Introduction

Dear Colleague,

I am pleased to submit this small communication “Advances in the Management of Primary Adult Glaucomas” as a CME effort of Academic & Research Committee of AIOS.

Dr. Devindra Sood an eminent glaucoma worker of country has compiled all up-dated information, you need to know about primary adult glaucomas. The topic of “Infective Keratitis” is under preparation and shall be released soon.

I am grateful to Prof. H.K. Tiwari our luminous guide and President of AIOS and also dynamic Prof. R.V. Azad the secretary of AIOS for encouragement and help.

With regards,

Yours truly,

(**Dr. K.P.S. Malik**)
Chairman,
Academic & Research Committee

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This CME Material has been supported by the funds of the AIOS, but the views expressed therein do not reflect the official opinion of the AIOS.

(As part of the CME Programme)

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Published by:

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CME SERIES (No. 10)

Advances in the Management of Primary Adult Glaucomas

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Printed by :
Syntho Pharmaceuticals Pvt. Ltd.

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The current understanding of glaucoma has undergone a significant change over the last few years. Epidemiological data, newer diagnostic procedures, collaborative planned trials, basic research, better documentation and analysis of clinical data, long term follow up of patients and a better understanding of ocular behaviour and newer drugs have all contributed to the current understanding of the glaucomas.

A shift in understanding has logically lead to a change in the approach and strategy in glaucoma management. Raised intraocular pressure (IOP) has been a cardinal sign of glaucoma. The relevance of a raised intraocular pressure has to be understood in its proper perspective. In essence a raised IOP does not always need treatment. The ability to distinguish and decide when to treat and how much to treat is today a more scientific step than in yester years.

IOP no longer defines glaucoma. Both pressure dependent and pressure independent factors are responsible for the pathogenesis of the glaucomatous damage. Even though factors other than IOP are involved, IOP is the most important risk factor because it is the only risk factor which we can pharmacomodulate todate. The primary aim in glaucoma management is to preserve visual function. Lowering of IOP is only a secondary goal.

Primary glaucomas: Glaucoma is the second leading cause of blindness worldwide (1) accounting for 67 million suffers. Primary Open Angle Glaucoma (POAG) is estimated to affect 33 million people worldwide, majority of whom (about 26 million) reside in developing countries. 90-100% of those affected in developing countries are unaware that they have the disease. Visual impairement is also more severe (1,2). The estimated risk of blindness (over 12-20 years) from POAG ranges from 14.5% to 27% (unilateral) and from 7-9% (bilateral) (3-5). With an expected increase in the population and longevity, POAG is likely to become a major cause of ocular morbidity in the developing world.

GLAUCOMA IS THE SECOND LEADING CAUSE OF BLINDNESS THE WORLDOVER

Prevalence in India:

Population based studies : 12 million people in India are affected by glaucoma accounting for 12.8% of the blindness in the country. Early population based studies reported a prevalence of glaucoma between 2% and 13% (6).

Three population based surveys, with modern techniques have been recently conducted in India.

Table 1 : Comparison of results of Vellore Eye Survey and Andhra Pradesh Eye Disease Survey.

	VES	APEDS
Age	30-60 years	³ 30 years
POAG (95% CI)	0.41% (0.008-0.81)	1.62% (0.77-2.48
OHT (95% CI)	3.08% (1.98-4.19)	0.32% (0.10-0.78)
PACG (95% CI)	4.32% (3.01-5.63)	0.71 % (0.34-1.31)
Occludable Angles (95% CI)	10.3% (8.9-11.7%)	1.41% (0.74-2.09)

The Vellore Eye Survey (VES) reported a prevalence of Primary open angle glaucoma (POAG) as 0.41%, ocular hypertension (OHT) 3.08 and 4.32% for primary angle closure glaucoma (PACG). Occludable angles accounted for 10.3% of the population (7).

The Andhra Pradesh Eye Disease Survey (APEDS) reported a prevalence of 1.62% for POAG, 0.32% for OHT. Primary ACG was 0.71% and occludable angles accounted for 1.41% of the study population(8,9). The difference in the prevalence of POAG, PACG and occludable angles in the above studies can be explained by the age groups sampled, definitions of POAG, PACG, occludable angles and also the methodology used.

The Aravind Comprehensive Eye Survey (ACES) reported a prevlence of 1.7% for POAG, (95% CI 1.3 - 2.1) and 0.5% PACG (95% CI 0.3 - 0.7) (10). The reported prevalence of glaucoma in the ACES study is higher than that reported by the VES and lower than the APEDS although the CI's overlap. The VES and APEDS did not perform threshold perimetry on all participants.Another reason could be the difference in the age of the study

participants, 40-90 years in the ACES study (VES did not include people more than 60 years of age). However prevalence of POAG even in the ACES study was 0.7% (95% CI 0.5 – 1.0) amongst 40 – 60 years, similar to the VES.

GLAUCOMA IS THE THIRD MOST COMMON CAUSE OF BLINDNESS IN INDIA

The VES criteria of occludable angles (inability to visualize 180 degree of the functional trabecular meshwork) and the use of indentation gonioscopy lead to higher prevalence of PACG and occludable angles. The APEDS used the epidemiological criteria for occludable angles.

Hospital based data from India reported POAG as common as PACG, with 45 to 55% of primary glaucomas being PACG (11,12)**.** Aphakic glaucoma (37.7%) is the commonest type of secondary glaucomas reported in a hospital setting, lens induced (12.5 %) corneal pathology (12.2%), neovascular (9.6%), traumatic (8.4%) and chronic uveitis (8.2%). Steroid induced glaucoma and trauma are common causes for secondary glaucoma amongst young people. A prevalence (95% CI 5.3 – 6.6) of pseudoexfoliation was 6. 0%. The prevalence increased with age and was more in males. The prevalence of glaucoma among subjects with pseudo exfoliation was 7.5%. Pseudo exfoliation was present in 26.7% of these with POAG. A hospital based study in 1968 reported a prevalence of 34% pseudo exfoliation amongst glaucoma patients (13).

Epidemic dropsy (14) results from mustard oil contamination. It was first reported in 1877 as an epidemic outbreak in Calcutta. Widespread epidemics have been reported from India especially in Bengal, Bihar, Assam, Orissa, Madhya Pradesh, Gujarat, Maharastra and Andhra Pradesh. Delhi experienced its third outbreak in 1999. Epidemic dropsy has also been reported due to ingestion of a wide variety of oils including coconut oil, linseed oil, groundnut oil, sesame oil and gingelly oil.

The ocular presentation is often bilateral patients usually give a history of irritation and burning sensation, diminution of vision (with a steamy cornea) and colored haloes. The rise in intraocular pressure tends to develop 4-8 weeks after the onset of dropsy. The eye is white with a normal anterior chamber depth with no sign of uveitis and a high intraocular pressure. Epidemic dropsy is characterised by a sudden or insidious non inflammatory bilateral edema of the lower limbs, often associated with redness, pain and blurring of the lower limbs, often associated with redness, pain, and blurring of the overlying skin in otherwise healthy individuals. Anemia,

gastrointestinal disturbances, low grade fever, dyspnea and eventually death from cardiac failure may follow.

… Non progressive disc and field damage with IOP in the normal statistical range from a past episode of EPIDEMIC DROPSY can often make one suspect damage at low IOP …

Primary glaucomas have been classified into primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG).

Primary Open Angle Glaucomas (POAG): Traditionally POAG was characterised by the classical triad of a raised IOP, optic nerve head damage and corresponding visual field defects in the presence of open angles on gonioscopy. **Today POAG is a chronic, progressive optic neuropathy characterised by morphological changes at the optic nerve head and retinal nerve fibre layer in the absence of other ocular disease or congenital anomalies (with / without a raised IOP).**

The Problem, worldwide: Depending on the definition of POAG, the prevalence of the disease in population based studies ranged from 0.4-8.8% (15-26). Most of these studies used the appearance of both the optic nerve head and visual field as a part of the diagnostic criteria. A prevalence of 5-6% was reported by the Blue Mountain's Eye Study when optic nerve damage alone was deemed sufficient to satisfy the diagnosis of POAG (25). When both optic nerve head and automated visual fields criteria were used, the prevalence fell to 2.4%.

The current definition of POAG does not include IOP. Population based studies which included IOP in their diagnosis of POAG (15-26) have shown higher prevalence of POAG amongst whites and African Americans with higher levels of screening IOP. In 1989, Sommer discussed the importance of IOP only as a risk factor in POAG. In the Baltimore Eye Survey, 47 of the 3571 eyes with an IOP of 16-18 mmHg (0.01%) met the definition of POAG (27). Though these statistical associations are all consistent with IOP as a risk factor for POAG, they however do not prove that IOP causes POAG in all cases. There is however evidence to suggest that IOP is a causal risk factor for POAG.

Magnitude of the problem in India: The Andhra Pradesh Eye Study (8) indicated a prevalence of 2.56 % for POAG and 0.42% for ocular hypertension among 934 people more than 40 years of age. The Vellore Eye Study reported 0.4% POAG and 3.08% ocular hypertension (7). The Aravind Comprehensive Eye Survey reported a prevalence of 1.7% for POAG (10). Using recommendations defining glaucoma from the International Society of Geo-

graphical and Epidemiologic Ophthalmology, another study in a rural South Indian population reported a prevalence of 1.62% for POAG (28).

PRIMARY OPEN ANGLE GLAUCOMA: Risk factors are factors, the presence of which increases the possibility of having glaucoma.

IOP: Several studies have demonstrated that with an elevated IOP, the prevalence of POAG increases (15-19). Several population based studies have shown a consistent association between the level of IOP and POAG (L16,19,20,23,25). The Baltimore Eye Study (27) reported an increase in the strength of the association between POAG with higher IOP's. Compared to eyes with screening IOP less than or equal to 15 mmHg the relative risk for POAG was higher (12.8) with IOP's of 22-29mmHg and 39 for eyes with IOP of 30-34 mmHg.

...The relative risk for POAG rises with the increasing IOP level ...

Vascular ischemia, decrease perfusion of the optic nerve head, mechanical compression of the lamina cribrosa and decrease axoplasmic flow are all important features of glaucomatous optic nerve damage which can be caused by a raised IOP. The temporal relationship between IOP and POAG has been emphasized in the non human primate model of glaucoma (29) and also in human eyes with acute angle closure glaucoma, where a raised IOP causes glaucomatous optic nerve damage.

Kass and co workers also demonstrated that lowering the IOP in ocular hypertensives reduces the risk of developing POAG (30). The Ocular Hypertension Treatment Study (OHTS) further bolstered this view. Lowering IOP by 20% in eyes with an elevated IOP reduced the probability of developing POAG to 4.4% after 5 years, as compared to the untreated group. The treatment of glaucoma, to lower the IOP to a level where further damage to the optic nerve or visual field is prevented is coherent with a causal role of IOP (27). The possibility that IOP causes POAG is supported by the observation that eyes with higher screening IOP have a larger relative risk of for POAG (27). Likewise patients with asymmetric glaucomatous optic nerve cupping usually have a large cup in the eye with a higher IOP (31,32)

Even the collaborative Normal-Tension Glaucoma Study found that by reducing the IOP by at least 30%, a significant reduction in vision loss can be achieved as compared to controls (33).

AGE: Nearly every population based study has shown a statistical association between increasing age and POAG (15-26). Most chronic diseases are more common in the elderly population. However we do not know why POAG is more prevalent in the elderly. Genetic, biological or environmental factors may be responsible.

GENDER: There is a marked discordance amongst population based studies on the association between gender and POAG. The Framingham (28) and Barbados (23) studies reported higher rates of POAG amongst males. The Blue Mountains (26) and St. Lucia Study (24) reported higher rates in females. Others found no significant statistical association (16,19,20,).

Race: The importance of ethinicity in POAG has been demonstrated by several studies (19,17,35) showing that individuals of African heritage were at an increased risk of developing POAG. The exact cause of this higher prevalence of glaucoma in those of African origin is unknown. It is hypothesized that larger cup disc ratios (36), large discs and more nerve fibers may be contributory. The Baltimore Eye Survey found a greater prevalence of POAG in African American at each specific level of IOP, as compared to whites even though they had similar IOP distribution.

Steroid usage: POAG has a strong association with steroids. The strength of the association is reinforced by the strong tendency to have a steroid induced rise in IOP amongst POAG patients as also the connection between the glaucoma gene, MYOC (GLCIA, TIGR), and its glucocorticoid induction in the trabecular meshwork.

