a magnification factor depending on lens power. Since a 78D lens was used, the value read off the slit lamp was multiplied by 1.1 to determine the actual vertical disc diameter.

    a. Vertical and horizontal cup : disc ratio was determined by stereoscopic assessment of the disc and careful examination of the vasculature at the disc. For assessing the cup : disc ratio, the disc and the cup need to be made out. The disc outline was taken as the inner margin of the scleral ring. The cup margin was based on the contour. It is more difficult to assess the cup if it is less deep or poorly defined as opposed to a deep cup with steep sides. The cup margin is most clearly demarcated nasally where the central retinal vessels are positioned against it. The inferior and superior margins are the next most prominent, usually with a well defined neural edge with the blood vessels turning over the edge of the cup to advance on to the retina. The circumlinear artery also courses round the superior and inferior rim edges. The temporal edge is the most difficult to define as it constitutes a sloping surface. The cup : disc ratio was interpreted in context with the disc size.
    b. Central Corneal Thickness (CCT) was estimated by ultrasound pachymetry (Tomey Bio&Pachymeter AL-1000) pre-operatively.

Baseline Heidelberg Retina Tomograph and Optical Coherence Tomography measurements were done pre-operatively for all patients. If there was a significant cataract leading to poor image quality on imaging, the baseline tests were done on the first post-operative day. Lens opacities can affect the RNFL thickness measurements, with increase in RNFL thickness noted after reducing media opacity by uncomplicated cataract surgery. This apparent increase in RNFL thickness was due to clearer media and was seen to correspond with increase in signal strength and not because of edema. (121–125) Hence, to obtain a good baseline, only cases with OCT signal strength of 6 and above were considered for the study. Scans done on the first post-operative day with good signal strength would serve as a better baseline than scans taken pre-operatively with poor signal strength due to the presence of dense cataract. However, if the pre-operative scans had good signal strength (if the cataract does not decrease the image quality), they were taken as the baseline and post-operative scanning was not done. All cases with macular edema noted on OCT fast macula scanning were excluded from the study.

f. **Heidelberg Retina Tomograph (HRT) measurements –** HRT II Software version 1.5.0 (Heidelberg Engineering, Dossenheim, Germany) was used to perform confocal laser scanning tomography. The HRT optic disc scan was obtained by the principal investigator and an Optometrist. The optic disc margin was marked at the scleral rim by the principal investigator. The HRT software calculated the subsequent measurements based on this marking. The measurements are global as well as regional. Regional measurements are grouped under temporal, temporal/superior, temporal/inferior, nasal, nasal/superior and nasal/inferior.

Topographic HRT parameters included were disc area, cup area, rim area, cup:disc area ratio, rim disc area ratio, cup volume, rim volume, mean cup depth, maximum cup depth, height variation contour, cup-shape measure, mean RNFL thickness and cross sectional area, horizontal cup/disc ratio, vertical cup/disc ratio, maximum contour elevation, maximum contour depression, CLM, average variability, reference height, FSM linear discriminant function and R Bathija linear discriminant function.

All the parameters were considered for analysis and those showing significant change were further analyzed for correlation with other parameters.

g. **Optical Coherence Tomography (OCT) measurements –** Stratus OCT 3, version 4.0.7 was used in this study. The OCT images were taken ensuring good centration and signal strength (signal strength of 6 or more was required). The computer software then calculated the variables.

   i. **Optic nerve head analysis:** Fast optic disc scanning protocol was used to estimate disc area, cup area, rim area, cup volume, cup:disc area ratio, vertical cup:disc ratio, horizontal cup:disc ratio, vertical integrated rim area (VIRA) and horizontal integrated rim width.

   ii. **RNFL thickness:** Fast RNFL thickness algorithm along a 3.4 mm diameter circular ring around the optic disc was used. The software provided the average RNFL thickness, the RNFL thickness quadrant-wise and clock hour- wise.

   iii. **Macular thickness (average retinal thickness in microns):** Fast macula thickness map of three concentric circles was used, which divides the map into 3 zones; less than 1 mm – fovea, 1-3 mm- inner macula, 3-6 mm – outer

macula. This test was done to rule out macular edema after surgery which can also lead to increased retinal nerve fiber layer thickness.

h. **Fundus Photography:** Fundus photographs were obtained Topcon TRC 50X Fundus photography machine using IMAGEnet R-3.04 (3.0.4.0) software. 35° photographs thus obtained were centered on the optic disc preoperatively as well as at 1, 3 and 6 months after surgery. These serve as a photographic documentation of the progression of the disc over time and as such were not used for quantitative analysis.

Statistical methods

a. Paired t test will be used to compare the difference in measurements of the RNFL and ONH before and after surgery at varying time points. These will be done for all parameters measured using clinical examination, HRT and OCT in glaucomatous eyes with successful trabeculectomy as defined in our protocol.
b. Correlation between IOP and HRT/OCT parameters may be evaluated using Pearson's correlation coefficient (r)
c. Correlation between HRT and OCT may be evaluated by Pearson's correlation coefficient.

Results and Analysis

92 eyes of 92 patients were enrolled for the study. Of these 15 cases were excluded due to poor signal strength on OCT during the follow up visits. 3 patients developed cystoid macular edema, 4 patients were noted to have optic disc pallor during the course of the study and 2 patients had moderate non-proliferative diabetic retinopathy. These patients were also not included in the analysis. Another 10 patients did not come for adequate follow up and 15 patients did not meet the criteria for a successful trabeculectomy. Therefore 43 eyes of 43 patients were considered for final analysis.

Gender distribution among the selected cases is as outlined in Table 4.

Table 4: Gender Distribution of patients who were included in the study

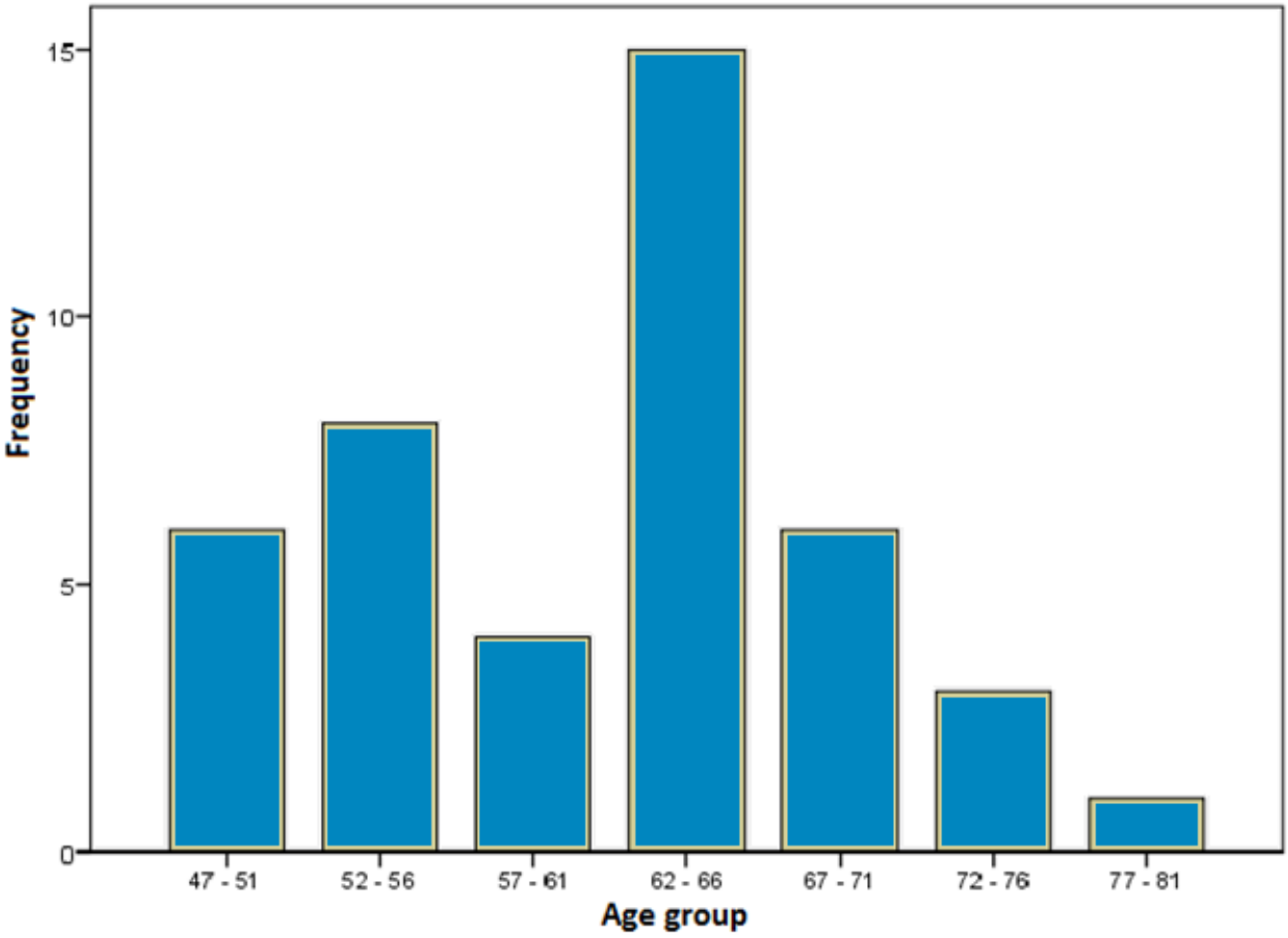
Gender		**Frequency**	**Percentage**
	Male	20	46.5
	Female	23	53.5
	Total	43	100.0

The age distribution of the patients enrolled for the study is given in Table 5 and is depicted in Graph 1.

Table 5: Age group distribution

Age group		Frequency	Percentage
	47 - 51	6	14.0
	52 - 56	8	18.6
	57 - 61	4	9.3
	62 - 66	15	34.9
	67 - 71	6	14.0
	72 - 76	3	7.0
	77 - 81	1	2.3
	Total	43	100.0

Graph 1: Age group distribution of patients



The patients' ages ranged from 47 to 78 years. For analysis, patients were categorized into seven groups with the age range of each group being 5 years. The maximum number of patients in the given categories is in the 62 to 66 years age group (n=15).

The 43 patients included in the study had varied diagnoses which is given in Table 6.The maximum number of patients were in the POAG group (44.2%) followed by NTG (27.9%).

Table 6: Diagnosis distribution

		Frequency	Percentage
	POAG	19	44.2
	NTG	12	27.9
	CACG	3	7.0
	Mixed mechanism	1	2.3
	PEX glaucoma	6	14.0
	Secondary glaucoma	2	4.7

Type of Surgery

The most commonly performed surgery was two site phacoemulsification cataract surgery with IOL implantation and trabeculectomy (83.7%) followed by single site manual small incision cataract surgery with IOL implantation and trabeculectomy (11.6%). Only 1 patient underwent trabeculectomy without cataract surgery.

The distribution is listed in Table 7a.

Table 7a: Distribution of patients according to type of surgery done

Type of surgery		Frequency	Percentage
	Phaco triple*	36	83.7
	MSICS triple**	5	11.6
	Trabeculectomy	1	2.3
	ECLX*** triple	1	2.3
	Total	43	100.0

* Phacoemulsification cataract surgery with intraocular lens implantation and trabeculectomy

** Manual small incision cataract surgery (Blumenthal technique) with intraocular lens implantation and trabeculectomy

*** Standard extracapsular lens extraction with intraocular lens implantation and trabeculectomy

Distribution of patients based on adjuvant usage

Either Mitomycin C (0.04%) or Ologen was used in all cases. In 74.4% of patients, Mitomycin C (MMC) was used as an adjuvant during the filtration surgery and in 25.6% of patients, Ologen was used. This is listed in Table 7b.

Table 7b: Distribution of patients based on adjuvant used			
		Frequency	Percentage
	MMC	32	74.4
	Ologen	11	25.6
	Total	43	100.0

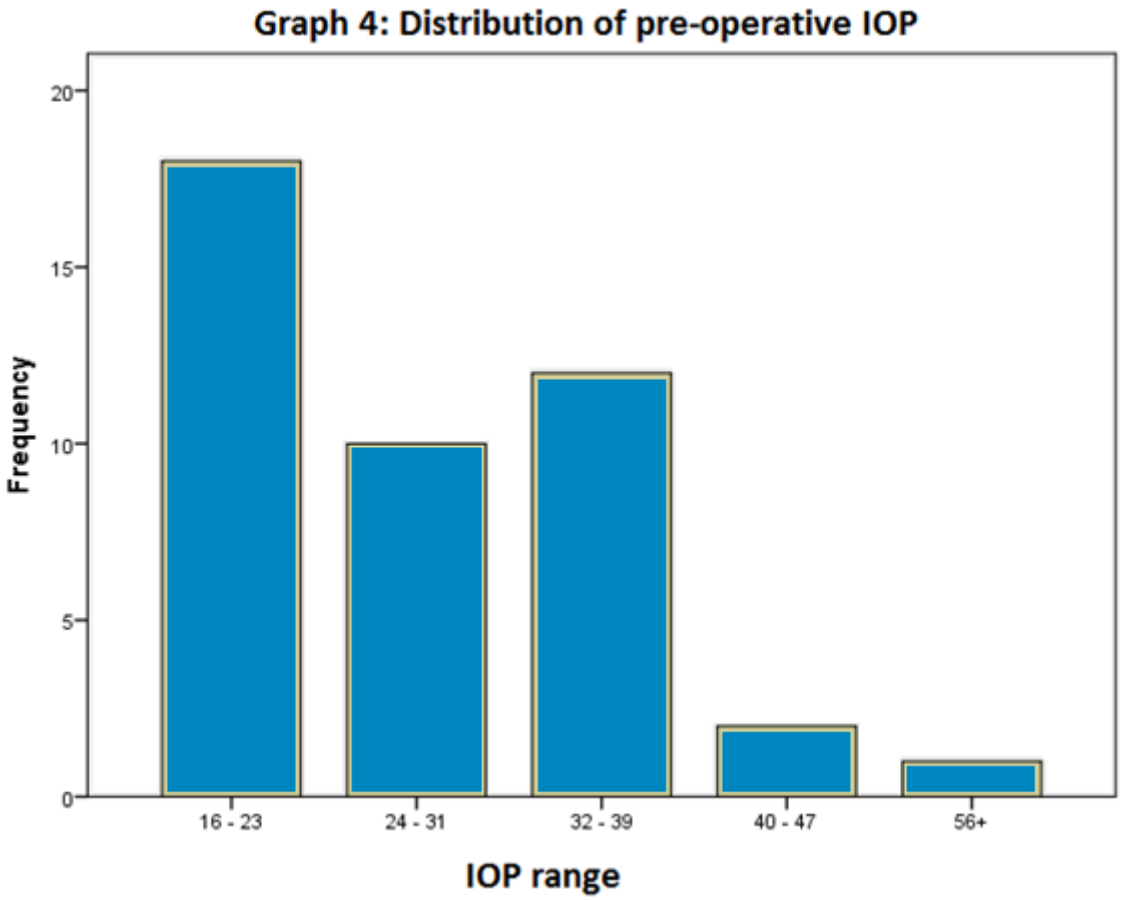
I. Intraoocular pressure (IOP)

1. Preoperative IOP

The mean pre-operative IOP was 27.37mm Hg (n=43, SD=8.19), the minimum and maximum IOP being 16 and 56mm Hg respectively. All baseline IOPs considered were the highest IOPs off treatment. The IOP distribution is listed in Table 8 and Graph 4.

Table 8: Distribution of pre-operative IOP			
IOP range		Frequency	Percentage
	16 – 23	18	41.9
	24 – 31	10	23.3
	32 – 39	12	27.9
	40 – 47	2	4.7
	56+	1	2.3
	Total	43	100.0

41.9% of patients had IOP between 16 to 23 mm Hg. Only 3 patients had IOPs of more than 40mm Hg.



Post op IOP

During the follow up visits, a significant drop in IOP was noted. The mean IOP at the follow up visits are given in Table 9.

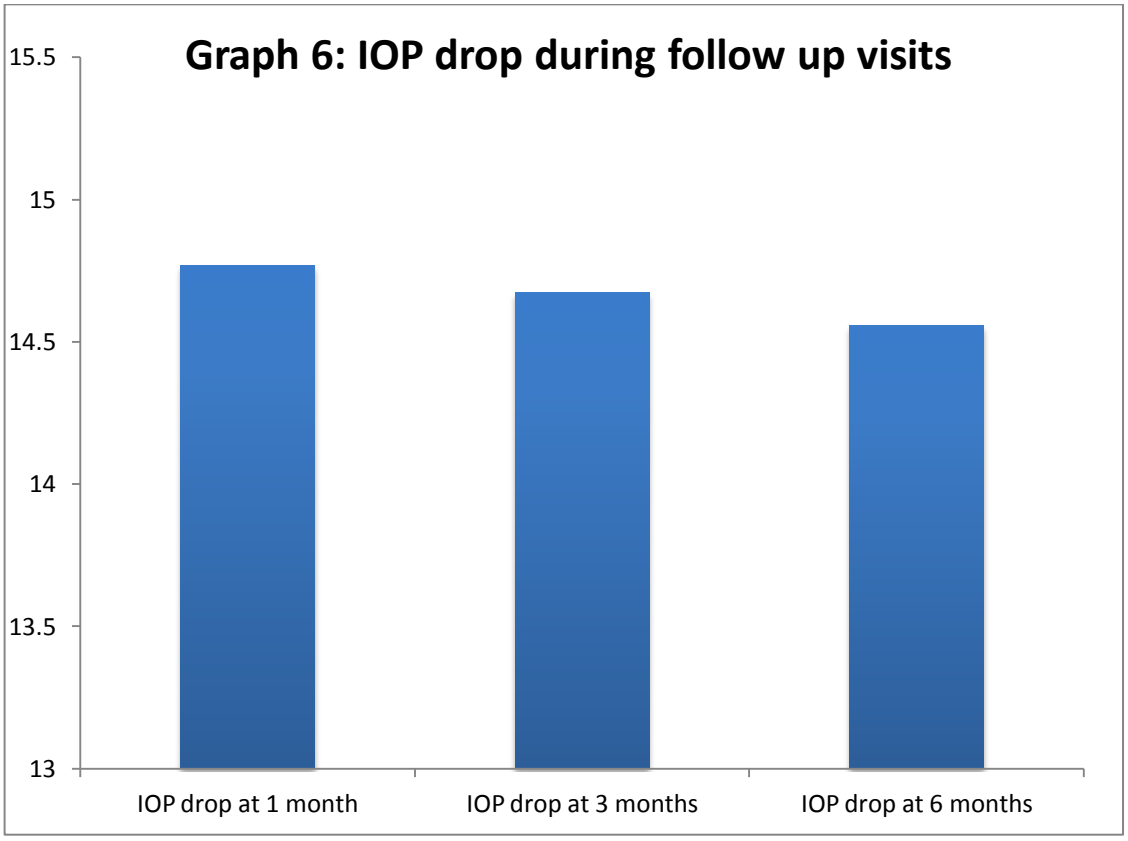
Table 9: Mean IOP at follow up visits

Follow up at	N	Mean	SD	SE
Pre-op	43	27.37	8.19	1.25
1 month	43	12.60	3.87	0.59
3 months	43	12.70	3.79	0.58
6 months	43	12.81	2.91	0.44

The mean decrease in IOP with respect to the pre-operative IOP was highest in the 1st month, followed by 3rd and 6th months. This is listed in Table 10 and graphically depicted in Graph 6.

Table 10: IOP drop during the follow up visits

	Mean	SD	SE
IOP drop at 1 month	14.77	8.80	1.34
IOP drop at 3 months	14.67	8.29	1.26
IOP drop at 6 months	14.56	8.00	1.22



II Cup:Disc Ratio (CDR)

1. Preoperative CDR

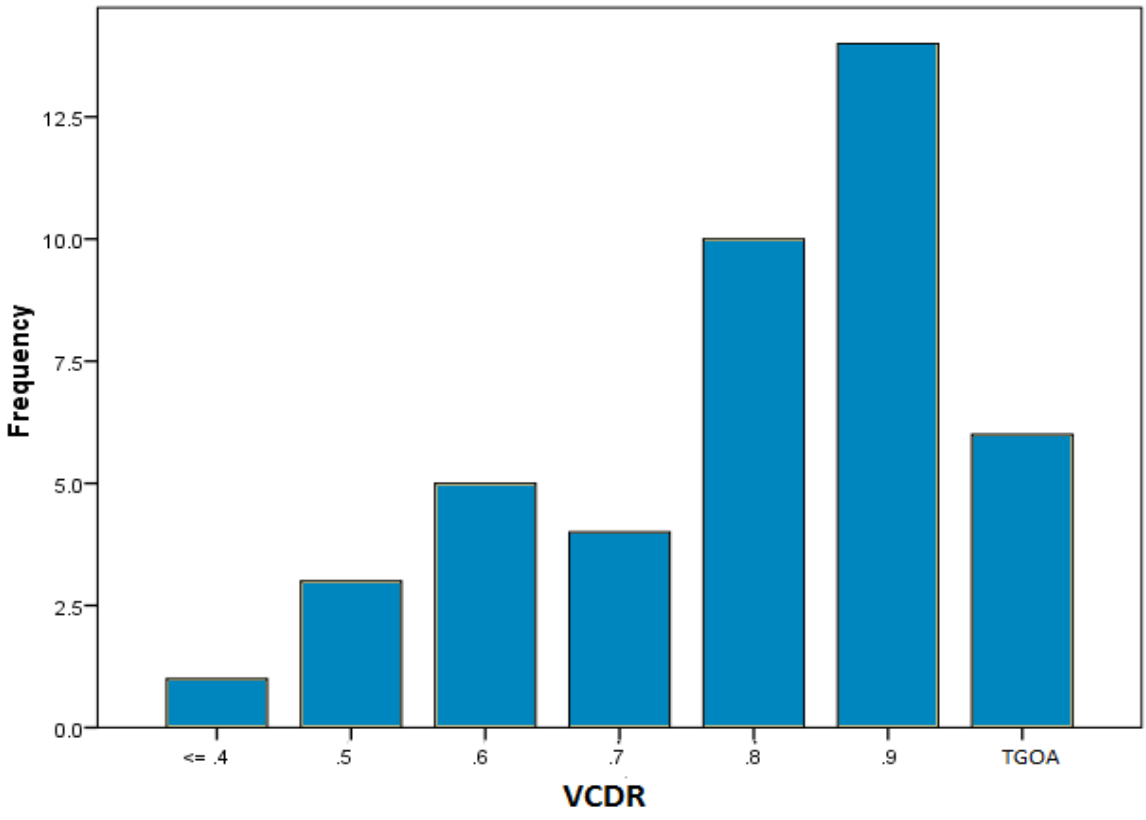
The mean pre-operative vertical CDR (VCDR) was 0.80 ± 0.16 and mean pre-operative horizontal CDR (HCDR) was 0.69 ± 0.19. The frequencies of each CDR value is listed in Tables 11 and 12 and graphically represented in Graphs 7 and 8.

Almost 70% of the eyes had a VCDR of 0.8 and above, suggesting that most of the patients had advanced glaucomatous disease.