Family history: Population based studies have supported an association between a positive family history for glaucoma and POAG. In the Barbados Eye Study (37) undiagnosed subjects were more likely to develop glaucoma if they had a history of glaucoma in one or more siblings (odds ratio = 4.5). In Rotterdam (38) the population based familial aggregation study showed a life time risk of glaucoma in siblings and offspring of glaucoma patients was 9.2 times higher than in controls. The Baltimore Eye Survey revealed an age-race adjusted odds ratio of 2.85 for an association between POAG and a history of glaucoma amongst first degree relatives (39).

... Pressure independent risk factors have a relatively greater importance if glaucomatous optic neuropathy occurs with IOP in the statistically normal range ...

Central corneal thickness (CCT): Goldmann applanation tonometry is affected by the CCT. An increase in the CCT is associated with an artificially raised IOP, while a decrease in the CCT causes the IOP to be less than the actual IOP.

Optic Nerve cupping: The size of the physiological cup also appears to be another possible risk factor for POAG (40). Wide deep physiological cups have been observed to be at higher risk of developing glaucomatous visual field loss. The strong association of race and family history with POAG is suggestive of a significant genetic basis for many cases of POAG.

The OHTS study confirmed the contribution of age, large horizontal and vertical cup to disc ratio and higher IOP (41). It also identified the pattern standard deviation on full threshold perimetric testing and thin corneal measurements as risk factors for POAG.

Table 2: Risk factors in Primary Open Angle Glaucoma

IOP
Optic head cupping
Age
Race
Family History
Steroid usag
Thin Central Corneas
Diabetes
Systemic Hypertension
Myopia
Migraine

Diabetes Mellitus: A statistical association between diabetes and POAG has been reported in several case control studies (42,43,44). This may be because diabetics often undergo a detailed eye examination to rule out retinal involvement. The Baltimore Eye Survey did not find any statistical correlation between diabetes mellitus & POAG. However individuals where POAG was diagnosed prior to the study, a positive correlation did exist (45). The Beaver Dam (46) and Blue Mountain studies found that the odds of a diabetic having POAG were two times greater than those of a non-diabetic.

Diabetes mellitus may or may not be a risk factor for POAG. However diabetics tend to have higher IOP than non diabetics.

Systemic Hypertension: The Barbados and Baltimore study did not find a statistical correlation with systemic hypertension. However individuals with diastolic perfusion pressures less than 30 mmHg were six times more likely to have POAG than those with a perfusion pressure of 50 mmHg or more.

Myopia: Myopes have more problems with vision, need glasses and are more frequently subjected to ocular examination, thus having greater opportunity to be diagnosed as POAG. Wilson et al in a case control study have (47) reported that patients with POAG were twice more likely to have myopia than controls. The Blue Mountain Study showed a statistical association between POAG and myopia of 1.5 dioptres and more (48).

Migrane: Migraine headaches or a vasospastic tendency are risk factors for POAG (49). However this association remains controversial (50,51). Vasospasm can theoretically encourage optic nerve head damage by decreasing blood flow to the optic nerve head.

Disc Hemorrhages: Disc hemorrhages are suggestive of microinfarction and ongoing optic nerve head ischaemia. In one study 56% of eyes with disc hemorrhages had progressive optic nerve head damage as compared to 13% in eyes with no hemorrhages (52)

Pathogenesis:

RAISED IOP: A raised IOP usually results from obstruction of the aqueous humour outflow. This obstruction in POAG has been associated with alterations in the conventional outflow pathway. In the trabecular meshwork there is a decrease in the endothelial cell number (53) though cellular activity may increase with thickening of the basement membrane (54,55,56). The normal continuous loss of trabecular meshwork cells is exaggerated in POAG (53,57). Loss of the trabecular beams is associated with an increased resistance to aqueous outflow resulting in decreased outflow facility. Alteration in the endothelial cell function also contributes to decreased aqueous outflow.

Collagen abnormalities within the trabecular meshwork beam in eyes with POAG include fragmentation, orientation changes and abnormal spacing (58-60). Even the inter trabecular spaces are decreased. There is a progressive increase in **plaque** like deposits, derived from elastic – like fibres (61) and a decrease in giant cell vacuoles (62,63).

MECHANISM OF OPTIC NERVE DAMAGE: Glaucoma today is looked upon as a progressive optic neuropathy characterized by specific morphological changes (optic disc cupping) resulting in loss of the retinal ganglion cells (RGC) which can be pressure dependent or pressure independent. Ganglion cell death in glaucoma is a form of programmed cell death called apoptosis. It is a cell autonomous phenomenon, in that the death of the cell is already pre-programmed in the genes. A wide variety of hypothesis explain the pathogenesis of the optic neuropathy in glaucoma, including ischaemia of the papillary nerve head, blockage of retrograde axonal transport, alteration of laminar glial or connective tissue, direct mechanical effect on retinal ganglion cells, and now neurotransmitter (glutamate) mediated excitotoxic death of the retinal ganglion cell. Nitric acid can also trigger apoptosis. Nitric acid is found in higher concentration in the optic nerve of rats and humans with glaucoma. Inhibitors of nitric oxide formation (aminoguanidine) retard ganglion cell death in experimental glaucoma in rats. An injury can be propagated beyond its original extent by secondary degeneration. NMDA inhibitors can slow or stop this process

DIAGNOSIS:

Symptomatology : POAG patients have few symptoms in the early stages. Rarely a high IOP may cause browache. Transient corneal edema from a raised IOP may cause coloured haloes. Patients with advanced damage often have altered vision.

Evaluation: Careful determination of history and physical findings often helps in timely diagnosis. These are centred around ocular and systemic risk factors. A review of past records helps in detailing refractive error,ocular and / or systemic disease, medication used (with a special emphasis on steroid usage), intolerance to medication and previous ocular surgery. Involvement of glaucoma amongst family members and impact on quality of life, should also be inquiried.

Examination: Stereo - biomicroscopic examinaion of the anterior segment in POAG is usually normal. However slit lamp examination helps exclude secondary glaucoma with open angles. Measurement of IOP, assessing structural damage to the optic nerve, documenting functional loss with automated perimetry and evaluating the status of the angle outflow structures on goinioscopy are essential pre- requisites to diagnosis of POAG.

1) IOP: The diagnosis of POAG generally includes an IOP measurement > 21mmHg.

CURRENT SIGNIFICANCE OF 21 mmHg: The distribution of IOP in the general population as studied by Leydecker (normal IOP was statistically defined two standard deviations above and below mean, as 11-21 mmHg) is not Gaussian, but is slightly skewed towards higher IOP's (figure 1). Nearly 10% of the population over 40 years can have IOP's higher than 21 mmHg, in the presence of open angles and normal optic discs. Such individuals, who were often labeled ocular hypertension, may not develop glaucoma.

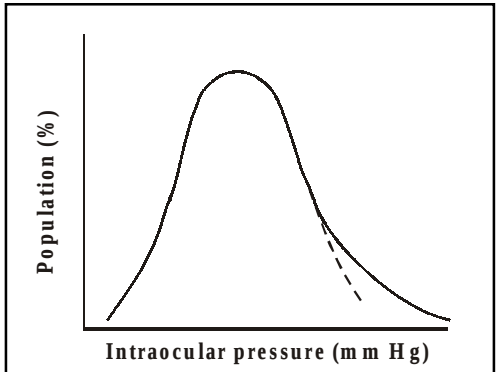


Fig. 1 : Distribution of IOP in the general population (solid line) versus Gaussian distribution (dotted line)

..... AN IOP MORE THAN 21 mmHg DOES NOT ALWAYS INDICATE GLAUCOMA .....

Classical cases of open angle glaucoma have a raised IOP, characteristic optic nerve head changes and visual field changes in the presence of open angles on gonioscopy. It is now realized that nearly 40-50% of cases of open angle glaucoma can have an IOP less than 21 mmHg but with characteristic optic nerve head and visual field changes (normal tension glaucoma). In such cases ischaemia of the optic nerve plays an important role and IOP is of secondary importance. It is thus obvious that not all cases with IOP greater than 21 mmHg can be labeled as glaucoma, just as glaucoma can exist with IOP in the normal statistical range. Normal IOP (11-21 mmHg) is only a statistical description of the range of IOP in the population, and is not applicable to the individual patient.

Mesurement of IOP:

In clinical tonometry, IOP measurement is by correlating the deformation of the globe to the force responsible for the deformation. Typically the globe is deformed by corneal indentation (indentation tonometry eg Schiotz tonometer) or by corneal applanation, resulting in surface flattening, either directly by tonometer contact (Goldmann) or indirectly by non-contact with a puff of air. Measuring the IOP by applanating the sclera has shown vari-

able results owing to non uniformity of the conjunctiva and ciliary body (64). These tonometers have been used primarily to quantitate the IOP at any particular point of time. Some designs have been adapted, in an attempt to monitor the diurnal variation of IOP. An additional tonometric technique, manometry directly measures the IOP by means of ocular cannulation and has both experimental and clinical application in special situations.

Goldman applanation tonometry (GAT) is the proven gold standard for variable force tonometry in patients with normal corneas and normal or abnormal scleral rigidity. It is based on the Imbert- Fick Law. Mounted on the slitlamp, illumination of the biprism tonometer head with a blue light from the cobalt filter, an adjustable force is applied to a standard central corneal area of 3.06 mm in diameter, after applying topical anesthesia and fluoreescein in the tear film. With this diameter, the force from the surface tension, negates the elastic force of the cornea, resulting in a more accurate grams force x 10 scale conversion to millimeters of Hg (65).

Goldmann tonometry is the GOLD STANDARD for assessing the IOP in an eye with a smooth , clear cornea

Corneal thickness above or below the normal standard 0.52 mm may also impact erroneous IOP measurements, approximately 0.5mmHg per 10 mm difference from the standard (66).

Indian studies on corneal thickness: While assessing peripheral and central corneal thickness with IOP changes in rhegmatogenous retinal detachment in 1990, a central corneal thickness of 0.5685 +/- 0.0153 mm was measured in the twenty eyes used as controls (67). Another study assessed the effect of central corneal thickness (CCT) on applanation tonometry amongst 50 normals, 25 glaucomatous eyes and 23 ocular hypertensives (69). Using the optical pachymeter a statistically significant difference in the mean CCT of ocular hypertensives (0.574 +/- 0.030mm) as compared to glaucomatous eyes (0.534 +/- 0.030mm) and normals (0.537 +/- 0.034mm) was reported. There was no difference in the CCT between glaucomatous and normal eyes. Applying the described correction factors 39% of " ocular hypertensive " eyes had corrected IOP of 21 mmHg or less. **Corneal thickness readings from the central 2-3 mm of the cornea are more replicable than from paracentral or peripheral corneal locations.**

There is only one available study assessing techniques of CCT measurements amongst normals and a glaucomatous population in Indian eyes (68). This study using optical and ultrasound pachymetery reported an error

range in IOP correction for corneal thickness to be lower with the ultrasound pachymeter (-1.2 to +1.4mmHg) as compared to the optical pachymeter (-5.6 mmHg to +8.5 mmHg).

A tight collar or tie, Valsalva's maneuver, breath holding or squeezing the lids can erroneously increase the IOP reading.

Table 3 : Central Corneal Thickness Measurements

- Are needed to correct Goldmann IOP readings,
- Thicker corneas may co relate with Ocular hypertension,
- Thinner corneas may co relate with Normal Tension Glaucoma and
- Are important while co relating IOP after refractive corneal surgery

Advantages of the Goldmann tonometry (65,70-74) include little inter examiner variability, suitable for gas filled eyes, follow penetrating keratopasty and measurements are independent of scleral rigidity. It is however unreliable on scarred, irregular corneas and with thick/thin corneas

The **TonoPen** is a miniaturized modification of the MacKay-Marg (74). The Tonopen is commercially available, battery operated and portable electronic tonometer. The tip of the TonoPen is protected by a disposable latex cover, containing a 1.02 mm diameter plunge attached to a strain gauge transducer that similarly extends beyond the footplate. When the plunger is perpendicularly flattened against the corneal surface, a voltage change is amplified by the transducer, that is digitized and stored by a single chip microprocessor if the voltage waveform notch is adequately configured.