Table 11: Pre-operative VCDR distribution

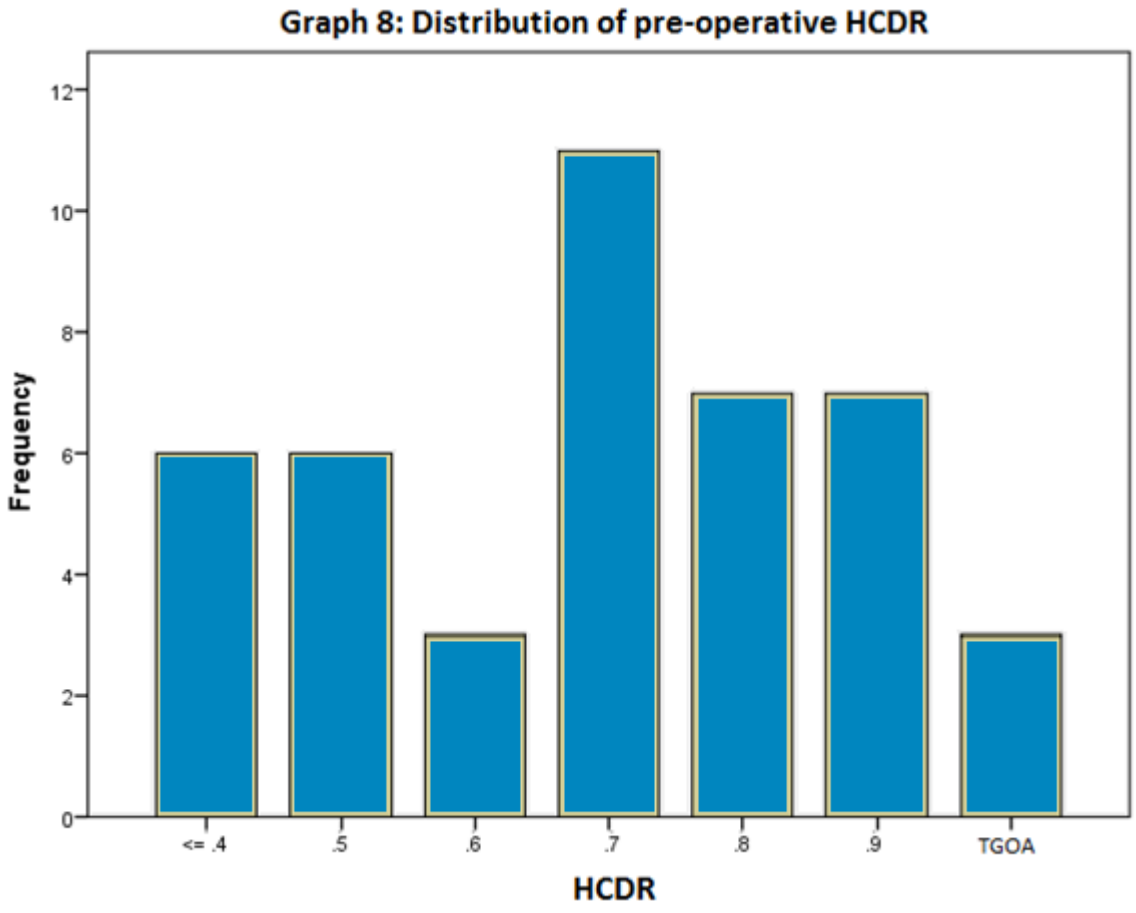
		Frequency	Percentage
	<=0 .4	1	2.3
	0.5	3	7.0
	0.6	5	11.6
	0.7	4	9.3
	0.8	10	23.3
	0.9	14	32.6
	TGOA	6	14.0
	Total	43	100.0

Graph 7: Distribution of pre-operative VCDR



65.2% of patients had a HCDR of 0.7 and above.

Table 12: Distribution of pre-operative HCDR		
HCDR	Frequency	Percentage
<= .4	6	14.0
.5	6	14.0
.6	3	7.0
.7	11	25.6
.8	7	16.3
.9	7	16.3
TGOA	3	7.0



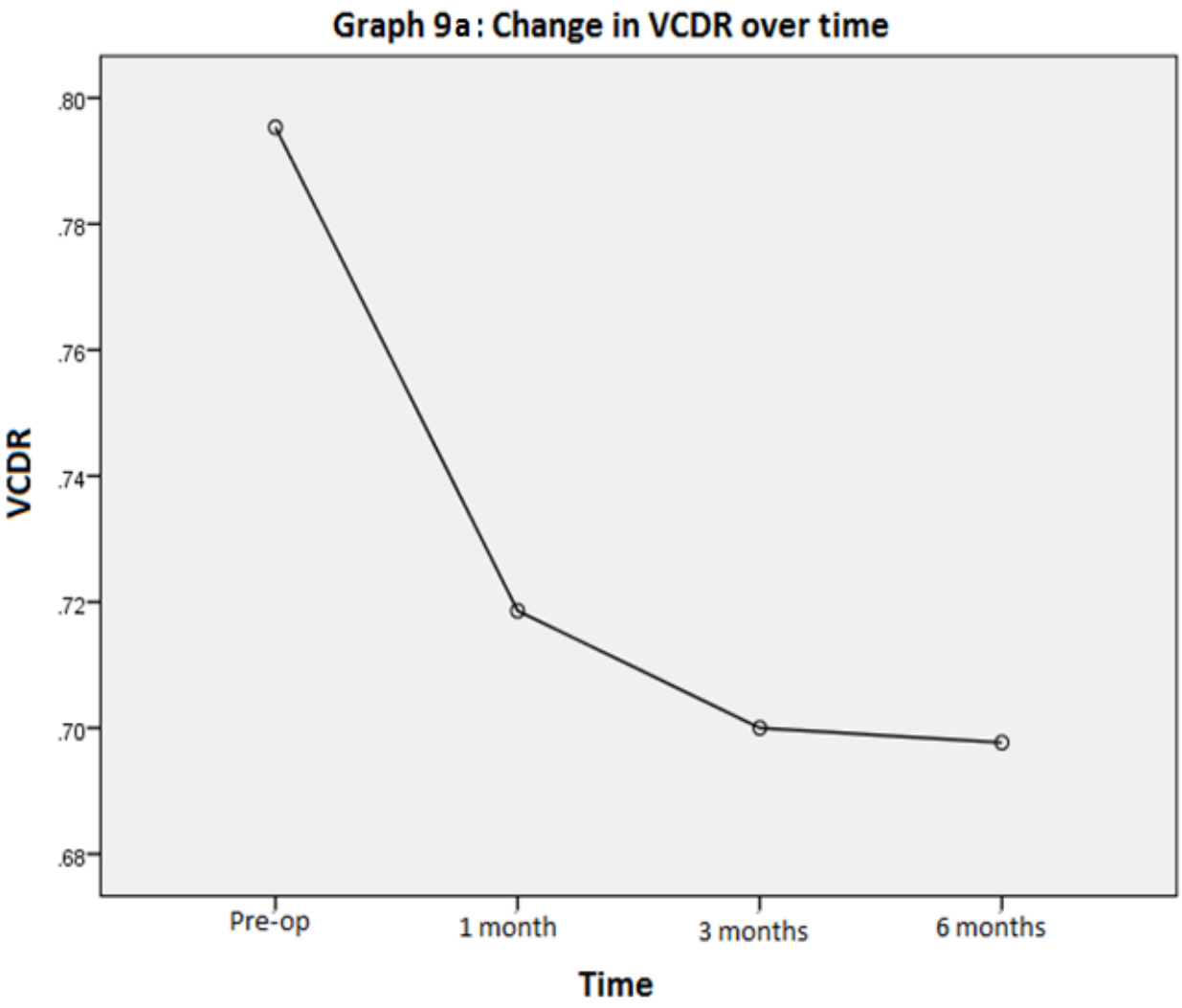
Post operative CDR

The mean post-operative VCDR values at 1, 3 and 6 months were 0.72 (SD 0.20), 0.70 (SD 0.20) and 0.70 (SD 0.21) respectively. The mean post-operative HCDR values at 1, 3 and 6 months were 0.62 (SD 0.20), 0.64 (SD 0.20) and 0.63 (SD 0.21) respectively. This is listed in Tables 13 and 14.

Table 13: Mean post-operative VCDR

Follow up at	N	Mean	SD
Pre-op	43	0.80	0.16
1 month	43	0.72	0.20
3 months	43	0.70	0.20
6 months	43	0.70	0.21

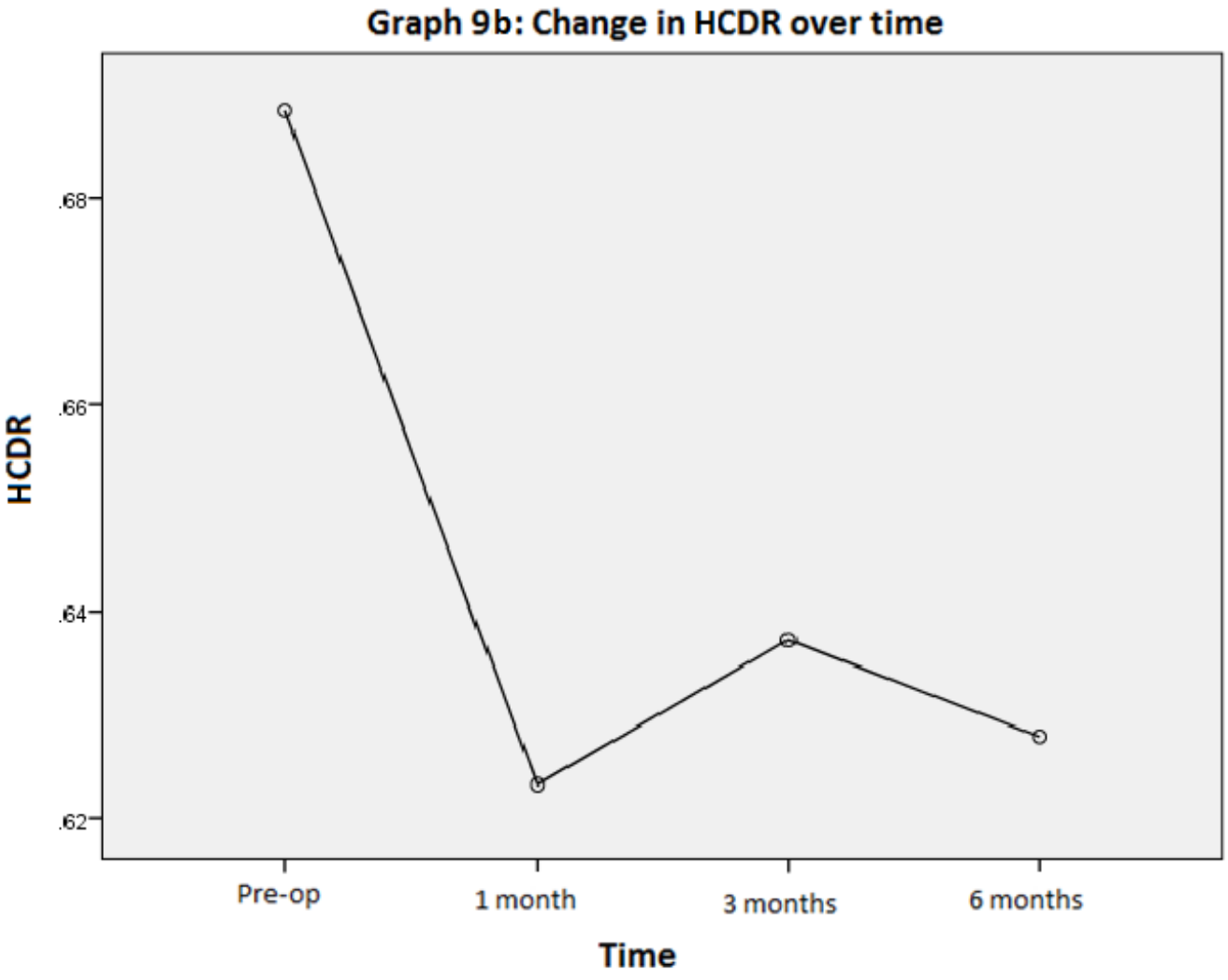
The decrease in VCDR noted at the post-operative visits with respect to the baseline values were statistically significant on Pillai's trace ($p<0.001$) and Mauchly's test of sphericity ($p=0.014$). This is graphically depicted by the line graph in Graph 9a.



The decrease in HCDR noted at the post-operative visits with respect to the baseline values were statistically significant on Pillai's trace (p=0.002). However, this was not significant as per Mauchly's test of sphericity (p=0.08). This is graphically depicted in Graph 9b.

Table 14: Mean post-operative HCDR

Time period	N	Mean	SD
Pre-op	43	0.69	0.19
1 month	43	0.62	0.20
3 months	43	0.64	0.20
6 months	43	0.63	0.21



III. Heidelberg Retinal Tomography Parameters (HRT)

1. Pre-operative HRT

The pre-operative mean values of the global parameters are shown in Table 15.

Table 15: Pre-operative HRT global parameters

Parameter	Mean	SD	SE
Global disc area [mm^2]	2.22	0.41	0.07
Global cup area [mm^2]	1.22	0.63	0.10
Global rim area [mm^2]	0.95	0.47	0.07
Global cup/disc area ratio	0.56	0.25	0.04
Global rim/disc area ratio	0.44	0.25	0.04
Global cup volume [mm^3]	0.48	0.42	0.06
Global rim volume [mm^3]	0.25	0.29	0.04
Global mean cup depth [mm]	0.36	0.19	0.03
Global maximum cup depth [mm]	0.81	0.32	0.05
Global height variation contour [mm]	0.48	0.33	0.05
Global cup shape measure	-0.06	0.10	0.01
Global mean RNFL thickness [mm]	0.10	0.12	0.02
Global RNFL cross sectional area [mm^2]	0.53	0.65	0.10
Global horizontal cup/disk ratio	0.75	0.20	0.03
Global vertical cup/disk ratio	0.74	0.27	0.04
Global maximum contour elevation [mm]	-0.04	0.14	0.02
Global average variability (SD) [mm]	0.10	0.09	0.01

2. Post operative HRT

The parameters which showed significant change using the Paired T test are listed in Table 16a-c. Most significant changes were noted during the third month after surgery. No significant change was noted for global rim area, cup area, cup depth, rim volume, VCDR or HCDR during the follow up visits.

Table 16a: HRT parameters that showed significant change post-operatively at 1 month

Parameter	Pre-op mean ± SE	1 month mean ± SE	p value
Global cup shape measure	-0.06 ± 0.01	-0.09 ± 0.01	0.02
Global maximum contour elevation	0.04 ± 0.02	-0.06 ± 0.05	0.04
Nasal cup shape measure	-0.10 ± 0.02	-0.14 ± 0.02	0.01
Nasal-Superior cup shape measure	-0.04 ± 0.02	-0.08 ± 0.02	0.03

Table 16b: HRT parameters that showed significant change post-operatively at 3 months

Parameter	Pre-op mean ± SE	3 month mean ± SE	p value
Global average variability	0.10 ± 0.01	0.03 ± 0.01	0.04
Temporal rim volume	0.03 ± 0.005	0.02 ± 0.002	0.05
Temporal cup shape measure	-0.003 ± 0.02	-0.05 ± 0.02	0.002
Nasal-Superior mean RNFL thickness	0.14 ± 0.03	0.18 ± 0.03	0.04

Table 16c: HRT parameters that showed significant change post-operatively at 6 months

Parameter	Pre-op mean ± SE	6 month mean ± SE	p value
Global maximum contour elevation	0.04 ± 0.02	0.003 ± 0.02	0.02
Global average variability	0.10 ± 0.01	0.06 ± 0.006	0.01
Temporal cup shape measure	-0.003 ± 0.02	-0.03 ± 0.02	0.03
Nasal-Superior RNFL cross sectional area	0.09 ± 0.02	0.13 ± 0.02	0.05

IV. Optical Coherence Tomography Parameters

1. Preoperative OCT

OCT Optic Nerve Head (ONH) and Retinal Nerve Fiber Layer (RNFL) 3.4 parameters assessed pre-operatively are shown in Tables 17 and 18.

Table 17: Pre-operative OCT Optic Nerve Head parameters

Parameter	Mean	SD
VIRA	0.08	0.09
HIRW	1.03	0.31
Disc Area	2.70	0.56
Cup Area	1.96	0.75
Rim Area	0.74	0.56
CDAR	0.72	0.22
HCDR	0.86	0.15
VCDR	0.84	0.21

(VIRA: Vertical Integrated Rim Area; HIRW: Horizontal Integrated Rim Width; CDAR: Cup Disc Area Ratio)

The mean average RNFL thickness was 64.15 microns (SD 19.79). Quadrant wise RNFL thickness was highest for the superior quadrant (76.74 microns, SD 32.34) followed by the inferior quadrant (73.16 microns, SD 28.58). The mean RNFL thickness was least in the temporal quadrant (48.81 microns, SD 12.76).

Table 18: Pre-operative OCT RNFL parameters		
	Mean	**SD**
Average thickness	64.15	19.79
Superior quadrant	76.74	32.34
Temporal quadrant	48.81	12.76
Inferior quadrant	73.16	28.58
Nasal quadrant	57.84	20.57

2. Post operative OCT

OCT -ONH done at baseline and during the follow up visits revealed changes that were significant using Paired T test and are listed in Tables 16a to c. At 1 month, VIRA, HIRW, rim area, cup area, CDAR and HCDR showed significant change. At the third month follow up, VIRA, HIRW, cup area, CDAR and HCDR (except VCDR and rim area) showed significant change. At six months, cup area, CDAR and HCDR showed significant change. Significant changes were not noted at six months for VIRA, HIRW, Rim area and VCDR. Cup Disc Area Ratio (CDAR) showed statistically significant change during all the follow up visits ($p<0.001$ at 1 and 3 months, 0.012 at 6 months). The parameters are listed in Table 19a-c.

Table 19a: OCT parameters that showed significant change post-operatively at 1 month

Parameter	Pre-op mean ± SE	1 month mean ± SE	p value
VIRA	0.08 ± 0.01	0.14 ± 0.04	0.04
HIRW	1.02 ± 0.05	1.18 ± 0.06	0.003
Cup Area	1.96 ± 0.12	1.81 ± 0.13	0.01
Rim Area	0.74 ± 0.09	0.89 ± 0.10	0.02
CDAR	0.72 ± 0.03	0.66 ± 0.04	<0.001
HCDR	0.86 ± 0.02	0.81 ± 0.03	<0.001

Table 19b: OCT parameters that showed significant change post-operatively at 3 months

Parameter	Pre-op mean ± SE	3 month mean ± SE	p value
VIRA	0.08 ± 0.01	0.11 ± 0.02	<0.001
HIRW	1.02 ± 0.05	1.15 ± 0.04	<0.001
Cup Area	1.96 ± 0.12	1.76 ± 0.11	<0.001
CDAR	0.72 ± 0.03	0.66 ± 0.03	<0.001
HCDR	0.86 ± 0.02	0.82 ± 0.02	<0.001

Table 19c: OCT parameters that showed significant change post-operatively at 6 months

Parameter	Pre-op mean ± SE	6 month mean ± SE	p value
Cup Area	1.96 ± 0.12	1.78 ± 0.12	<0.001
CDAR	0.72 ± 0.03	0.69 ± 0.04	0.01
HCDR	0.86 ± 0.02	0.83 ± 0.03	<0.001

There was significant change in the Average RNFL thickness and in the temporal quadrant during all the follow up visits. The superior, inferior and nasal quadrant did not have significant change in RNFL thickness at 6 months. The parameters are listed in Table 20a-c. Graph 10 shows change in average RNFL thickness over time (p=0.02 on Pillai's trace).

Table 20a: OCT RNFL parameters that showed significant change post-operatively at 1 month

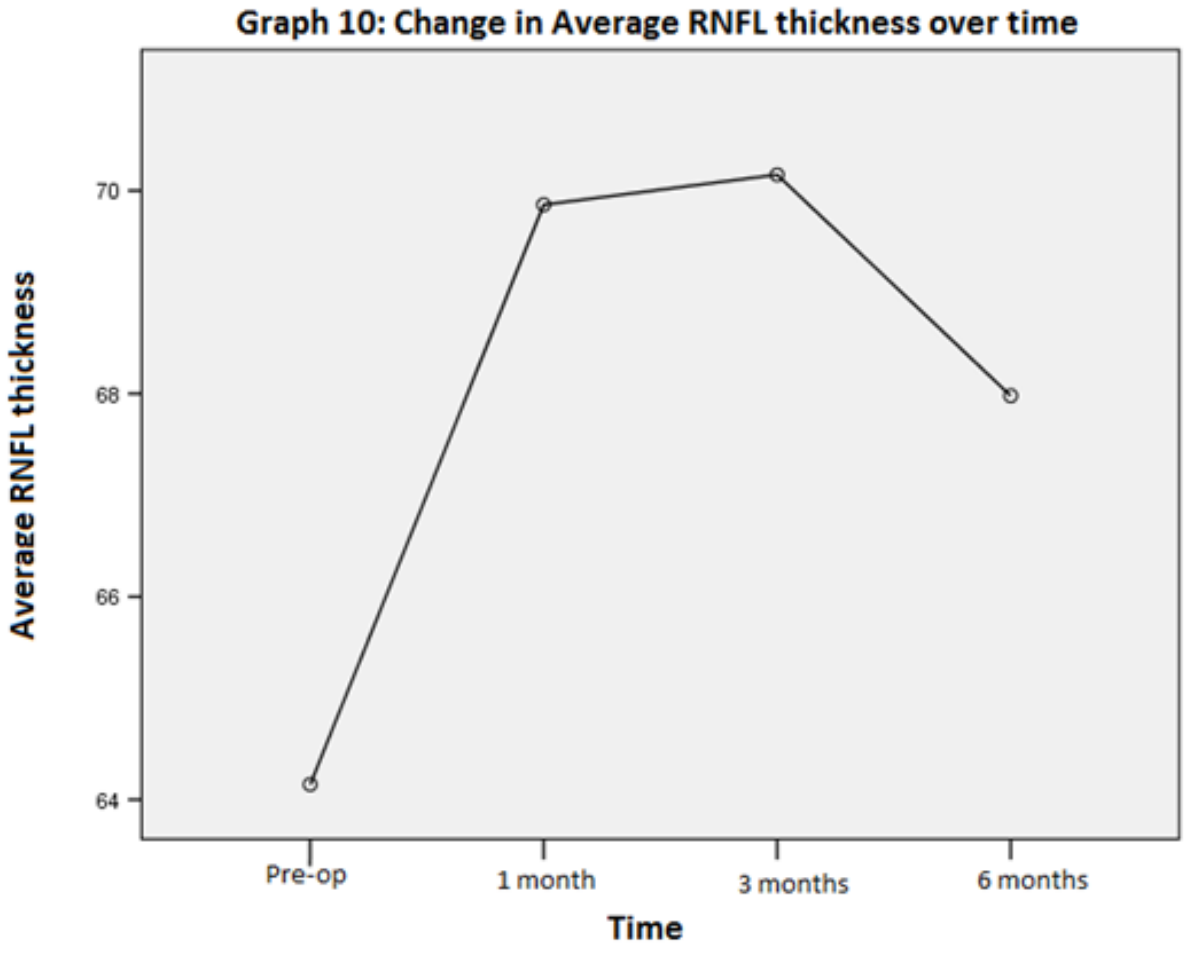
Parameter	Pre-op mean ± SE	1 month mean ± SE	p value
Average thickness	64.15 ± 3.02	69.86 ± 2.78	0.001
Superior quadrant	76.74 ± 4.93	84.63 ± 4.53	0.002
Temporal quadrant	48.81 ± 1.95	54.59 ± 2.00	<0.001
Inferior quadrant	73.16 ± 4.36	78.80 ± 4.28	0.02

Table 20b: OCT RNFL parameters that showed significant change post-operatively at 3 months

Parameter	Pre-op mean ± SE	3 month mean ± SE	p value
Average thickness	64.15 ± 3.02	70.16 ± 2.55	<0.001
Superior quadrant	76.74 ± 4.93	84.13 ± 4.27	0.002
Temporal quadrant	48.81 ± 1.95	55.54 ± 1.92	<0.001
Inferior quadrant	73.16 ± 4.36	79.46 ± 3.93	0.002

Table 20c: OCT RNFL parameters that showed significant change post-operatively at 6 months

Parameter	Pre-op mean ± SE	6 month mean ± SE	p value
Average thickness	64.15 ± 3.02	67.98 ± 2.83	0.003
Temporal quadrant	48.81 ± 1.95	53.61 ± 1.97	0.002



V. Correlations between parameters tested:

1. Correlation between IOP and VCDR/HCDR (clinical)

No correlation was noted using Pearson's correlation coefficient (r) between the change in IOP and VCDR or HCDR during all the post-operative visits. This is given in Table 21.

Table 21: Correlation of CDR with IOP (clinical)

Parameter	Follow up	Pearson's coefficient (r)
VCDR	1 month	.09
	3 months	.09
	6 months	.16
HCDR	1 month	.06
	3 months	.26
	6 months	.24

2. Correlation between IOP and HRT/OCT

All the parameters which showed significant change over time were checked for correlation with IOP variation using Pearson coefficient. The parameters which showed significant correlation and the respective follow up time are given in Table 22. OCT HCDR showed moderate correlation with IOP variation at 1 and 6 months.