The measurement is rejected if the microprocessor does not sense a proper shape to the voltage waveform. Two to ten valid pressure measurements are collected, as indicated by audible clicks and a beep indicates the endpoint. The mean digitized value in millimeter of mercury is displayed along the bar over a range of the coefficient of variance, from 5-20% in 5% increments on a liquid crystal readout. When readings of more than 30 mmHg are detected, the transducer sensitivity changes to accommodate the higher pressure range. Advantages of the Tonopen include (72,75-78) scarred, irregular corneas, post keratoplasty, IOP through bandage contact lens, IOP post PRK/LASIK, similar accuracy in gas field eyes upto 30 mmHg and reduced risk of, pathogen transfer. However the Tonopen underestimates

IOP > 30mmHg, over estimates IOP < 10mmHg, diurnal pressure reading unreliable for glaucoma screening.

If the detected waveforms are inadequate or variability is excessive within a 20 second interval, the TonoPen will not provide a reading and re-tapping the cornea is necessary. Clearing the tip of residual corn starch from the latex cover with an air jet and calibrating the instrument daily for proper functioning are essential pre-requites.

The Goldmann, Proton (an electronic tonometer sharing similar measurement principles to the TonoPen) and the Schiotz tonometer were compared in Indian eyes: normal (125 eyes), scarred corneas (17 eyes) and 21 eyes following keratoplasty. The Proton, in clinical practice had higher levels of accuracy than the Schiotz tonometer in normal corneas. In scarred and post keratoplasty eyes Proton and the Schiotz tonometer were inaccurate as compared to Goldmann applanation tonometry (79).

… Schiotz tonometry is less accurate than Goldmann tonometry …

Sterilisation of Tonometers: Tonometry in the presence of clinically manifest conjunctivitis and keratitis should be avoided. In recent years isolation of the human immunodeficiency virus (HIV) from the human conjunctiva and tears as also hepatitis B has renewed interest in the office sterilisation of tonometers. Techniques for Goldmann tonometer prisms include a mechanical wipe with disposable kim wipe and sterile gauze, wipe with wipes soaked (or pre soaked) in 70% isopropyl alcohol or 3% hydrogen peroxide, soaking the prism tip in 70% isopropyl alcohol, 3% hydrogen peroxide or 1:10 household bleach.

… AVOID TONOMETRY IN THE PRESENCE OF A CLINICALLY MANIFEST CONJUNCTIVITIS AND KERATITIS…

Schiotz tonometers should ideally be disassembled between each use with cleaning the barrel, the foot plate and plunger with alcohol. The test cornea also needs to be swabbed with alcohol. A more practical approach would involve keeping the base of the tonometer continuously dipped in a solution of 1: 1000 merthiolate solution. Prior to use, the footplate can be rinsed in saline / distilled water. After usage it should be replaced in the merthiolate solution (80).

… WIPING WITH AN ALCOHOL SPONGE PROVIDES ADEQUATE DISINFECTION FOR GOLDMANN AND SCHIOTZ TONOMETERS…

Measurement of Diurnal Variation in IOP

The IOP varies over a 24 hour period with a maximum between 8.00 – 11 am and a minimum between midnight and 2am.This diurnal rhythm is more dependent on the sleep cycle (81-84). The diurnal IOP can vary from 3-5 mmHg and is wider in untreated glaucoma.

The word Diurnal / Phasing typically describes this. The pressure peaks or troughs on different subjects do not occur at the same time but may vary throughout the day and are more marked in glaucoma patients.

Office Diurnal: A commonly used technique where information on the diurnal IOP variations consists of performing repeated tonometry in the clinic during working hours. IOP measurements can also be over a number of days, at different times of the day. Though office diurnal's are practical and inexpensive. There is only a 40-50% chance of detecting a pressure peak (78). IOP measurements here are limited to a single set of measurements when patients are not performing their routine activities.

… For a patient with a normal IOP and suspicious disc and / or visual field (glaucoma suspect), progressive disc / visual field damage (with good IOP control) measurement of diurnal variation of IOP is desirable

Nocturnal Diurnal: Involves measuring the IOP at various point of time at night. A combined office and nocturnal diurnal increases the likelihood of detecting a IOP peak.

Home Tonometry: Applanation and indentation tonometry can be done at home, with proper patient instruction, to obtain diurnal curves. Wilensky and co – workers used the Self Tonometer (85) to show that a large number of patients with apparently well controlled IOP, have peaks above the measured IOP. The IOP peaks were associated with progressive visual field loss, independent of the mean IOP. In certain patients, IOP peaks which may have a direct effect on vision loss, usually disappear before the patient can reach his doctor and may actually prognosticate glaucomatous progression.

In the same study, with a population having a 30% prevalence of progressive loss of visual fields with office IOP's less than 22 mmHg, 75% of patients who had peaks in IOP with the Self Tonometer had progressive visual loss and 75% of those without peaks did not have visual field progression. The Self-Tonometer is no longer being manufactured. However Proview, a non-corneal- dependent tonometer with a pressure phosphene endpoint may prove beneficial in detecting abnormal pressure peaks not recorded on an outpatient basis (86).

The timing of medication can also be individualized so that the peak effects coincides with the diurnal IOP spikes to maximally retard it.

2) Examination of the nerve head

Glaucomatous optic neuropathy is described by morphological changes in the intra papillary and para papillary region of the optic nerve head and retinal nerve fiber layer.

A) Intra papillary changes
- Disc size
- Disc shape
- Rim size & cup size
- Rim shape (Vessel signs)

B) Parapapillary characteristics
- RNFL
- Hemorrhages
- Vessel diameter
- Parapapillary atrophy (alpha and beta)

The **optic disc area** is not constant among individuals. Normal eyes can have small optic discs, while others can have large optic discs (72). Optic disc area is independent of age beyond 3-10 years. The increase in disc size from –5 to +5 diopters of refractive error is slight (87). Myopic discs have larger optic disc size as compared to hyperopia where the disc size is smaller. The optic disc is usually slightly oval. An abnormal **shape,** correlates with an increased incidence of corneal astigmatism and amblyopia. In normal eyes, the **neuroretinal rim** shows (figure 2) a characteristic conformation, based on the vertically oval shape of the disc and horizontally oval shape of the optic cup. The neuroretinal rim is the widest in the inferior disc region, followed by the superior disc region, the nasal disc area and finally the temporal disc region **(ISNT rule)**.

In glaucoma, the neuroretinal rim is lost in all sections of the optic disc with regional preference depending on the stage of the disease (88,89) - early glaucoma, neuroretinal rim loss is predominately in the inferio temporal and superior temporal disc regions, moderate glaucoma, marked loss of rim in the temporal horizontal disc region and in advanced glaucoma rim remanants are located mainly in the nasal disc sector with layer of rim in the upper nasal than the lower nasal region.

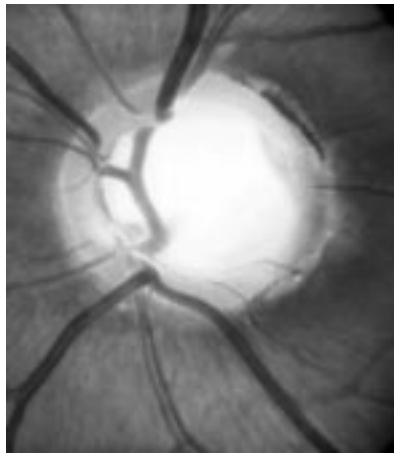
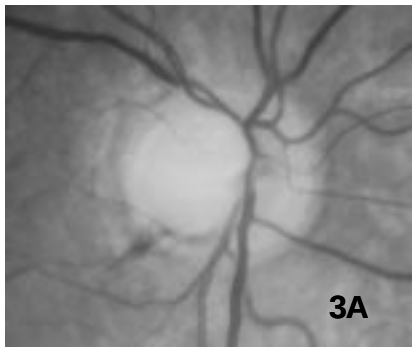


Fig. 2 : A large but normal optic disc with a large cup disc ratio.Note the normal shape of the neuroretinal rim - broadest inferiorly, followed by the superior disc region. The rim is smallest in the temporal disc region. **"ISNT" rule**

This regional loss of the disc sector (inferotemporal, supero-temopral, temporal horizontal, inferio nasal and superionasal,) correlates with progression of the visual field changes with early perimetric defects in the nasal upper quadrant of the visual field and lastly, the island of vision in inferiotemporal, the visual field in the pre final stage of glaucoma. For an early diagnosis, the infero temporal and super temporal disc sectors in particular should be checked for glaucomatous changes (89-91).

Splinter / flame shaped haemmorhages at the border of the optic disc are a hall mark of glaucomatous optic nerve damage. Disc haemorhages, rarely found in normal eyes, are present in 4-7% glaucomatous eyes. In an early glaucoma, they are usually located in the infero temporal or supero



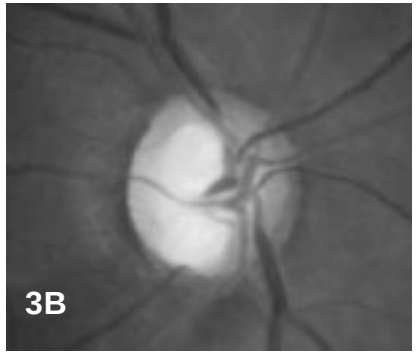


Fig. 3a: Splinter or flame shaped haemorrhages, in early glaucoma are usually located at the inferotemporal or superotemporal margin of the disc. Though not pathognomic for glaucoma they are only suggestive of a progressive disc damage in glaucoma.
Fig. 3b: Evident inferior notch

temporal disc region. They are associated with localized retinal nerve fibre layer defects, neuroretinal rim notches and circumscribed perimetric loss.

Disc haemorhages are indicative (figure 3) of glaucomatous optic nerve damage, even if the visual fields are unremarkable. In addition they are suggestive of glaucoma progression. Disc haemorhages are however not pathogenic for glaucoma. They are occur in other disc diseases like disc drusens.

GLAUCOMATOUS OPTIC NERVE DAMAGE: EARLY DIAGNOSIS

The most important variables for early (or pre perimetric glaucoma) detection of glaucomatous optic nerve damage in ocular hypertensive eyes before the development of visual field loss are:

1) Shape of neuroretinal rim (Figure 2)
2) Size of optic cup in relation to size of the optic disc.
3) Decreased visibility of the retinal nerve fiber layer.
4) Occurrence of localized retinal nerve fiber layer defects and hemorrhages.

If the rim is not markedly broader in the inferior and superior disc region compared to the temporal disc region, a glaucomatous loss of rim tissue may be suspected in the inferior and superior disc regions of the optic disc (88)

In eyes with small discs, the neuroretinal rim cannot be clearly delineated from the optic cup, so the shape of the rim cannot be well determined. In these eyes, the variable cup size in relation to the disc size is the most important intra papillary factor to detect glaucomatous optic nerve damage. (88)

GLAUCOMATOUS VERSES NON GLAUCOMATOUS OPTIC NEUROPATHY: Glaucomatous and non glaucomatous optic neuropathy have the following in common.

1) A decreased diameter of the retinal arterioles including the presence of focal arteriole narrowing
2) Reduced visibility of the retinal nerve fiber layer (88),

Localized defects in the retinal nerve fiber layer can be found in many types of non glaucomatous optic nerve damage such as in optic disc drusen, long standing papilledema. In comparison to non glaucomatous optic atrophy, the glaucomatous optic neuropathy is characteristic by an enlarging optic cup which deepens, and in a complementary manner the neuroretinal rim decreases. Enlargement of the optic cup and loss of neuroretinal rim may also be found in eyes with arteritic anterior ischaemic optic neuropathy and

in a few patients who have intrasellar tumors.

Since parapapillary atrophy is usually, not markedly increased in eyes with non glaucomatous optic nerve damage, para papillary atrophy helps in differentiating between glaucomatous and non glaucomatous optic neuropathy (88).

Several techniques have been used to evaluate changes in the optic nerve head.

Table 4 : Techniques of Optic Disc Evaluation

Technique	Advantage	Disadvantage
Direct Ophthalmoscopy	High magnification Portable Easily available Small pupil	No stereopsis
Slit lamp techniques Goldmann, Zeisis Lenses	Upright direct image No air cornea interface	Coupling fluid
60 D, 78D & 90D lenses	Convenient,good stereopsis and illumination	Virtual & inverted image Air corneal interface

A magnified stereoscopic view and a dilated pupil are preferred to visualize changes. Stereopsis is best obtained at the slit Lamp with fundus lenses like the Goldmann/ Zeiss four mirror contact lens, Hruby lens, El Bayadi lens, or the Volk 90D lens. The three dimensional view allows estimation of the cup depth, thinning of the neuroretinal rim, nerve fiber layer thickness, sloping of the cup walls and ONH tilting. A diagram aids documentation and is useful to document changes over a period of time.