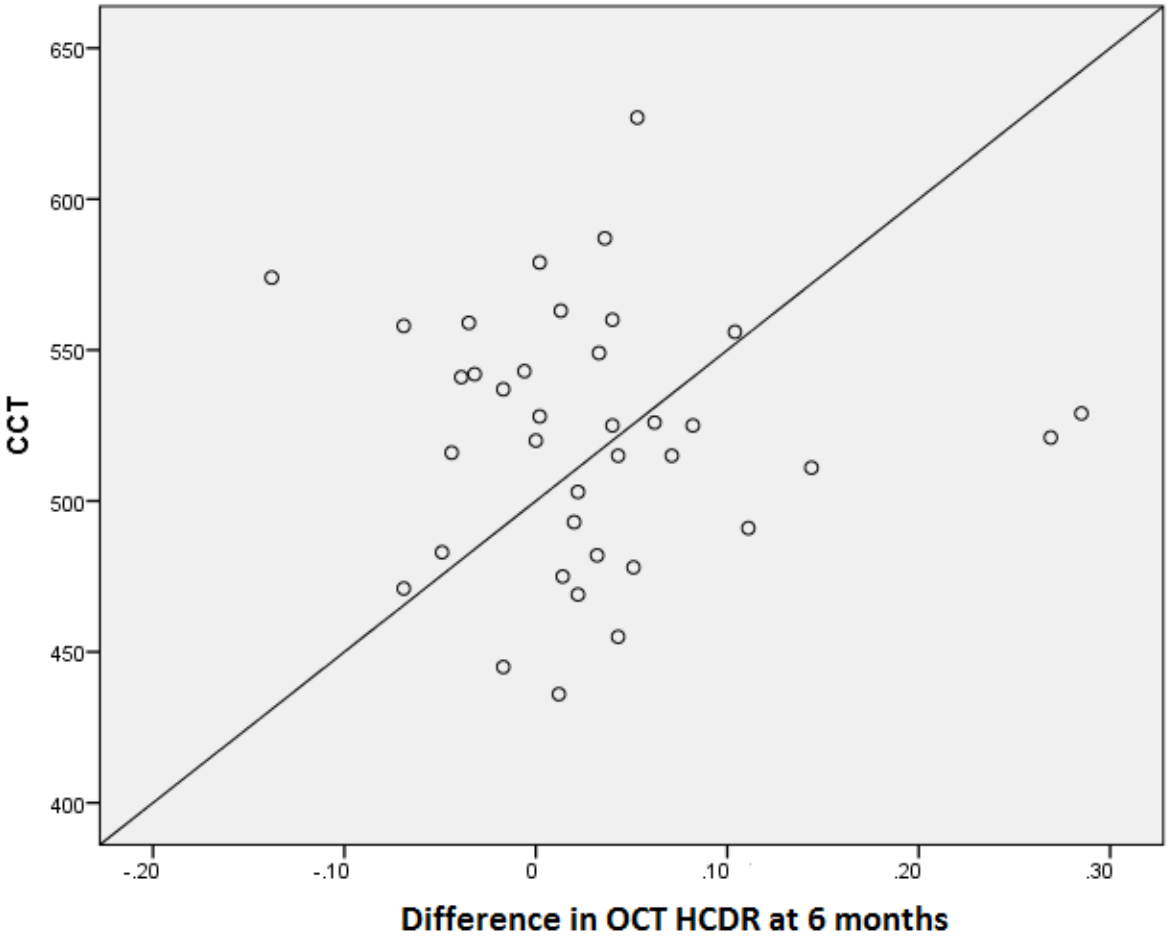
Table 22: HRT and OCT parameters showing moderate and strong correlation with IOP

Parameter	Time	Pearson correlation coefficient (r)
VIRA (OCT)	6 months	-0.44
OCT HCDR	1 month	0.37
OCT HCDR	6 months	0.37
Global cup shape measure	6 months	0.35
Temporal cup shape measure	6 months	0.30
Nasal-Superior cup shape measure	1 month	0.32

3. Correlation with CCT

No parameters showed significant correlation with CCT. Graph 11 shows a scatter-plot showing no correlation (r=-0.03) between CCT and difference in OCT HCDR at 6 months.

Graph 11: Correlation between CCT and difference in OCT HCDR at 6 months



4. **Correlation between HRT and OCT parameters**

Correlation between HRT and OCT parameters were assessed using Pearson's correlation (r). The parameters which were compared were vertical and horizontal cup disc ratios, rim area and cup area. The values are given in Table 19.

Table 19: Correlation between HRT and OCT parameters

Parameter	Time	Pearson correlation coefficient (r)
Vertical CDR	Pre-op	0.34
	1 month	0.80
	3 months	0.84
	6 months	0.81
Horizontal CDR	Pre-op	0.55
	1 month	0.78
	3 months	0.84
	6 months	0.73
Rim Area	Pre-op	0.36
	1 month	0.71
	3 months	0.78
	6 months	0.62
Cup Area	Pre-op	0.69
	1 month	0.87
	3 months	0.86
	6 months	0.90

Discussion

Glaucomatous damage to the optic nerve head (ONH) is considered to be due to compression of neurons by the posteriorly bowed lamina cribrosa, which is distorted, leading to lack of nourishment to retinal ganglion cells. (1,2) In advanced cases, distortion may be permanent, but in early disease, both the ONH and visual field can show improvement with decrease in IOP. (3,4) One of the main reasons postulated for an apparent improvement in the appearance of ONH is a reduction in the posterior bowing of the lamina cribrosa, thus relieving the compressed nerve fibres. (2)

Improvement in the appearance of the ONH has been well demonstrated in congenital and juvenile glaucoma demonstrated by the improvement in cup disc ratio or reversal of cupping. (5–8) However, it is less frequently described in adults with glaucomatous nerve damage. Clinical evaluation of the ONH and techniques like disc photography may not be sensitive enough to pick up the changes if any that may occur following reduction of IOP. Our study however, showed a statistically significant improvement in the vertical cup disc ratio at 6 months post operatively. In other words, reversal of cupping was noted clinically after surgical reduction of IOP which was maintained till 6 months.

Newer image analysis techniques have enabled detailed analysis of the optic nerve head and recognition of changes more objectively over time with enhanced accuracy. Given the subjectivity of clinical evaluation of the disc, HRT and OCT (ONH analysis and RNFL 3.4) were used in our study for examination of the optic nerve head and peripapillary area. Cross-sectional imaging by the OCT is considered to give a better representation of the reduction of the posterior bowing of the lamina cribrosa when compared to the images acquired by HRT scanning.

In our study, the global cup shape measure showed a more negative change at 1 month which was significant. This is in keeping with the work done by Topouzis et al. (9) Quadrant wise analysis localized this change to the nasal and nasal-superior quadrants. The nasal-superior disc parameters did not show any significant change at 3 and 6 months but there was a significant change in the RNFL in these quadrants. However, at 3 months, the temporal cup shape measure showed a significant negative change with an increase in temporal rim volume which persisted upto 6 months.

The last area to be affected in glaucomatous optic nerve head damage is the nasal part (10,11). It is possible that since the nasal fibers are the ones to be affected last, they are in a state of reversible damage and can be revived. (12) This may explain the improvement in the nasal parameters after surgery. Similar findings were noted by Kotecha et al (13).

Decrease in the cupping involves reduction of the maximum cup depth on HRT. There was no significant correlation between decrease in IOP and change in cupping as reflected in the maximum cup depth. Similar findings were noted by Irak et al (14). However, the work done by Topouzis et al (9) showed a significant decrease in the mean cup depth at 2 weeks which became insignificant at 4 and 8 months.

HRT did not show any statistically significant changes with regard to the volume or area parameters of the optic disc other than the temporal rim volume at 3 months. The only RNFL parameters which showed significant change (nasal-superior mean RNFL thickness at 3 months and RNFL cross-sectional area at 6 months) may indicate reversal of transiently damaged nerve fibers in this area.

Existing literature shows conflicting results when OCT - RNFL or HRT is used to assess reversal of cupping after glaucoma surgery. The variable results of these studies may be due to other factors like stage of the disease, age and also the postoperative IOP. All the patients considered for analysis in our study had ≥30% reduction in IOP at 6 months which is a substantial reduction in IOP post-operatively and the significant reversal of cupping noted may be the result of this.

Till date there is only one study which looked at OCT of the optic nerve head (OCT-ONH) for evaluating reversal of cupping. (15) The OCT- ONH parameters also demonstrated a statistically significant reversal of cupping which was more marked at 1 and 3 months post-operatively and less marked at 6 months. All OCT-ONH parameters showed significant change at 1 and 3 months. Cup area, CDAR and HCDR showed significant change till 6 months. Raghu et al (15) noted significant change only for the cup area and CDAR and that too at 1 week post-operatively. The changes were not significant thereafter in their study and no correlation was found between decrease in IOP and OCT ONH parameters. Our study demonstrated correlation between reduction in IOP with OCT HCDR at 1 and 6 months and VIRA at 6 months. Of the many reasons for reversal of cupping, the most accepted one is that the lamina moves anteriorly with reduction in IOP. The decrease in the mean cup depth and reduction of the cup disc ratio noted on OCT-ONH in our patients can be attributed to reduction in the posterior bowing.

In our study, significant increase in average and temporal quadrant RNFL thickness was noted during all the post-operative visits. Aydin et al (16) had noted a similar increase in average RNFL thickness. However, in their study, only a single reading was taken at 6-12

months post operatively. Hence the results at 1 and 3 months could not be compared. In contrast, Chang et al(17) did not find any significant change in RNFL thickness with significant IOP reduction at 1-2 months in 21 patients who were managed both medically and surgically. Raghu et al (15) noted significant changes in the average, inferior and temporal RNFL thickness at 1 week only, which reverted to near baseline values at 3 months in 17 patients.

The immediate increase in RNFL thickness after surgery may be considered to be due to the reversal of the compressive effect on the RNFL by the elevated preoperative IOP, resulting in restoration of normal size and shape by the retinal ganglion cell axons.(2) Retinal swelling from acute postoperative reduction in IOP may also explain the increase in RNFL thickness after surgery.(1)

Even though a significant increase in RNFL thickness was noted during the post-operative visits in our study, these did not correlate significantly with the decrease in IOP. This is in contrast to the work done by Aydin et al. who noted a significant correlation between the IOP decrease and mean RNFL thickness even at 6 to 12 months. (16)

The short term increase in RNFL thickness and ONH changes noted at 1 month may be attributed to acute post-operative drop in IOP which results in release of the physical compression on the RNFL. (2) However, in our study, the significantly increased average and temporal quadrant RNFL thickness persisted upto 6 months (the whole duration of the study). Removal of cataract during a combined procedure will lead to increase in signal strength of the OCT scans and may in turn show increased RNFL thickness. (18–

22). Since increase in signal strength should cause a uniform increase in RNFL thickness in all quadrants on OCT, this probably is not the reason for the significant increase in temporal RNFL thickness alone on quadrant-wise analysis.

The absence of significant reversal of cupping in other studies may be attributed to inadequate sample size. (9,15,23) A more plausible reason may be that we had less advanced cases in our study when compared others which did not show significant reversal of cupping beyond 3 months (CDAR in Raghu et al 0.87±0.37 vs 0.73±0.20 in our group; mean rim volume 0.163 in Topouzis et al vs 0.230 in our group). Reversal of cupping is more likely to occur in the early stages of the disease (3,4,24,25) and can explain the reversal of cupping noted in our study group. However, no definitive functional conclusions can be derived from the anatomical changes that were studied upon lowering IOP.

This study shows that there is significant reversal of cupping clinically and significant increase in RNFL thickness and changes in the optic nerve head as assessed by OCT imaging after successful glaucoma surgery which persisted for 6 months. Due to increasing costs of anti-glaucoma medications, the socio-economic status of our population, poor compliance and shortage of government health insurance schemes we do early surgical intervention for glaucoma. Thus, the recruitment of patients with less advanced glaucoma as compared to other studies may be the reason for the significant reversal of cupping noted in our study even upto 6 months after surgery. Another reason could be that we had more stringent inclusion criteria which included a 30% reduction in IOP postoperatively. Other studies did not have such a consideration.

We hitherto report improvement in optic nerve head parameters in adults who have undergone successful trabeculectomy. We postulate that early surgical intervention may be considered in moderate glaucomas in the light of these findings.

Limitations

1. HFA could have been done as functional improvement is better than structural.
2. The surgeries were not performed by a single surgeon.
3. Baseline scans were taken before surgery in some cases and on the first post-op day in others. This could have been standardized.
4. Reversal of cupping after surgical intervention could have been compared with medical management.

Summary and Conclusions

This study was aimed at exploring change in optic disc and retinal nerve fiber layer after successful glaucoma surgery. We defined success as 30% reduction in IOP from baseline and only those patients who met this criterion was included. Thus, 43 eyes of 43 patients were considered for analysis. All of them underwent pre-operative evaluation for establishing a baseline and further evaluation at 1, 3 and 6 months after surgery. In addition to clinical examination, HRT and OCT-ONH and RNFL 3.4 were done for objective assessment.

Our study had patients with comparatively less advanced glaucoma when compared to other similar studies. The results of our study were suggestive of reversal of cupping after successful glaucoma surgery. There was decrease in the vertical and horizontal CDR after surgery which was statistically significant.

Using HRT, a more negative trend in global cup shape measure was noted 1 month after surgery. Changes suggestive of reversal of cupping were noted in the nasal-superior quadrant during the follow up visits. This may be because of restoration of the temporarily damaged nasal nerve fibers after reduction of IOP by surgical intervention.

Our analysis of the OCT-ONH parameters also suggested reversal of cupping. Cup area, horizontal CDR and cup disc area ratio showed significant change during all the follow up visits till 6 months.

Analysis of the OCT-RNFL revealed significant increase in the average and temporal quadrant RNFL thickness which persisted till 6 months. The superior and inferior quadrants also showed significant increase during the 1 and 3 month follow up but not at 6 months.

We further analyzed the correlation between the above parameters with decrease in IOP during each follow up visit. At 1 month, only OCT HCDR and nasal-superior cup shape measure showed moderate correlation with decrease in IOP. At 6 months, OCT HCDR and global and temporal cup shape measure showed moderate correlation whereas VIRA showed strong correlation with decrease in IOP.

Moreover, we assessed correlation between similar parameters measured by OCT and HRT. Both vertical and horizontal cup disc ratios as well as rim area and cup area showed strong correlation.

Overall, we noted an improvement in optic nerve head parameters in adults who have undergone successful trabeculectomy. In the light of the above findings, we postulate that early surgical intervention may be considered in moderate glaucomas.

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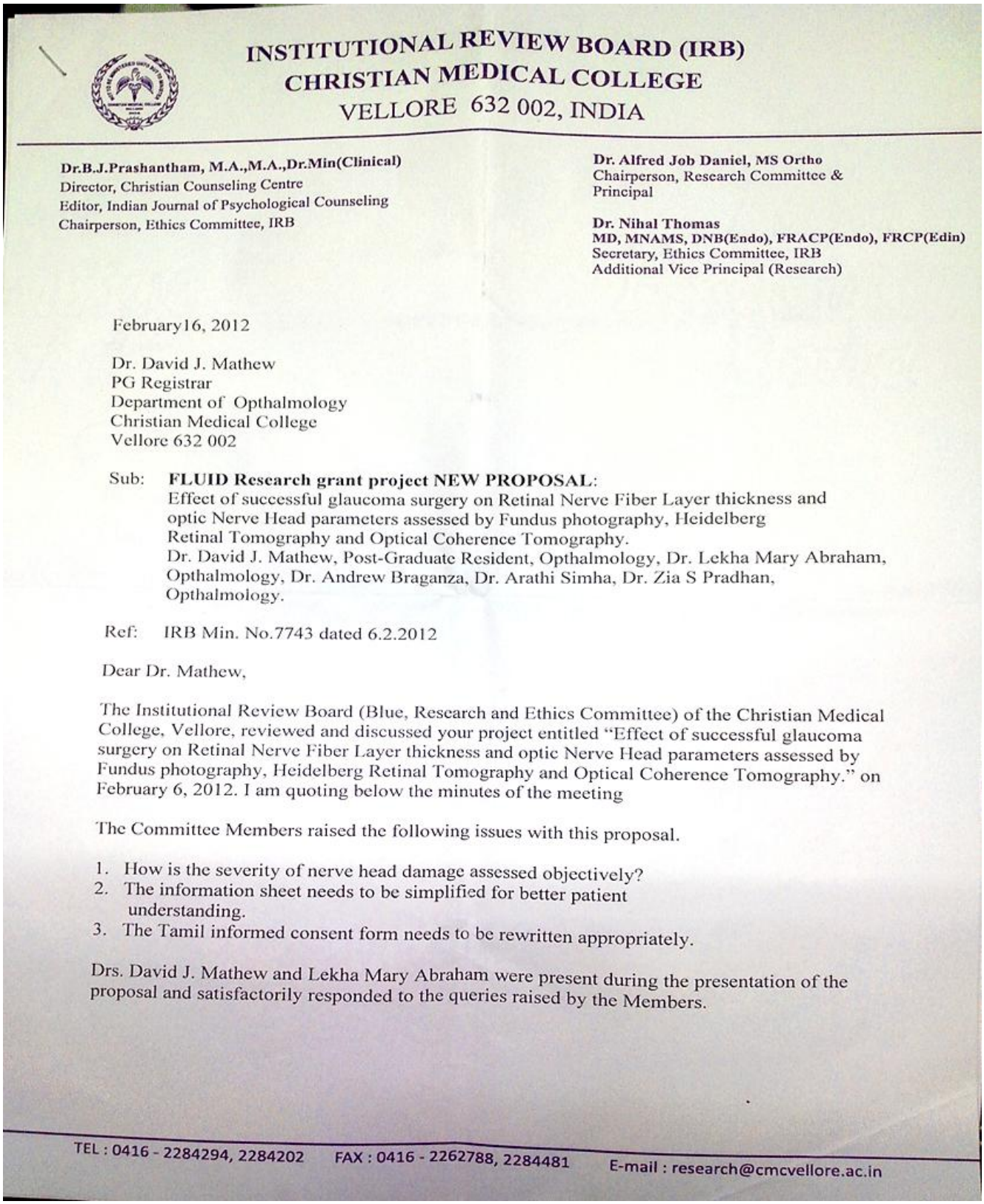
APPENDIX A: IRB APPROVAL LETTER



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Additional Vice Principal (Research)

February16, 2012

Dr. David J. Mathew
PG Registrar
Department of Opthalmology
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL**:
Effect of successful glaucoma surgery on Retinal Nerve Fiber Layer thickness and optic Nerve Head parameters assessed by Fundus photography, Heidelberg Retinal Tomography and Optical Coherence Tomography.
Dr. David J. Mathew, Post-Graduate Resident, Opthalmology, Dr. Lekha Mary Abraham, Opthalmology, Dr. Andrew Braganza, Dr. Arathi Simha, Dr. Zia S Pradhan, Opthalmology.

Ref: IRB Min. No.7743 dated 6.2.2012

Dear Dr. Mathew,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Effect of successful glaucoma surgery on Retinal Nerve Fiber Layer thickness and optic Nerve Head parameters assessed by Fundus photography, Heidelberg Retinal Tomography and Optical Coherence Tomography." on February 6, 2012. I am quoting below the minutes of the meeting

The Committee Members raised the following issues with this proposal.

1. How is the severity of nerve head damage assessed objectively?
2. The information sheet needs to be simplified for better patient understanding.
3. The Tamil informed consent form needs to be rewritten appropriately.

Drs. David J. Mathew and Lekha Mary Abraham were present during the presentation of the proposal and satisfactorily responded to the queries raised by the Members.

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

After discussion, it was resolved to **ACCEPT** the proposal.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Secretary
Institutional Review Board
(Ethics Committee)
Christian Medical College
Vellore - 632 002, Tamil Nadu, India

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

APPENDIX B: INFORMATION SHEETS AND CONSENT FORMS

Effect of successful glaucoma surgery on Retinal Nerve Fiber Layer thickness and Optic Nerve Head parameters using Fundus Photography, Heidelberg Retinal Tomography and Stratus Optical Coherence Tomography

Information sheet

You are being requested to participate in a study to study the effect of successful glaucoma surgery (surgery to reduce the pressure in the eye) on retinal (sensory part inside the eye) nerve fiber layer thickness. This is done by a few special tests like Fundus Photography, Heidelberg Retinal Tomography and Stratus Optical Coherence Tomography. The details of the tests have been listed below.

We hope to include about 100 people from this hospital in this study.

What is Fundus Photography?

This test is done after the eye to be photographed is dilated (requires putting of dilating drops).

Fundus photography involves taking a picture of the patient's retina (sensory part inside the eye). The patient will be seated on a chair, asked to rest his/her forehead or chin on a support and asked to look at a fixed object or light while the test is carried out. Due to the flash of the camera there will be dazzling of the eye for a few minutes.

What is Heidelberg Retinal Tomography?

Just as in Fundus Photography, the patient will be seated on a chair, asked to rest his/her forehead or chin on a support and asked to look at a fixed object or light while the test is carried out. The HRT test uses a special light beam, which is of low energy and has almost no effect on the eye. During the test, there will be a high frequency buzzing noise that will subside as soon as the test is over.

What is Optical Coherence Tomography?

The OCT test uses special light rays which again causes negligible effects on the eye. The patient is seated on a chair and asked to rest his/her forehead or chin on a support and asked to look at a fixed light while the test is carried out.

If you take part what will you have to do?

Prior to the surgery and at 1, 3 and 6 months after surgery when you come for follow up visits, you will have to undergo the tests mentioned above, i.e. Fundus Photography, HRT and OCT. You will not be charged for any of these tests.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

Will your personal details be kept confidential?

The results of this study may be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

CONSENT TO TAKE PART IN THE STUDY

Study Title: *Effect of successful glaucoma surgery on Retinal Nerve Fiber Layer thickness and Optic Nerve Head parameters using Fundus Photography, Heidelberg Retinal Tomography and Stratus Optical Coherence Tomography*

Study Number:

Hospital Number:

Date of Birth / Age (in years):

I_____, son/daughter of _____

declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights. I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published. I voluntarily agree to take part in this study.

Name of the patient:

Signature:

Date:

Name of witness and signature:

Relation to participant:

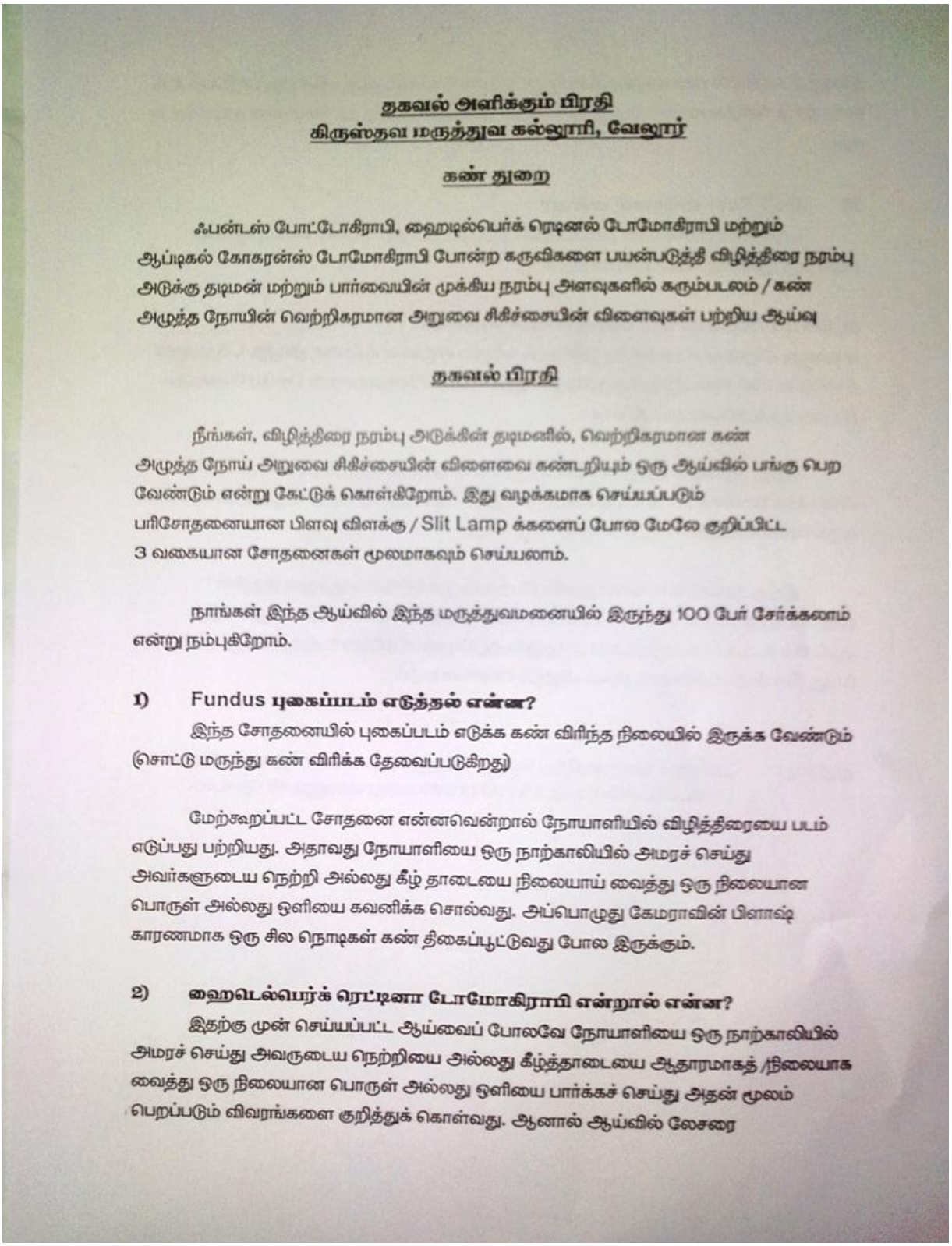
Date:

Name of the doctor:

Signature:

Date:

INFORMATION SHEET IN TAMIL



தகவல் அளிக்கும் பிரதி
கிருஸ்தவ மருத்துவ கல்லூரி, வேலூர்

கண் துறை

ஃபன்டஸ் போட்டோகிராபி, ஹைடில்பெர்க் ரெடினல் டோமோகிராபி மற்றும் ஆப்டிகல் கோகரன்ஸ் டோமோகிராபி போன்ற கருவிகளை பயன்படுத்தி விழித்திரை நரம்பு அடுக்கு தடிமன் மற்றும் பார்வையின் முக்கிய நரம்பு அளவுகளில் கரும்படலம் / கண் அழுத்த நோயின் வெற்றிகரமான அறுவை சிகிச்சையின் விளைவுகள் பற்றிய ஆய்வு

தகவல் பிரதி

நீங்கள், விழித்திரை நரம்பு அடுக்கின் தடிமனில், வெற்றிகரமான கண் அழுத்த நோய் அறுவை சிகிச்சையின் விளைவை கண்டறியும் ஒரு ஆய்வில் பங்கு பெற வேண்டும் என்று கேட்டுக் கொள்கிறோம். இது வழக்கமாக செய்யப்படும் பரிசோதனையான பிளவு விளக்கு / Slit Lamp க்களைப் போல மேலே குறிப்பிட்ட 3 வகையான சோதனைகள் மூலமாகவும் செய்யலாம்.

நாங்கள் இந்த ஆய்வில் இந்த மருத்துவமனையில் இருந்து 100 பேர் சேர்க்கலாம் என்று நம்புகிறோம்.

1) Fundus புகைப்படம் எடுத்தல் என்ன?

இந்த சோதனையில் புகைப்படம் எடுக்க கண் விரிந்த நிலையில் இருக்க வேண்டும் (சொட்டு மருந்து கண் விரிக்க தேவைப்படுகிறது)

மேற்கூறப்பட்ட சோதனை என்னவென்றால் நோயாளியில் விழித்திரையை படம் எடுப்பது பற்றியது. அதாவது நோயாளியை ஒரு நாற்காலியில் அமரச் செய்து அவர்களுடைய நெற்றி அல்லது கீழ் தாடையை நிலையாய் வைத்து ஒரு நிலையான பொருள் அல்லது ஒளியை கவனிக்க சொல்வது. அப்பொழுது கேமராவின் பிளாஷ் காரணமாக ஒரு சில நொடிகள் கண் திகைப்பூட்டுவது போல இருக்கும்.

2) ஹைடெல்பெர்க் ரெட்டினா டோமோகிராபி என்றால் என்ன?

இதற்கு முன் செய்யப்பட்ட ஆய்வைப் போலவே நோயாளியை ஒரு நாற்காலியில் அமரச் செய்து அவருடைய நெற்றியை அல்லது கீழ்த்தாடையை ஆதாரமாகத் /நிலையாக வைத்து ஒரு நிலையான பொருள் அல்லது ஒளியை பார்க்கச் செய்து அதன் மூலம் பெறப்படும் விவரங்களை குறித்துக் கொள்வது. ஆனால் ஆய்வில் லேசரை

குறைந்த சக்தியில் பயன்படுத்தப்படுகிறது. இதனால் கண்ணுக்கு எந்த வித பாதிப்பும் இல்லை. இந்த சோதனையின் போது ஒரு சத்தம் ஒலிக்கும் அத்துடன் சோதனை முடிவுக்கு வரும்.

3) OCT Test என்றால் என்ன?

கண்ணில் மோசமான விளைவுகள் ஏற்படும் பட்சத்தில் அகச் சிவப்பு கதிர்கள் கொண்டு இச்சோதானை செய்யப்படுகிறது.

இதில் பங்கேற்பவர்கள் என்ன செய்ய வேண்டும்?

அதாவது அறுவை சிகிச்சைக்கு முன்னும் மற்றும் அறுவை சிகிச்சை முடிந்த 1, 3 மற்றும் 6 மாதங்களில் தொடர்ந்து வந்து மேலே குறிப்பிட்ட பரிசோதனைகள் செய்ய வேண்டும். இதற்கு எந்த கட்டணமும் இல்லை.

இந்த ஆய்வில் இருந்து எப்பொழுது வேண்டுமானாலும் நிபந்தனையின்றி விலகிக்கொள்ளலாம். அப்படி செய்யும் பட்சத்தில் உங்களுக்கு இந்த மருத்துவமனையில் வழக்கமாக கொடுக்கப்படும் சிகிச்சை பாதிக்காது.

இந்த ஆய்வில் உங்கள் மூலம் பெறப்பட்ட தகவல்கள் மருத்துவ இதழில் வெளிப்படுத்தப்படும். ஆனால் உங்கள் பெயரை குறிப்பிடமாட்டோம். மேலும் இந்த ஆய்வில் உங்கள் சம்மந்தமான மருத்துவ குறிப்புகளை மட்டும் உங்கள் அனுமதியின்றி வேறு சில ஆராய்ச்சிக்காக பயன்படுத்திக் கொள்ளப்படும்.

CONSENT FORM IN TAMIL

ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு : ஃபன்டஸ் போட்டோகிராபி, ஹைடில்பெர்க் ரெடினல் டோமோகிராபி மற்றும் ஆப்டிகல் கோகரன்ஸ் டோமோகிராபி போன்ற கருவிகளை பயன்படுத்தி விழித்திரை நரம்பு அடுக்கு தடிமன் மற்றும் பார்வையின் முக்கிய நரம்பு அளவுகளில் கரும்படலம் / கண் அழுத்த நோயின் வெற்றிகரமான அறுவை சிகிச்சையின் விளைவுகள் பற்றிய ஆய்வு

ஆய்வு எண் :

மருத்துவ எண் :

பிறந்த தேதி வயது (வருடத்தில்)

....., நான் திரு / திருமதி என்பவருடைய மகன் /மகள் ஆகிய நான் தகவல் பிரதியில் உள்ள ஆய்வைப் பற்றி விவரமாக படித்து அறிந்து கொண்டேன். இந்த ஆய்வில் என்னுடைய பங்கேற்பு நிபந்தனையில்லாதது என்றும் எந்த நேரத்திலும் நான் விலகிக் கொள்ளலாம் என்றும் அதனால் எனக்கு கொடுக்கப்படும் மருந்து சிகிச்சை எந்த விதத்திலும் பாதிக்காது என்றும் அறிந்திருக்கிறேன். நான் விலகிக் கொண்டாலும் என்னுடைய மருத்துவ விவரங்களை இந்த மருத்துவமனையின் ஆய்வாளர்கள் பயன்படுத்திக் கொள்ளலாம் என்று அறிந்திருக்கிறேன். என்னுடைய மருத்துவ விவரங்களை மூன்றாம் நபர் யாருக்கும் தெரிவிக்கப்படமாட்டாது என்றும் அறிகிறேன். எனவே நான் இந்த ஆய்வில் பங்கேற்க முழு மனதுடன் சம்மதிக்கிறேன்.

நோயாளியின் கையொப்பம்:

நோயாளியின் பெயர் :

தேதி :

சாட்சியின் கையொப்பம் :

நோயாளிக்கு என்ன உறவு :

தேதி :

மருத்துவரின் பெயர் :

கையொப்பம் :

தேதி :

APPENDIX C: DATA COLLECTION PROFORMA

Name:

Age:

Hospital Number:

Study Number:

Address:

Phone/Mobile:

Diagnosis:

Date of recruitment: **Date of baseline investigations:**
Consent: Y/N

Date of surgery:

Surgery done:

Ologen: Y/N **MMC: Y/N** **Duration:**

5-FU : Y/N

CCT:

Other details:

Expected date of first post op visit:

Actual date of first post op visit:

Expected date of second post op visit:

Actual date of second post op visit:

Expected date of third post op visit:

Actual date of third post op visit:

BASELINE/POST OP VISIT 1 / 3 / 6 MONTHS HRT
(Global parameters)

PARAMETER	RE/LE
BCVA	
IOP	
Vertical CDR	
Horizontal CDR	
Vertical disc diameter	
Target IOP	
Other features(RAPD etc)	

PARAMETERS	VALUE
Disc area	
Cup area	
Rim area	
Cup disc area ratio	
Rim/disc area ratio	
Cup volume	
Rim volume	
Cup shape measure	
Mean RNFL thickness	
RNFL cross sectional area	
Horizontal CDR	
Vertical CDR	

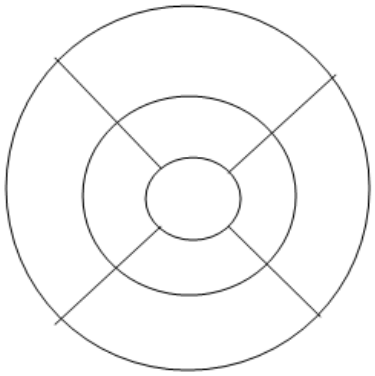
Date:

OCT

b. Optic nerve head analysis

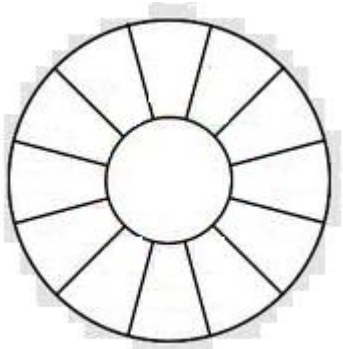
PARAMETER	VALUE
Vertical integrated rim area(volume)	
Horizontal integrated rim width(area)	
Disc area	
Cup area	
Rim area	
Cup disc area ratio	
Horizontal CDR	
Vertical CDR	

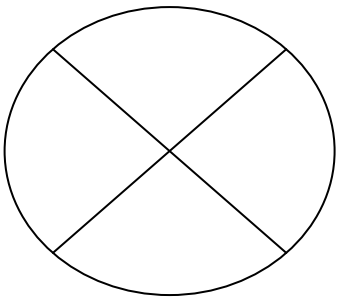
c. Macular thickness (average retinal thickness in microns)