While examining the optic disc a set routine should be followed Table 5.

The direct opthalmoscope provides a highly magnified view, which is useful in evaluating the nerve fiber layer thickness and also subtle changes like nerve fiber layer haemorrhages when used in conjunction with the stereoscopic techniques. The direct ophthalmoscope helps provide information in difficult situations and is indispensable in evaluating patients who are unable to withstand slit lamp examination.

... lack of stereopsis and high magnification with the direct ophthalmoscope makes it undesirable to describe optic nerve head changes ...

The emphasis should be on stereoscopic evaluation of the optic nerve head with changes in the neuroretinal rim and not just estimation of the cup disc ratio. This will aid in early diagnosis of glaucoma alone (92).

Table 5 : Checklist to assess changes in the optic nerve head

1. Determine disc size (Elschnig's canal)
2. Check for unusual disc shape
3. Determine cup / rim size in relation to disc size
4. Evaluate rim shape (smallest rim width?)
5. Check RNFL (red-free illumination)
6. Look for disc hemorrhages: Rule out glaucoma

High myopia: Rule out glaucoma

Optic Nerve Imaging Techniques in Glaucoma

The evaluation of the ONH and nerve fiber layer, essential and critical in glaucoma, until recently have been subjective with a high inter observer and intra observer variability. The parameters of IOP and automated perimetry can miss the diagnosis of glaucoma, especially in the early stages. In fact upto 40% of the ganglion cells must be lost for a detecable loss on automated perimetry because optic nerve damage is irreversible. Early detection is crucial. The objective of imaging of the optic nerve head and retinal nerve fibre layer is to precisely quantify (with maximum reproducibility) these and also help in the early detection of glaucoma.

Stereoscopic photography allows the physician to document longitudinal changes in the optic nerve head. Colour photography with a 15 degree field gives optimal magnification. Interpretation may be subjective. Two National Eye Institute sponsored clinical trials and also the Memantine Study have used qualitative evalution of stereoscopic optic disc photographs as an outcome measure indicating an acceptance of stereoscopic optic disc photography as a valid tool for detection and monitoring of glaucoma.

Evaluation of the optic nerve fibre analysis, **Scanning Laser Polarimetry (SLP), GDX VCC,** provides for a quantitative assessment of the nerve fibre layer by measuring the rotation of polarized light reflected from the retina. It is assumed that the rotation is proportional to the thickness of the nerve fibre layer and the main birefringence tissue is the retina and its birefringence is homogeneous. Birefringence from the cornea and the lens are additional confounding factors and require compensation. Recently the fixed anterior segment compensator has been replaced by a custom anterior segment birefringence compensation (ASBC).

SLP with the ASBC appears to accurately reflect RNFL structure with high resolution and reproducibility of measurements, although histological validation in human eyes is not yet available. Literature on SLP relates more to images with the fixed ASBC and hence needs to be viewed with caution. Important clinical studies with the new device with the fixed ASBC are still limited. Studies into the accuracy of ASBC, effects of any inadequate ASBC, reproducibility of measurements, diagnostic accuracy, followup and histological validation need to be conducted.

However two major applications in glaucoma for SLP with the ASBC are glaucoma detection and also monitoring progression. However it is not clear whether SLP with the ASBC will be an equally sensitive and specific monitor from early to end stage of the disease. And this needs to be investigated.

The **Optical Coherence Tomograph** (OCT) provides for high resolution cross sectional imaging of the human retina and nerve fiber layer. The nerve fiber layer measurements are automated and displayed by quadrants, clock hour and an overall mean. OCT assessment of peripapillary retinal nerve fiber layer thickness has been reported to differentiate normal from glaucomatous eyes. Available longitudinal data at present, is insufficient to make conclusions about the ability of the OCT to detect change over time.There is also no evidence at present to suggest that OCT can be used as a screening tool for glaucoma.

CONFOCAL SCANNING LASER OPHTHALMOSCOPY

The Heidelberg Retinal Tomograph (HRT), (Heidelberg Engineering GmbH, Heidelberg, Germany) is a scanning laser ophthalmoscope utilizing confocal scanning diode technology to provide topographic measurements of the optic disc and peripapillary retina (93). In a confocal system a laser beam is scanned across the retina and reflected back to a detector through a system of two conjugate pinholes, one in front of the laser source and the other in front of the detector. Through the use of algorithms that account for eyes movements, each scanned image in the series can be aligned (94).

The original HRT has been used extensively in research. The newer HRT II uses a fixed 15^0 field of view with 384 x 384 pixels per image plane and is more friendly clinically with automated fine focus and quality control checks to ensure image quality (94). Moorfields regression analysis is based on samples with a refractive error of $\pm$ 6 Dioptres and a disc size between 1.2 and 2.8mm2.

HRT II is most helpful in evaluating the optic nerve for change, for evaluating glaucomatous progression. Measurements of optic disc stereomet-

ric parameters by HRT are highly reproducible. Research suggests that there may be a subset of patients with ocular hypertension in whom sequential follow-up with HRT may reveal optic nerve head changes which predate development of glaucomatous field changes (95). Advantages of the HRT II include rapid image acquisition time, lack of need for pupillary dilation and images can be obtained through contact lenses or refractive errors can be compensated for prior to scanning.

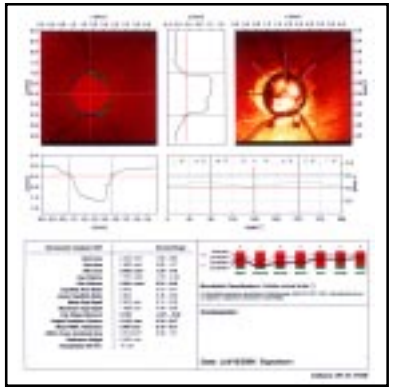


Fig. 4: HRT initial report for a glaucoma suspect

Once the scan is obtained, a contour line must be drawn around the disc, which is most easily accomplished utilizing the black and white image or three-dimensional image of the nerve on the monitor. The recommended location to draw the contour line is on the inner edge of Elschnig's scleral ring (96).

The following are displayed on the initial HRT II printed report (97) (figure 4)

A topography image, where the cup is displayed in red and the rim in blue and green, representing sloping and stable neuroretinal rim, respectively.

Reflection image of the optic nerve is divided into 6 sectors. The rim (green and blue) and the disc area (red, green and blue) for each sector are compared to a normal database and classified by Moorfield's Regression Analysis as within normal limits (signified by a green ✓ mark), borderline (yellow ! point), or outside normal limits (red x).

A graph with red and green vertical bars represents the **results of Moorfields regression analysis.** Each whole column represents the total optic nerve head area for a specific sector and is divided into the percentage of rim area (green) and cup area (red). Four black lines across the red / green graph reflect the percentage of optic nerve heads (ONH) in the normal database that have a rim area larger than the limit delineated by the line. The "predicted" line indicates that 50% of the ONH in the normal database have a larger rim area than this limit. From upper to lower, respectively, the lower lines indicate that 95.0 / 99.0 / 99.9% of the ONH in the database have a larger rim area than these limits. If the percentage of the patient's rim area is [3] the

95% limit, the respective sector will be classified with a green ✓ (within normal limits), between 95% and 99% limits with a yellow ! (borderline), and with red x (outside normal limits) if lower than the 99% limit (94,97).

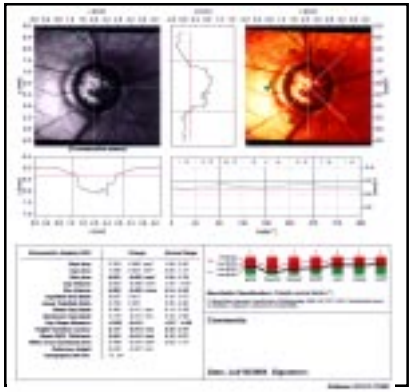


Fig. 5: HRT followup report. Areas with increased cupping are represented in red in the black and white image. Change in parameters are listed in the stereometric parameters

A table with the **stereometric analysis** of the ONH. This table provides absolute quantification of the patient's optic nerve head parameters and is not a comparison to a database. The most important parametrers here are the rim area, rim volume, cup shape measurement, height variation contour, and mean RNFL thickness, of which cup shape measure appears to be the more predictive characteristic(98) – the more negative the better. The cup shape summarizes the distribution of depth within the cup (94) and is independent of the reference plane. The topography standard deviation number serves as an image, quality control. It should be as low as possible and ideally below 30.

Mean height contour graph, where the height difference between the red reference line and the green height profile line corresponds to the thickness of the RNFL along the contour line drawn in the reflectance image. The profile line always starts temporal at 0^0 and is drawn clockwise for the right eye and counterclockwise for the left. The subadjacent red reference line indicates the location of the reference plane (separation between cup and neuroretinal rim); it is approximately at the base of the nerve fibre layer.

Horizontal and vertical height profiles- provide information about the shape, slope, and the depth of the cup and its walls. Walls that tend to be steep or deep are suspicious.

*A **FOLLOW-UP REPORT*** (figure 5) can be generated beginning with the second follow-up examination (third actual scan; the first and second scans are used to determine a baseline). The viewer will diplay a row of topographic and reflectance images of the first and subsequent examinations. The quality of all the examinations being compared should be of similar quality (assessed via the standard deviation value). For objective comparability. All follow-up examinations are matched to the initial one, correcting for possible shift, tilt, rotation, or magnification differences. These

displacements can be cause black edges to appear around the images of the follow-up examination (99). With the HRT II, the contour line drawn in the first examination will automatically be placed in the same location on subsequent tests to allow for proper serial analysis. On the printed follow-up report, the image is always in black and white, with significant changes in the ONH displayed in red (decreased height) or green (increased height) overlays. A stereometric analysis table will show any changes in the values (97).

The HRT is a patient and technician friendly technique with excellent reproducibility (HRT II) allowing it to better detect topographical changes over time. It is also the automated technique with the longest track record and largest number of publications.

Indian studies on optic nerve head : A population based study in South India studying optic disc paramters (non stereo photo manual planimetry) in one hundred and fifty three subjects reported optic disc parameters with a 95 % confidence interval : disc area 3.37mm2 (2.04 – 4.7), vertical disc diameter 2.12 mm (1.67 – 2.57), vertcal cup disc ratio of 0.37 (0.19 - 0.55) and neuroretinal rim area of 2.8mm2 (1.76 – 3.84). As compared to other studies using various methods (stereo photo manual planimetry, digitized stereo photography,stereo photo comp. planimetry and Rodenstock analysis) to assess disc area, this study reported disc areas larger than that reported by the Baltimore Eye Survey amongst blacks (100).

The only other study assessing the normal optic nerve head in Indian eyes (and the first using the Heidelberg Retinal Tomograph (HRT II) reported the average disc size as 2.34 mm2 +/ - 0.47mm2. This difference between the two studies within the same geographical region may represent a variation within the population or a variation related to the different techniques used (101).

Disadvantages include an operator dependant contour line, caucasian database and small sample size for the Moorfields analysis.

… Imaging techniques provide objective measurements of the optic nerve head alongwith statistical information for assessing changes over time …

3) Visual field examination (102) is a clinical component of glaucoma management. In the early stages perimetry is important as a diagnostic tool. Accepted definition of POAG today includes the presence of visual fields as a cardinal sign. When performed as a diagnostic tool in glaucoma the question is "Is the field normal or abnormal". And in case it is abnormal "Are the defects glaucomatous"

Automated static perimetry has been reported as being more superior to the Goldamnn perimeter to documente and also demonstrate progression of visual field defects (103). The sensitivity of the visual field is by determining the threshold value at each point by the bracketing technique (4-2 on the Humphrey and 4-2-1 on the Octopus perimeter). After presenting a light stimulus the machine waits for a yes / no response. If the stimulus is not seen, the intensity of the light seen is increased in steps of 4dB, till it is seen (machine records this as supra threshold level). Subsequently, light stimuli are decreased in steps of 2dB till the stimulus is not seen (infra-threshold). Octopus perimeters make one more movement in steps of 1dB. The actual threshold is between the supra-threshold and infra threshold.

Newer Strategies: Threshold determination at each point of the visual field is tedious and time consuming. Because by definition threshold is tested by the staircase algorithm, where every patient can see only 50% of the stimuli presented, newer techniques aim to make the procedure as short as possible, to ensure that the patient maintains concentration and thus provides better reliability.