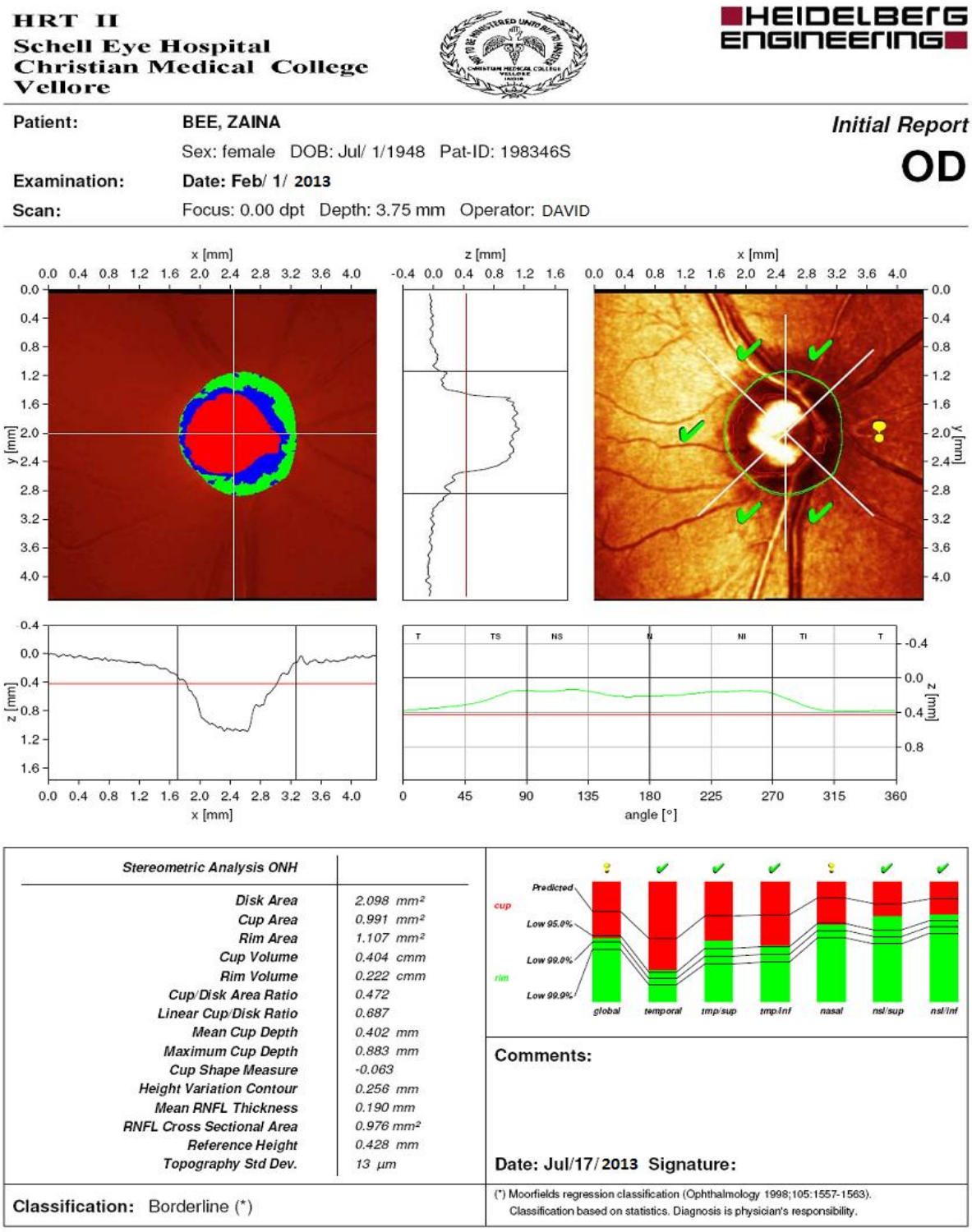
d. RNFL thickness

Average thickness:





APPENDIX D: HRT IMAGES AND REPORT



HRT II report

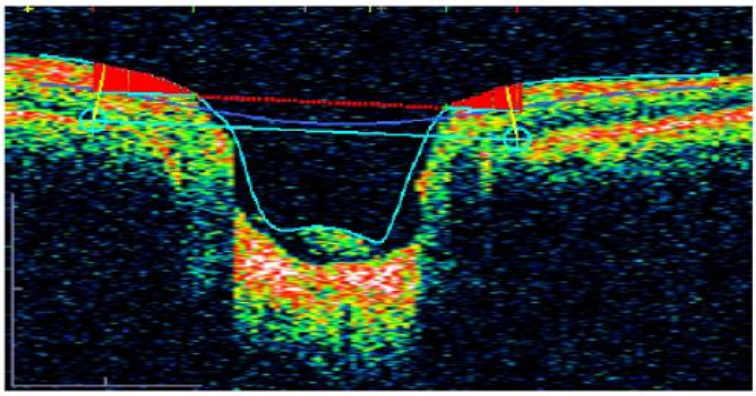
APPENDIX E: OCT IMAGES AND REPORTS

STRATUS OCT
Optic Nerve Head Analysis Report - 4.0.7 (0132)

BEE, ZAINA

DOB: 7/1/1948, ID: 198346S, Female

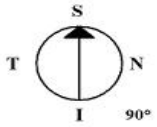
Scan Type: Fast Optic Disc OD
Scan Date: 11/18/2012
Scan Length: 4.0 mm



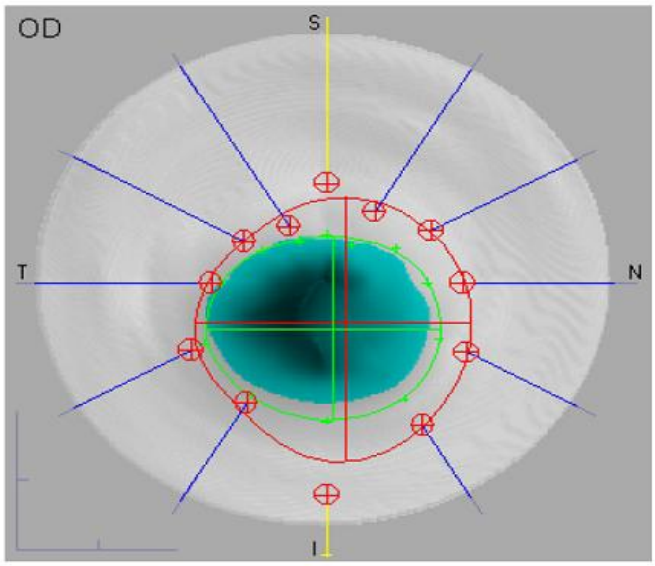
Individual Radial Scan Analysis

Rim Area (Vert.Cross Section):	0.082 mm²
Avg Nerve Width @ Disk	0.29 mm
Disk Diameter:	2.25 mm
Cup Diameter:	1.35 mm
Rim Length (Horiz.):	0.91 mm

Cup Offset (microns): 150



Signal Strength (Max 10)	10



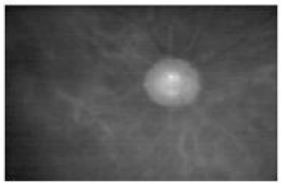
Optic Nerve Head Analysis Results

Vert. Integrated Rim Area (Vol.)	0.089 mm³
Horiz. Integrated Rim Width (Area)	1.262 mm²
Disk Area	2.471 mm²
Cup Area	1.524 mm²
Rim Area	0.947 mm²
Cup/Disk Area Ratio	0.617
Cup/Disk Horiz. Ratio	0.847
Cup/Disk Vert. Ratio	0.692

Plot Background:

☐ None ☐ Absolute ☑ Aligned and Shaded

Cup Offset for Topo (microns): 150
Cup Area (Topo): 1.29 mm²
Cup Volume (Topo): 0.348 mm³



SCAN 1 : Results not Modified.
SCAN 2 : Results not Modified.
SCAN 3 : Results not Modified.
SCAN 4 : Results not Modified.
SCAN 5 : Results not Modified.
SCAN 6 : Results not Modified.

Signature: _____

_____

Physician: CHRISTIAN MEDICAL COLLEGE HOSPITAL,VELLORE.

Stratus OCT Fast optic disc report for OD

STRATUS OCT
RNFL Thickness Average Analysis Report - 4.0.7 (0132)

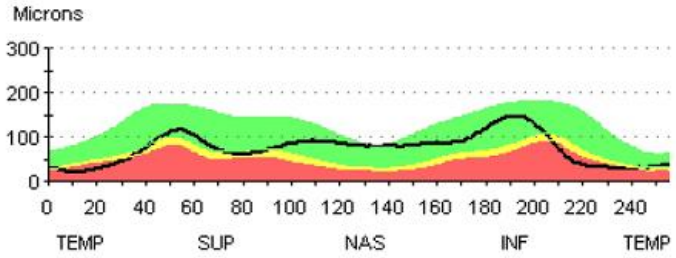
BEE, ZAINA

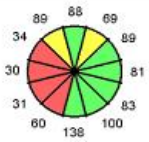
DOB: 7/1/1948, ID: 198346S, Female

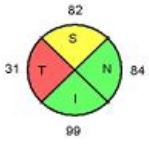
Scan Type: Fast RNFL Thickness (3.4)

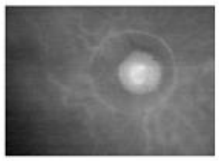
Scan Date: 11/18/2012

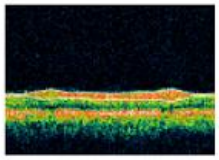
Scan Length: 10.87 mm





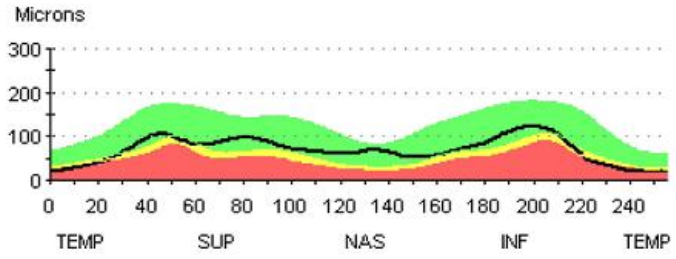


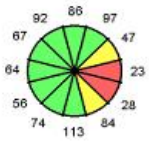


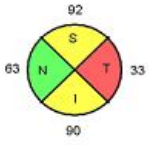


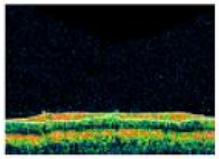
OD

Signal Strength (Max 10)	9



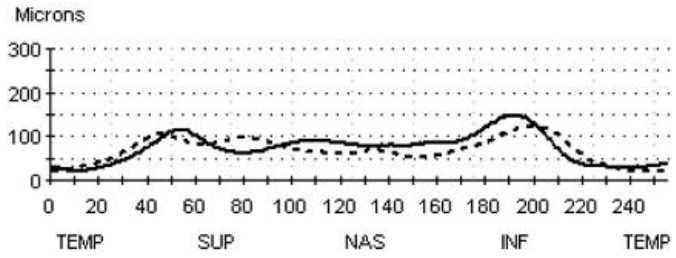






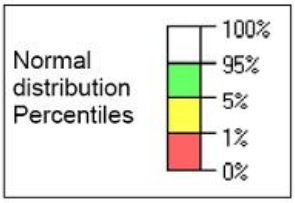
OS

Signal Strength (Max 10)	6



OD ----- OS

OD	Scans used	1, 2, 3
OS	Scans used	1, 2, 3



	OD (N=3)	OS (N=3)	OD-OS
Imax/Smax	1.27	1.16	0.12
Smax/Imax	0.79	0.87	-0.08
Smax/Tavg	3.66	3.22	0.44
Imax/Tavg	4.66	3.72	0.94
Smax/Navg	1.37	1.69	-0.32
Max-Min	124.00	101.00	23.00
Smax	115.00	106.00	9.00
Imax	147.00	122.00	25.00
Savg	82.00	92.00	-10.00
Iavg	99.00	90.00	9.00
Avg.Thick	74.36	69.37	4.98

Signature: _____

_____

Physician: CHRISTIAN MEDICAL COLLEGE HOSPITAL,VELLORE.

Stratus OCT Fast RNFL report

APPENDIX F: EXCEL DATA SHEET (MINIFIED)

The following excel sheet has been minified due to large number of parameters (over 550). The data sheet can be clearly visualized in the soft copy submitted alongwith in PDF format.