Swedish Interactive Thresholding Algorithm (SITA) is similarly based on the fact that a response at one location has implications at the point tested and also its neighbouring points. Just as one tested point is normal, other points on the visual field are likely to be normal too.

Tendency Oriented Perimetry (TOP) is available on the Octopus perimeter and takes advantage of each response of the patient five fold. It tests and adjusts the location where the stimulus is presented and assess the threshold of the four neighbouring locations by interpolation.

Several threshold tests are available on the two commonly available Octopus and Humphrey perimeters. In each test a certain number of points can be tested. The number of points tested in a given test is actually a compromise between between the time applied and precision,which depends on the type of damage looked for as well as the diagnostic and therapeutic implications resulting therein. The response at each thresholded point is compared with a group of normal patients. The likelihood of such a response in this population of normal patients is expressed as a probability symbol for each tested point These probability symbols increase in significance from a set of 4 dots to a black box, p<5%, <2%, <1% and 0.5%. A blackened box indicating that few normal subjects will have that score, does

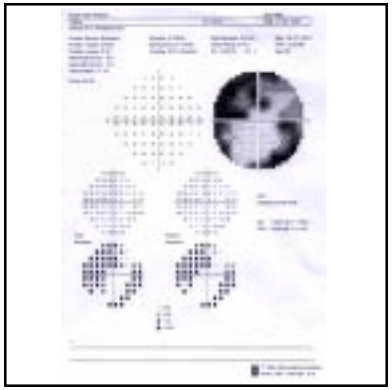


Fig. 6: Humphrey single field printout with a moderately advanced glaucoma.

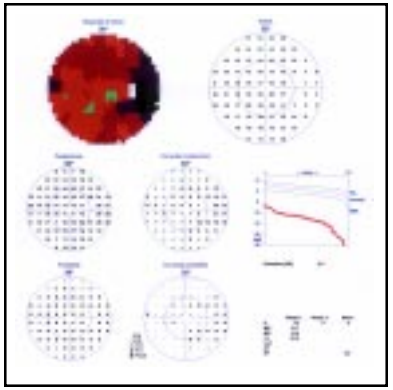


Fig. 7: Octopus single field printout from a patient with a moderately advanced glaucoma.

not necessarily correspond to an absolute defect. Many points with p<0.5% are relative defects, their actual threshold is available from the raw data.

TEST PROGRAMMES: The standard programmes on the Humphrey are the 30-2, 24-2, 10-2 and the macular grid program.In the 30-2 the central 30 degrees of the visual field are tested. It consists of 76 points 6 degrees apart on either side of the vertical and horizontal axes, such that the innermost points are three degrees from fixation.. In the the 24-2 program 54 points are examined. It is near similar to the 30-2 except that the two peripheral nasal points at 30 degrees on either side of the horizontal axis are included while testing the central 24 degrees. The 10-2 programm tests 68 points 2 degrees apart in the central 10 degrees. This program helps to assess and followup fixation characteristics in patients with an advanced disease alongwith the macular test which examines sixteen points in the central five degrees, each being 2 degrees apart. The efficiency and results of an examination are reflected by the location of the points tested.

The two commonly used programs on the Octopus are the G1X and the G2 which test 59 locations in the central 30 degrees. Here the test points are concentrated in the central field, arcuate region and nasal midperiphery to maximise detection of significant changes Fixation characteristics are assessed with the macular programme M2X which tests 45 locations, in the central 4 degrees, which are 0.7 degrees apart.

There are eight parts (reproducibility, reliability , gray scale, total deviation and pattern deviation plot, numeric data, global indices and lastly the glaucoma hemifield test)

to the **Humphrey single field printout** (figure6). Each has to be examined serially before drawing a conclusion (104 – 106).

The **Octopus single field printout** (figure 7) again uses the seven in one printout and is near identical to the Humphrey single field printout. A systematic and sequential approach reproducibility, catch trials (reliability), grayscale, comparison, corrected comparison, numeric data visual field indices and Bebie ' s Curve helps in interpretation. As before there are eight parts to the single field printout. Each has to be examined serially before drawing a conclusion (106).

After determining the presence of the disease visual field examination is used to stage the disease. Shallow / isolated field defects are characteristic of early glaucoma, whereas extensive deep deficits, encroaching fixation are characteristic of late or end stage glaucoma.

In patients with mild / moderate glaucoma visual field examination is usually to determine if disease progression has been halted. This would also hold true for patients with advanced glaucoma. In advanced glaucoma, assessing fixation characteristics is important to plan ahead.

How often should the fields be done ? This is a question often asked in glaucoma management. Though there is no consensus guidelines do exist.

(1) If the results of the field test are sufficient to confirm the diagnostic conclusion, fields may be repeated at least once more (36). A change in therapy on the basis of a single abnormal visual field test is only rarely appropriate.

(2) Ocular hypertension : Establish a baseline and perform followup fields on the basis of degree of risk for developing glaucoma. Patients with low IOP, negative family history, or optic nerves that appear healthy, test every one or two years. Patients with unstable high IOP or other risk factors, every 3-6 months.

(3) Stable glaucoma : Initially every 6-12 months. Patient compliance needs to be kept in mind. Visual fields by measuring the cumulative damage are sensitive to detect progression especially when IOP appears to be well controlled (assessment of compliance).

(4) Unstable glaucoma : One can ask for several fields within a span of few months. This would hold good people who have a relative contraindication to surgery.

WHILE ASSESSING THE VISUAL FIELDS THE FOLLOWING SHOULD BE KEPT IN MIND

- After the first field test the patient becomes more proficient. The resulting improvement in the fields is called " learning curve '. Thus first tests in an inexperienced patient may be taken with caution . More so if they do not correlate with the disc status .
- To be clinically significant the visual field should be reproducible.
- Miotic pupils and media opacities cause a generalised depression of the visual fields .
- Cataracts in particular are considered to cause a diffuse field loss which can be determined by the total deviation plot. Localised field defect from cataract , but mimicking the focal loss of glaucoma has also been reported (104).
- Changes in the visual field must corelate with changes in the optic nerve head.
- Unexplained visual field defects must be substantiated by a clinical evaluation of the retina , optic nerve or visual pathways .

5) Aqueous outflow structures are typically open on gonioscopy. Its important to rule out intermittent closure in an angle which is open with a tendency to close. Likewise when dealing with an asymmetrical rise in IOP, traumatic angle recession also needs to be excluded.

... Gonioscopy to rule out closure should be done every time a raised IOP is documented ...

5) Ocular blood flow : Glaucomatous optic neuropathy can occur from pressure dependant and pressure independent factors. Pressure independent factors may be related to optic nerve head blood supply.

This is indicated by the presence disc haemmorrhages, retinal vein occlusion, association of normal tension glaucoma (NTG) with migraine, vasospasm and Raynaud's phenomenon, systemic hypotension, nocturnal dips in diastolic blood pressure, myocardial and cerebral infarcts, blood loss and altered coaguibility.

Vascular risk factors should be taken into consideration in the management of intermittent glaucoma when the intraocular pressure is never more than 21 mmHg (diurnal variation) with a normal central corneal thickness and when visual fields show severe and progressive alterations.

Methods to assess ocular blood pressure include fluorescein angiography, scanning laser ophthalmoscopy, videography, laser Doppler velocimetry, laser speckle phenomenon, blue field entoptic phenomenon, pulsatile ocular blood flow, colour Doppler imaging and oculodynamography.

Current status: At the present time role of blood flow measurement influencing clinical decisions in relation to glaucoma management and also changes noted with drugs are unclear. These techniques remain more of research tools.

Table 6 : Differential Diagnosis of POAG

Diagnosis	Differentiating Features
Normal-tension glaucoma	IOP < 21 mm Hg on diurnal testing
Creeping angle closure glaucoma	Closed angle on gonioscopy
Ocular hypertension	Lack of optic nerve damage
Pseudoexfoliative glaucoma	Exfoliative material seen on lens capsule with dilation, irregular trabecular pigment
Steroid-induced glaucoma	History of steroid use
Pigmentary glaucoma	Iris transillumination defects, concave iris contour, marked trabecular pigment
Undiagnosed traumatic glaucoma	Subtle angle recession, pigment deposition in angle; history of trauma
Juvenile onset glaucoma	Anterior iris insertion
Mild inflammatory glaucoma	Subtle anterior chamber cells and
Elevated episcleral venous pressure	flare Dilated episcleral veins

Management:

Principles

1) One of the important principles in the management of glaucoma, which must be clearly defined and understood by both the physician and the patient deals with

(1) What glaucoma is

(2) What the therapeutic goal in glaucoma is

What is glaucoma ?

In glaucoma damage to different eye tissues is common, however the primary concern is the damage to retinal ganglion cells and the optic nerve head. POAG put simply is damage to the optic nerve head with the glaucomatous cupping, at least partially related to IOP.

What is the therapeutic goal in glaucoma ?

The objective of treatment (irrespective of the disease) is to maintain or enhance a person's health. In the context of glaucoma this would involve maintaining or enhancing the health of the person, restoring or at least preventing visual loss and enhancing the person's emotional, spiritual, psychological and physical health without causing any damage by the therapeutic modalities used. That is to prevent further damage of the retinal ganglion cells.

To date, the only proven method to prevent damage to the optic nerve head is by reducing the IOP.

2) Awareness of goal of therapy is improvement or maintenance of patients health.

3) All treatments have side effects hence no treatment can be justified without assessing the risk to benefits of treatment.

4) Assess the clinical course of the disease. In early stages, there is ample time to make a decision. For many years, it was assumed that treating patients with a raised IOP was beneficial, because it was believed that those with raised IOP developed visual field loss and become blind. Most patient's with raised IOP were then treated. The amount of damage caused to the patient by treatment was probably more than that caused by the glaucoma itself. However, had they not been treated 90% of those individuals would never have developed damage to the ONH, while the treatment itself caused unnecessary problems. Only 5-10% of ocular hypertensive's in the OHTS actually developed visual field loss, the possible benefit of treatment would need to be assessed more meaningfully.

Ocular hypertension

Traditionally OHT has been defined by an IOP > 21 mmHg in the absence of glaucomatous optic nerve damage and visual field loss with open angles on gonioscopy. Since there is a strong association between IOP and glaucoma, these patients are at risk of developing such changes with time and warrant regular measurement of IOP and examination of optic nerve damage. However not all patients are at risk of developing POAG. There is also no way of predicting with certainity who will progress on to POAG.

… gonioscopy to rule out intermittent angle closure glaucoma is a must, more so in the Indian scenario …

Elevated IOP, abnormalities of the optic nerve head, black race, advancing age, myopia, family history of glaucoma, and cardiovascular disorders are significant risk factors for development of the disease. However it is important to know that no single risk factor or group of factors has yet been able to predict the development of glaucomatous damage with reliability.

Most treating physcians would prefer to initiate treatment at a certain level of IOP even if the optic nerve and fields are normal based on the belief that beyond that pressure, there is a greater likelihood to develop glaucomatous damage, thus justifying treatment. Gold mann (107) preffered starting treatment at an IOP level of 25 mmHg. Others have suggested 30mmHg as a guideline for initiating treatment in the absence of any apparent damage.

…Thicker corneas may co relate with Ocular hypertension…

Situations where initiation of treatment at low IOP can be considered include, in addition to risk factors described earlier, venous occlusion, one eyed, unlikely to come for followup and where disc and field assessment is not possible.

In respect to trials it is important to use the **NUMBER NEEDED TO TREAT (NNT)** to extrapolate the data from trials to the individual patient (108).

NNT tells us the number of patients we need to treat with a particular drug or procedure to achieve one benefit as compared to an alternative approach . NNT is obtained from the absolute risk reduction .

In the Ocular Hypertension Study (OHTS) 1637 patients with an IOP >21 mmHg, no disc or visual field damage were subjected to a 20% reduction in IOP versus observation for visual field loss and nerve damage (109). At the end of 5 years a 20% reduction in IOP reduced the risk of developing field loss from 9.5% to 4.4 %.

For patients recruited in the OHTS, NNT is 20. Implying that 20 patients with ocular hypertension need to be treated for five years to prevent one patient from progressing to early POAG. The rate of conversion of ocular hypertensive's to POAG is approximately 1% per year (110-112). OHTS suggested a conversion rate of 2%. The cost of treating such a large number of patients most of whom would not even progress to POAG would not justify the efforts.

However if we look for subgroups where the absolute risk reduction is higher and hence the NNT is lower, the cost of treatment and their justification would be more acceptable.If an IOP more than 25.75 mmHg was considered, the risk of progression in these patients is three times higher and the NNT is three times lower – six patients. This would be more acceptible. In the same study, patients with IOP more that 26 mmHg and corneal thickness less than 555 micrometer, the rate was over 7% per year (36% after 5 years of follow up)

Ophthalmologists are frequently confronted with treatment options shown to be **statistically significant or better** than those in vogue. Its important to remember that statistical significance does not suggest clinically significant or better.

… Statistically significant does not mean clinically significant …

All patients with an IOP more than 21mmHg do not need treatment. It would perhaps be reasonable to say that all IOP's more than 30 mmHg need be treated. In the presence of risk factors described, treatment may be started at lower IOP.

Ophthalmologists should take into account the clinical significance of the employed treatment modalities however high tech, whatever the sales pitch, and however strong the peer or market pressure maybe (108).

POAG: Though there is enough evidence that the damage in glaucoma can be pressure dependent or pressure independent, IOP is the only factor which can be modulated to date.

...IOP is the only the factor which we can modulate to date…

The aim of treatment today is to lower the IOP to a level where the rate of loss of ganglion cells does not exceed the loss of ganglion cells from the

normal age related.

decay, without affecting the patients quality of life. This level of IOP is called **target pressure**.

… In glaucoma , Primary aim is to preserve visual function Control of IOP is only a secondary goal …

CHOOSING A TARGET PRESSURE : Although it is difficult to specify exact guidelines for target IOP levels, the following levels may be used as a reasonable guide (90)

1. IOP level prior to treatment: Any IOP greater than 30 mmHg should be reduced to at least the low 20s.

2. Optic nerve related damage:

a) Eyes with cup-to-disc ratios greater than 0.5, slight asymmetry of the cup-to-disc ratio or IOP, high myopia, a strong family history of glaucoma, or African ancestry should have IOPs below 18mmHg.

b) Patients with early glaucomatous optic disc damage and visual field loss above or below central fixation should have IOPs below 18 mmHg.

c) Patients with moderate to advanced glaucomatous optic disc damage (cup-to-disc ratios greater than 0.8) and superior and inferior arcuate scotomatous visual field loss should have IOPs consistently below 15 mmHg (many would choose a target of 12mmHg)

d) Patients with advanced glaucomatous optic disc damage (cup-to-disc ratios greater than 0.9) and extensive visual field loss within the central 10 degrees of fixation require an IOP below 12 mmHg.

3) Rate of progression of glaucoma

4) Age of patient

5) Life expectancy of patient

6) Presence of other risk factors necessitates lower IOP.

The target pressure varies amongst patients and may need to be modified during the course of the disease, if damage to the ONH progresses despite IOP's within the desired target range.

Treatment

A) Intraocular pressure can be reduced either by decreasing the amount of aqueous humor produced by the ciliary body or by increasing its outflow

through the trabecular meshwork, through the uveoscleral pathway, or through a surgically created pathway.

Treatment is usually begun with a topical drug. If necessary, other topical or systemic drugs are added. When drugs fail to control the intraocular pressure, laser energy applied to the trabecular meshwork (laser trabeculoplasty) may be used to increase aqueous outflow. When drugs and laser trabeculoplasty fail to control the intraocular pressure, a new route for aqueous egress can be created surgically.

MAJOR CHALLENGE OF GLAUCOMA THERAPY … MAXIMIZE BENEFITS AND MINIMIZE THE RISKS AND PROBLEMS …

MEDICAL TREATMENT is both, an art and a science. The goal of treatment is to preserve visual function. Lowering the IOP is only a secondary goal. It is necessary to tailor the treatment to the needs of the patient (113) and when doing so, the following need to be kept in mind -

A) The target tissues of topically applied ocular hypotensive medication are within the eye. Ocular conditions which can limit bio availability such as tear film deficiency, corneal scarring, chronic non-specific blepharoconjunctivitis and intra ocular inflammation and may co-exist.

B) Patient's compliance with instructions for instilling eye drops can be improved by

(i) Educating patient about nature of the disease

(ii) Emphasizing need for life long treatment.

(iii) Assessing patient's ability to instill eye drops correctly and in accordance to dosage schedule.

(iv) Educating patient about possible side effects

(v) Avoiding eye drops with specific side effects, on individual patients.

(vi) Use drops which affect patients daily routine minimally.

(vii) Can the treatment regimen maintain the desired target IOP for 24 hours in a day

(viii) Is the patient amenable to follow up to assess the reponse to treatment.

(ix) Simpler the treatment regimen, better the compliance.

(x) Fewer side effects mean better patient compliance

(xi) Topical preparations contain preservatives which may cause conjunctival inflammation and cytotoxic effects on the ocular surface. Preservative free preparations would be ideal, particularly when multiple drugs are being used. However no such drugs are available in India.

Most drugs for glaucoma are applied topically. Because of the brief contact time and the strong protective barrier of the eye, the drug solutions need to be concentrated. Excess drug drains through the nasolacrimal duct into the nose, where it may be absorbed into the systemic circulation. For example, Timolol administered to one eye enters the bloodstream in a concentration sufficient to cause a measurable decrease in intraocular pressure in the opposite eye (114,115). **Patients who use topical drugs should be taught to occlude the nasolacrimal duct with either digital pressure or simple eyelid closure for about five minutes, this maneuver increases intraocular drug concentrations and decreases systemic concentrations (116).**

There is no single accepted drug of choice in glaucoma therapy. The initial drug of choice could vary depending on the likely compliance with treatment, socioeconomic and health status of the patient, efficacy of the drug and the geographical location of the treating physcian (Table 12). The drug given initially to patients with most types of glaucoma is a non selective, topical beta adrenergic-antagonist drug, such as Timolol maleate (in the absence of any contraindication), because of the excellent pressure lowering efficacy, long duration of action, and few ocular side effects of this class of drugs. A second drug, if needed, might be a prostaglandin analogue (such as Latanoprost / Bimatoprost) or an alpha 2 adrenergic agonist (Brimonidine). **However the choice of the initiating drug could also be prostaglandin analogue or selective alpha 2 adrenergic agonist**s.

Topical carbonic anhydrase inhibitors (such as Dorzolamide) constitute the third choice. Cholinergics like Pilocarpine, have often been relegated to the last because of their ocular and visual side effects. However in the Indian context they provide effective IOP lowering which is cost effective. It is important to select the right candidates – aphakes and pseudophakes who are not high myopes.

When therapy with a topical drug is instituted, it is to be applied to one eye, with the opposite, untreated eye used as a control. This method makes it possible to determine whether any change in intraocular pressure is due to the drug or to the normal variation of intraocular pressure. However this is usually not possible in the Indian scenario.

If there is no response, the drug should be discontinued in order to avoid unnecessary cost and side effects. If there is a substantial decrease in intraocular pressure but the pressure remains high, another drug should be

added. Different classes of drug have additive effects on intraocular pressure (117-118). Exceptions are nonselective beta adrenergic-antagonist drugs and nonselective adrenergic agonist drugs, which have little additive effect when given together (118,119). Cholinergic drugs and Prostaglandins with adequate spacing can be used together.

Table 7 : Recommended washout period for topical drugs

Beta Blockers	:	2-5 weeks
Parasympathomimetics (Pilocarpine)	:	1-3 days
Sympathomimetics	:	2 weeks
Topical Carbonic anhydrase inhibitors	:	1 week
Systemic Carbonic anhydrase inhibitors	:	1 week
Prostaglandins / Prostamides	:	4-6 weeks

(xii) Multiple drops are less likely to be instilled correctly as compared to single preparations.

(xiii) Combination drops and more likely to be instilled correctly than drops from multiple bottles.

(xiv) Fixed drug combinations offer the advantage of less toxicity by preservatives and lower costs, than fixed preparations

(xv) Combination therapy with identical mechanism of action should be avoided.

Although there are numerous medications available with different modes of action, about 2/3 of patients require combination treatment. With monotherapy a 25 % reduction can be expected in the relative IOP. From combination therapy 35% and from maximal medical therapy 40% of IOP reduction from baseline.

... USE THE LEAST TREATMENT TO ACHIEVE THE DESIRED OUTCOME ...

Maximal Medical Therapy (MMT) : When patient is on representative medication from each of the of available groups of antiglaucoma medication.

Maximal Tolerable Medical Therapy (MTMT) : MMT where drugs to which the patient is intolerant, have been excluded, in an effort to achieve medical control of IOP.

Systemic carbonic anhydrase inhibitors may be added if the IOP remains uncontrolled with MMT or in situations where the IOP is extremely elevated. The patient's tolerance may dictate whether these medications are used for a short or long time. Because of there potential for side effects they are not used on a long term basis.

Laser treatment

Most patients with POAG can be controlled by antiglaucoma medications. Alternatively, argon laser trabeculoplasty (ALT) / selective laser trabeculoplasty (SLT) provides a clinically significant reduction of IOP in approximately 75% of initial treatments (120). The advantages of trabeculoplasty over medical treatment include lack of systemic adverse effects, minimal patient compliance, and decreased incidence of ocular problems that could possibly compromise subsequent surgical therapy (121).

Because it lacks the complications of filtering surgery, trabeculoplasty should also be considered for patients inadequately controlled on maximum medical therapy. However, it seldom reduces the number of required glaucoma medications. The AGIS noted that, in African American patients uncontrolled by medical therapy, initial treatment with ALT provided better preservation of visual function than trabeculectomy.

Indications for ALT are :-

1. Patients who are poor candidates for conventional medical management.
2. Patients in whom a target IOP level is unlikely to be achieved with topical medications.
3. Visual field loss such that any further progression would affect the patient's quality of life.
4. Patients who have a known rate of progression, such that quality of life would suffer unless rapid IOP stabilization occurs at a target pressure level.

Surgical treatment

Glaucoma surgery is needed in patients who have a progressive visual field loss or optic nerve damage on MTMT. Indications for primary filtering surgery include (122):

1) Patients who are poor candidates for conventional medical treatment.

2) Patients in whom the taget IOP is unlikely to be achieved with topical medications alone.

3) Visual field loss is such that further progression is likely to affect the patients quality of life

4) Patients with rapidly progressive glaucomatous optic neuropathy where quality of life would suffer unless rapid IOP lowering occurs to the desired target level.

Filtering surgery reduces the IOP and often eliminates the need for medical treatment. Although effective in 85 to 95% of previously unoperated eyes, the potential success of the operation must by measured against the potential effect of complications on the patient's quality of life.

Although long-term control is often achieved with filtering surgery, some patients may require repeat surgery or supplemental medical management, or both. Glaucoma surgery combined with cataract extraction, may be indicated in patients who require visual rehabilitation with cataract extraction, in addition to IOP lowering.

Aqueous drainage devices are generally reserved as a last resort for patients with glaucoma that is refractory to standard filtering surgery. This includes patients with extensive conjunctival scarring, chronic inflammation, and ocular trauma. IOP lowering with glaucoma drainage devices is generally not as effective as with filtering surgery. Cyclophotocoagulation is another alternative for patients with glaucoma that is refractory to other interventions and where the visual potential is poor.

The Indian Perspective :

In the late 1980's a hundred patients, with open angle glaucoma on treatment with any three of the then available topical drugs pilocarpine, timolol and epinephrine for an average of 3.3 years were assessed (123). The reported objective and subjective effects of long term medication were negligible. Most of the participants had a monthly income between Rs. 1000 – 2000. Only 18 % had an income more than Rs. 2000/-. The financial constraints were considerable. More than 70 % prefered laser and surgical options because of the cumbersome schedule and financial burden. The visit to the clinic was considered a time consuming process.

Today most of the newer antiglaucoma medications are available in India. Even combination drugs (pilocarpine with timolol and latanoprost with timolol are available). Topical dorzolamide too has become available.

However there are no published articles on the efficacy of newer drugs in Indian eyes. A prospective, non randomized, open label multicentric trial in 150 Indian patients with POAG and OHT has demonstrated a 35.25% IOP lowering from baseline on treatment with latnoprost (Xalatan 0.005%) after three months(6).

Results on outcome of ALT in Indian eyes are limited. An editorial in 1990 (124) revealed that few centers were indulging in argon laser trabeculoplasty. In a prospective trial comparing the efficacy of ALT with Pilocarpine 2% in 38 eyes with POAG, the fall in IOP post treatment at various follow up intervals was no different from the Pilacarpine treated eyes (125).

The socioeconomic status and need for long term treatment and followup (126) have often dictated the need for a primary trabeculectomy. The long term IOP control in Indian eyes following trabeculectomy has not been satisfactory, more so in high risk groups (127-128). Mitomycin is the preffered pharmacological adjuvant of choice for most glaucoma specialists in the country. 50% of the glaucomatologists in India would prefer some form of pharmacological adjuvant even with primary surgery. Similary most favor trabeculectomy to non penetrating surgery (6).

The complication rate following trabeculectomies has decreased and the drive to reduce this further is on (124). The ocurrence of shallow or flat anterior chambers postoperatively can now be done away with by applying sutures to the scleral flap, maintaining the anterior chamber in the early postoperative phase and by using argon laser suturolysis / releasable suture to titrate, depending on the patients IOP and chamber depth in the post operative period. 57 eyes of 56 patients with advanced glaucoma underwent trabeculectomy with 5 FU. An IOP less than 16mmHg was achieved without hypotensive medication in 73.7% of cases with a mean followup of 7.1 months.The commonest complication encountered was a superficial punctate keratopathy (129). A pilot trial of intraoperative 5FU with trabeculectomy in 13 eyes of 12 patients with a mean followup of 9.54 +/- 5.17 weeks, reported two patients developing shallow anterior chambers with choroidals postoperatively (130). Short term results of 5FU preoperative / postoperative achieved lower IOP than controls (131). There is currently no evidence in literature to confirm the role of artificial drainage devices as a primary procedure in most glaucomas (132).

Table 8 : Collaborative planned trials in glaucoma

Name	Study Design	No. of Patients	Follow up Duration	Results
Ocular Hypertension Treatment Study109-112	IOP>21 mmHg, no disc or VF damage. Effect of 20% medical lowering of IOP vs observation on visual field loss/ nerve damage	1,637 (25%) black	5+ years	20% lowering of IOP reduced risk of developing glaucomatous VF loss from 9.5% to 4.4%. Baseline age, disc damage, IOP, pattern standard deviation and corneal thickness good predictors for conversion to POAG.
Early manifest Galucoma Trial (EMGT) (132)	Newly diagnosed POAG; treatment with ALT plus beta blocker vs no treatment		4+ years	25% decrease in IOP from baseline and maximum absolute 25mmHg reduced risk of progression by 50%. Treatment beneficial for all groups of patients. Risk of progression less with larger initial drop in IOP Some patients did not progress even after several years of treatment.
Collaborative Initial Glaucoma Treatment Study (CIGTS) (135,136)	Newly diagnosed POAG, immediate filtering surgery vs initial treatment with medication	607 (38% black)	5+ years	No difference in VF change between treatment modalities. IOP lower with surgery Higher rate of cataracts with filtering surgery
Glaucoma Laser Trial (GLT) (137)	Newly diagnosed POAG	203	6-9 years	Initial laser trabeculoplasty found as effective as initial topical Timolol to lower IOP and preserve vision
Advanced Galucoma Intervention Study (AGIS) (138,139)	Black and white patiens with advanced POAG, laser trabeculo-plasty first vs	581 (57% black)	7 years	Greater IOP reduction with trabeculectomy first. For black patients, better visual preservation with laser first; for white patients,

Name	Study Design	No. of Patients	Follow up Duration	Results
	traveculectomy first, followed by opposite intervention if first intervention fails			better visual preservation with trabeculectomy first. Low IOP associated with reduced visual field defect progression
Normal Tension Glaucoma Study (140,141)	Combination of Medical, laser and surgical treatment to produce a 30% reduction in IOP vs no treatment in patients with progression normal tension glaucoma	140	5 years	Reduction of normal pressures by 30% slowed the rate of glaucomatous progression in a significant number of patients.

B) The end result in glaucoma is irreversible damage to the optic nerve head. Since the end result is damage to the retinal ganglion cells and because factors other than IOP can be responsible extensive research in vitro and in vivo is ongoing to detect **Pharmacological interventions aimed at preventing retinal ganglion cell death (neuroprotection). Some of these include include :**

a) Prevention of initiation of apoptosis programme by brain derived neurotrophin delivery to RGC, Forskolin 6 increases level of cyclic AMP and signal transduction inducers.

e) Protection of undamaged but at risk axons and ganglion cells from noxious stimuli released by proximate damage to issue or retrograde axonal degeneration-NMDA gulutamate receptor antagonists (block excitotoxicity), Calcium channel blockers (block program by which apoptosis is signaled) and active or passive immunization against myelin basic protein (MBP)

f) Rescue of marginally damaged axons and RGC – antioxidants (decrease levels of oxygen radicals), Nitric Oxide synthase inhibitors and Lazaroids (which block lipid peroxidation)

Various **strategies for regeneration** of RGC axons include:

a) Utilizing the ability of axons to extend into *peripheral* nerve grafts – autologous sciatic nerve or other nerve grafts, donor grafts with HLA matching, use of purified or engineered molecules from peripheral nerve to induce extension and genetically induce peripheral nerve molecules in optic nerve.

b) *Regulating the immune response* within the optic nerve- autologous activated macrophages to phagocytose myelin debris and active or passive immunization against myelin basic proteins.

Current status of neuroprotection : There are no proven agents currently available with proven neuroprotective capacity for glaucoma therapy.

PRIMARY ANGLE CLOSURE GLAUCOMA

Primary Angle Closure Glaucoma (PACG) has not received the same level of attention as POAG. Amongst other reasons, is the preponderance of POAG in caucasion eyes and also because gonioscopy has not become a routine in the workup of all glaucoma patients *(6).*

With damage to the optic nerve becoming the diagnostic hallmark of POAG, the definition for primary angle closure glaucoma has also undergone a change

Primary Angle Closure (PAC), there is a significant obstruction of the functional trabecular meshwork by the peripheral iris, in the absence of a secondary pathology. In **Primary Angle Closure Glaucoma (PACG)** this trabecular obstruction is present with glaucomatous damage to the optic nerve head. In this concept, people suffering from an acute rise in intraocular pressure are not considered to have glaucoma unless there is damage to the optic nerve head. This concept is able to explain why 60-75% of people with an acute symptomatic episode of angle closure, recover without optic disc or visual field damage (142,143)

Primary angle closure is different from primary angle closure glaucoma

The traditional classification of primary angle closure is based on symptomatology (acute, sub-acute and chronic) has its limitations. Estimating the prevalence of PACG and POAG in South Africa it was shown that people with chronic angle closure (white eyes and clear corneas) had intraocular pressure 's as high as 72 mmHg. They were unable to demonstrate an asssociation between symptoms and development of visual deficit

(144). Even in East Asia, asymptomatic angle closure is more common (145,146). Symptomology of angle closure does not specify the involved mechanism. Hence management strategies cannot be based on symptomology alone. Angle closure is a mechanical process and is best classified by physical signs.

Primary angle closure suspect (occludable angle) : Where on **gonioscopy** there is appositional contact between the peripheral iris and the posterior trabecular meshwork. For epidemiological studies an angle is considered occludable where more than 270 degrees of the trabecular meshwork cannot be seen (15).

Primary angle closure: An eye with an occludable angle on **gonioscopy** with peripheral anteripor synechiae, elevated intraocular pressure, or excessive pigment deposition on the trabecular meshwork. The optic disc and fields are normal. Iris whorling, stromal atrophy are evidence of an old acute attack of angle closure and represent an ischaemic process. Ocular tissues such as the iris and the ciliary body are sensitive to the ischemic process. Damage to the optic nerve occurs at high IOP. **Signs of anterior segment ischaemia are suggestive and not pathognomic of damage to the optic nerve.**

Primary angle closure glaucoma is characterised by glaucomatous optic atrophy, corresponding visual field defects with occludable angles on gonioscopy or signs of PAC.

Epidemiology of angle closure:

Prevalence : One of the major factors determining susceptibility to primary angle closure is the ethnic background. PAC is more common amongst Asians. In people more than 40 years of age the prevalence of PAC (number of cases present at one point in time) ranges from 0.09% in Europeans (147), 1.4% in East Asian (148,149) and 2.6% in Alaskan Inuit (150). Data from India VES and APEDS shows a prevalence of 4.32% and 0.71% for PACG. Hospital based data suggests an equal number of people with POAG and PACG.

Sex and Age : PAC and PACG tend to be higher in women than men (142,145,150) Incidence (number of cases / 100,000 persons / year for population aged 30 years and above) of PAC ranges from 4.7 %/ in Finland to 15.5% in Singapore. Incidence like prevalence increases with advancing age.

Anatomical factors predisposing to PAC include shallow anterior chamber (151), short axial length of the eye (152,153) increased lens thickness(154,155), forward position of the lens (156) and how tightly the iris hugs the lens.

Table 9 : Anatomical predisposition to angle closure

- Narrow anterior chamber angle
- Shallow anterior chamber depth
- Short axial length of globe
- Small corneal diameter
- Increased thickness of lens

Screening for Angle closure : 'Anatomical characteristics (Table 9) should make screening for PAC a viable proposition. The aim of screening is to detect disease at an early, pre-symptomatic phase in order to provide suitable treatment which slows or arrests progression.

Screening tests should be quick and reliable. In a routine clinical practice (157), screening for PAC would involve assessing all patients with age more than 30 years to determining the potential for angle closure in order to identify those who need a gonioscopic examination. Of the various tests available, two commonly used ones are :-

Flashlight test: A pen torch is held at the lateral canthus to shine a narrow beam of light across the anterior chamber. A shadow is cast on the nasal aspect of the iris with a shallow anterior chamber by the anteriorly situated iris and lens. Using a half iris shadow, clinic based data from India has shown a sensitivity of 45% and specificity of 83% and using a third of the iris shadow 86% sensitivity and 71% specificity (158). In another clinical practice amongst caucassion eyes sensitivity and specificity of 89% and 88% have been reported. Incorrect identification was more for eyes with plateau iris configuration.

Von Herrick's test is carried out at the slit lamp. A thin bright beam falls perpendicularly on the most peripheral point of the temporal clear cornea. The optical cross section is viewed at a high magnification (16x or 25x) from the nasal side. A sensitivity and specificity of 62% and 89% for detection of angles judged to be occludable on gonioscopic examination have been reported (158).

In a clinic based setup where the definitive test (gonioscopy) can be done using both the flashlight test to detect eyes with 1 / 3 iris in shadow and the limbal based test to detect a limbal chamber depth less than or equal to one quarter of the peripheral corneal thickness, few occludable angles would be overlooked.

Provocative test

Depending on the criteria used, occludable angles account for 1.4 – 10.3% the studied population (6,8). A small proportion of these individuals are at risk of develop PAC at some point of time. Since a laser iridotomy is a fairly safe and simple procedure that can eliminate this risk early identification of such patients and treating them prophylactically (159) can help eliminate this risk. Eyes at risk can be subjected to provocative testing – dark room test, prone test, dark room prone test or the mydriatic test.

Clinical relevance of provocative tests : Without treatment 50% of fellow eyes from patients with acute angle closure glaucoma developed acute angle closure within 5 years (160). In a prospective multicentric study 129 eyes considered at risk for developing ACG were evaluated by a number of provocative tests (161). They were then followed up for upto 6 years without any intervention. 25 eyes actually had positive provocative tests, but only six developed angle closure. However of the 35 eyes which developed angle closure, only 6 had a positive provocative test.

The overall sensitivity and specificity of provocative tests for identifying eyes at risk for angle closure is low. Of the 4870 patients, subjected to dilatation none developed acute angle closure glaucoma, even though 38 patients were found to have slit to closed angles (162).

Provocative testing can provide supportive evidence

(1) Intermittent headache / eye ache with history of colored haloes, normal intraocular pressure, but ? occludable angles on gonioscopy.

(2) Positive family history of glaucoma, normal IOP but suspect occludablity on gonioscopy.

(3) Suspect occludablity on gonioscopy on a routine eye examination for a patient on treatment with medication which can precipitate a pupillary block.

Gonioscopy

Gonioscopy is the examination of the anterior chamber angle of the eye with the aid of special contact lenses and biomicroscopy. It is an essential step in the evaluation of all glaucoma patients / glaucoma suspects. The primary aim is to determine if the patient has an open angle or angle closure. Additionally one would like to assess if the open angles have a tendency to close, or if the angles are narrow with no potential to occlude.

The angle of the anterior chamber is created by two lines. One tangential to the trabecular meshwork and the other along the iris plane. The aqueous outflow system comprises of:-

Schwalbes line representing the peripheral edge of Descemets membrane.

Trabecular meshwork the site of conventional aqueous outflow. It has two parts a lightly pigmented anterior part and a darker known zone, posteriorly over the Schlemm's canal. The posterior trabecular meshwork is where more aqueous flows and hence greater iris pigment is present.

Scleral spur is a white band just posterior to the pigmented trabecular meshwork. It is formed by a projection from the inner scleral and represents the posterior boundary of inner scleral canal on which Schlemm's canal rests.

Ciliary body band represents the anterior aspect of the ciliary muscle, into which the root of the iris inserts and appears as a dark brown band posterior to the scleral spur.

Because of the air-cornea interface, internal reflection prevents a direct inspection of the angle. However gonioscopic lenses negate the total internal reflection and exceed the critical angle by altering the cornea air-fluid interface. An excellent review to methodology and interpretation is available (163). Direct gonioscopy is not widely performed in routine clinical practice because the equipment is not readily available for the general clinician and the procedure is less convenient than indirect gonioscopy.

Direct Gonioscopes: Koeppes' lens, Swan-Jacob, Hoskin Barkan

Indirect Gonioscopes : Goldmann lenses, Thorpe and Ritch lens

Indentation : Zeiss, Posner, Susmann

While performing gonioscopy, the room should be dark and width of the slit beam should not cross the pupil so that light induced miosis does not result in misinterpretation of a narrow angle as not occludable.

Assessing potential occludability of an angle. A dark room and small beam of light not crossing pupil is essential to prevent light induced contraction and artificial opening of the angle

Physiological factors which can change angle configuration include parasympthomimetic (causing forward movement of lens iris diaphragm) and sympathetic stimulation (dilation which can produce additional bunching of the iris into the angle). Because of the potential variability in the appearance of the angle, more than one gonioscopic examination is often necessary to determine the risk of developing angle closure.

More than one examinations may be needed to determine the risk of developing angle closure.

Gonioscopy is a dynamic process and needs to be repeated every year…

Q. Is this angle occludable ?

When performing gonioscopy in a dark room with width of the light aperture not crossing the pupil, the aim is to assess if the drainage angle being examined has a potential to close or if there is any evidence that closure may have occurred in the past.

In order to allow comparison of studies (epidemiological research) occludable angles have been defined as one in which the posterior, pigmented trabecular meshwork is not visible for more 270 degrees or more, without indentation or manipulation of the gonioscope (164-166). Using the same definition APEDS reported 1.41 % of occludable angles.

The big question is : Is this definition applicable to clinical practice. Wider angles may become occludable, and narrow angles may never close. Since gonioscopy is a dynamic process, evidence supporting suspect closure is possible.

- PAS in the superior angle are the most important and are pathognomic of angle closure in the absence of inflammation.
- Patchy pigmentation on the trabecular meshwork in the superior angle is also suggestive of angle closure.
- Alternating opening and closure of the beam, a narrow angle may be seen to close and open, demonstrating the potential for closure of the angle **("on-off" sign).**

The VES defined occludable angles when at least 180 degrees of the posterior trabecular meshwork was not seen. (10.3%).

Ultrasound biomicroscopy (UBM): Ultrasound biomicroscopy of the anterior segment allows accurate visualization of the iris, iris root, corneoscleral junction and ciliary body and lens. It is of help to elucidate the mechanism of angle closure. However it is expensive with limited availability.

Mechanism: The final common pathway in the development of PAC is the formation of irreversible synechial adhesions between the peripheral iris and uveal surface of the trabecular meshwork. This is preceded by the development of appositional contact between the peripheral iris and trabecular meshwork.

It is important to identify the involved mechanism as this works as a guide to help plan the management. Its important to remember that more than one mechanism may be at work.

a) Pupillary Block : Obstruction to the flow of aqueous usually arises between the posterior surface of the iris, in the region of the pupillary sphincter and the anterior surface of the lens. With ongoing aqueous production, the posterior chamber bulges forward with increasing pressure and the peripheral iris comes in contact with the trabecular meshwork. *Gonioscopy reveals* a steeply convex iris which is suggestive of a pressure differential between the posterior and anterior chamber.

b) Plateaus iris mechanism: An anatomical abnormality, the peripheral iris crowds the recess of the angle. When the pupil dilates, the iris is thrown into circumferential folds which come in contact with the trabecular meshwork. *On Gonioscopy* the iris inerts anteriorly in the scleral spur or leaves only a narrow ciliary body band. The iris is almost flat from the periphery to the extreme periphery where it creates a narrow angle recess.

The pure form of the plateaus iris syndrome, is extremely rare and is proven by the occurrence of acute angle closure following dilatation despite a patent iridotomy with a deep central anterior chamber.

Since more than one mechanism of angle closure may be present, an iridotomy should be done first. Plateaus iris, may then be treated with argon laser iridoplasty and / or miotic therapy.

c) Lens induced angle closure: A large and / or anteriorly placed crystalline lens can also predispose to angle closure and can worsen the pupillary block.

d) Creeping angle closure starts within the depth of a narrow angle and then spread anteriorly to cover the posterior trabecular meshwork and then involve the anterior trabecular meshwork. This zippering effect leading to closure of the angle made Lowe describe it **as creeping angle closure**.

Chronic angle closure can result from synechial closure of the chamber angle from previous episodes of acute / subacute angle closure. In creeping angle closure the iris base creeps on to the trabecular meshwork leading to peripheral anterior synechiae. When more than ½ of the angle is closed the intraocular pressure rises. Creeping angle closure may arise from an undiagnosed intermittent angle closure. Even chronic miotic therapy may cause worsening of the pupillary block. Creeping angle closure is more common amongst Asians.

e) Cilio lenticular block: In some cases misdirection of the posterior aqueous can cause primary angle closure. Typically the ciliary processes come in contact with the lens equator, and /or a firm zonule / posterior capsule may cause flow of aqueous into the vitreous. The lens iris diaphragm is pushed anteriorly, occluding the angle. Typically such eyes have narrow anterior chambers and after an iridotomy the use of cycloplegics reduces the IOP and miotics paradoxically raise the IOP. Ultrasound biomicroscopy in such situations is very helpful.

f) Combined mechanism glaucoma: Here both pupillary block angle closure glaucoma and open angle glaucoma coexist. Typically a laser iridotomy alone fails to control the glaucoma. This is a form of chronic angle closure glaucoma where the trabecular meshwork may be damaged by intermittent or chronic trauma from the obstruction of the peripheral iris.

In such cases the iridotomy helps to prevent further closure of the angle. The damage to the trabecular meshwork further impedes the outflow of aqueous. Her in addition to the laser iridotomy the open angle glaucoma component needs further medical therapy.

Systemic drugs can induce angle closure in predisposed patients and include phenothiazines and their derivatives, antidepressants, antihistaminics,anti Parkinson drugs, tranquilizers and parasympatholytic and sympathomimetic agents.

Clinical presentation of angle closure :

1) Acute Angle Closure: The likelihood of a pupillary block producing angle closure depends on a shallow anterior chamber, short axial length of the eye, increased lens thickness and forward position of the lens and tightness of the contact between the iris and the lens. Critical anterior chamber depth most likely to lead to PACG is between 1.5 - 2.00mm. With the peripheral iris blocking the access of aqueous to flow out of the trabecular meshwork, the IOP increase.

Physiologic mydriasis (dark room, movie theater), pharmacologic mydrasis (mydriatics and cycloplegics) and anxiety (pain, fear, trauma and emotional disturbances can precipitate acute angle closure in predisposed eyes.

Table 10: Diagnosis of Acute Angle-Closure Glaucoma

Symptoms	Signs
Pain	Shallow anterior chamber, convex iris
Nausea, vomiting	Iritis, flare, ocular congestion
Blurred Vision	mid dilated pupil, poor reaction
Halos	Epithelial edema Glaukomflecken Closed anterior chamber angle with PAS Optic nerve head edema

Gonioscopic proof of a closed angle in the involved eye is the most important sign of angle closure. If visualization of the angle is prevented by the corneal edema, then the uninvolved (fellow) eye should always be examinied for a narrow angle. Other possiblities to keep in mind are a non pupillary block glaucoma, secondary pupillary block and an acute glaucoma in eyes with open angles.

2) Intermittent (sub-acute) Angle Closure: Here attacks occur under conditions similar to acute angle closure, but resolve spontaneously. The intraocular pressure increases causing mild symptoms. However the aqueous then breaks through the pupillary block flowing though the pupil into the anterior chamber again. The peripheral iris falls back and aqueous gains flows through the trabecular meshwork. The likelihood of re occurrence is high till a laser iridotomy is performed. Without this alternate passage intermittent closure continues. Signs and symptoms are mild, and usually resolve spontaneously. The intraocular pressure is often normal between attacks. A shallow anterior chamber with / without PAS on gonioscopy is a hallmark. A history of intermittent rise in intraocular pressure is often present.

3) Chronic Angle Closure : Typically patients with chronic angle closure glaucoma have no symptoms and are often mistaken for open angle glaucoma. Gonioscopy is the only way to identify the closure and differentiate them. Intially the closure is appositional, but with time peripheral anterior synechiae develop leading to closure of the angle. This is accompanied with a raised IOP. Medical therapy initially shows a favourable response. However the IOP often fluctuates on treatment. Synechial closure progresses even as more medications are added. The success of treatment here depends on gonioscopy for early diagnosis and laser iridotomy.

Management

PAC presents with a raised IOP which is often symptomatic with / without disc damage. Management resolves around immediate control of symptoms and raised intraocular pressure, modifying configuration of the angle and presenting further closure, detection and preventation of further damage to the optic disc and visual field, treating the fellow eye.

Medical treatment

Table 11: Medical management of acute angle closure

1. Acetazolamide (250-500mg) oral stat, then 125 to 250 mg t.i.d. / q.i.d, until symptoms subside
2. Topical Pilocarpine 2% stat, then q.i.d.
3. Analgesics and antiemetics as required.
4. Topical beta blockers b.d.
5. Topical steroids Loteprednol acetate q.i.d

Contra-indications and hypersensitivity to drugs should be excluded prior to starting treatment

- High doses of Pilocarpine should be used with caution as there is a risk of systemic pilocarpine toxicity .
- Paradoxical shallowing of anterior chamber can further aggravate the pupillary block
- Topical steroids help reduce the inflammatory reaction
- Often patients with PAC have other medical problems. Electrolyte disturbances, particularly hypokalemia can occur. Vomiting alongwith use of oral acetazolamide may cause or exacerbate this disturbance. Systemic hypotensive effect of beta blockers can be aggravated by the electrolyte disturbance further increasing the risk of circulatory disturbances. Intravenous hyperosmotics can also aggravate circulatory disturbances. Analgesics and anti emetics should be used as required.
- If topical and intravenous therapy is unable to reduce the intraocular pressure within 3-4 hours, additional measures such as corneal indentation, manual compression or a laser iridoplasty may be indicated.

Modification of angle configuration: A laser iridotomy is the definitive treatment for a pupillary block ACG. Since it is often difficult to rule out a pupillary block component in any case of PAC, a laser iridotomy is indicated in every case unless there is a contra indication.It is best performed

when the eye is quiet, cornea is clear and there is no intraocular inflammation or uveal congestion. This rarely occurs when a patient presents with an acute ACG.

- If the cornea is clear and inflammation is less a laser iridotomy can be performed.
- In case residual inflammation is present, after successfully breaking an acute attack, the iris tissue is boggy, in such cases the laser iridotomy can be deffered for a few days, maintaining the patient on glaucoma treatment and topical steroids.
- In case the cornea does not clear to allow an iridotomy despite adequate measures, a partial pupilloplasty (to peak the pupil) with low power applications of Argon laser to temporarily break the pupillary block can be considered. Alternatively the argon laser can be used to contract the peripheral iris and pull it away from the trabecular meshwork (peripheral laser iridoplasty)

As with medical treatment, neither of these alternative modalities provide permanent relief from a pupillary block and must be followed by a definitive laser iridotomy.

A laser iridotomy for angle closure glaucoma is not always successful. Treatment of acute angle closure glaucoma with an iridotomy alone or in combination with miotics controlled the intraocular pressure in 77% cases if there was no initial visual field loss (167,168). This dropped to 29% in the presence of initial visual field loss (169). Following laser treatment, if the glaucoma is due to a pupillary block or appositional closure the angle should open wider following treatment. However the central anterior chamber depth may not change (170-171). Failure of the angle to open following the laser iridotomy results from extreme PAS, or if the angle closure was not from pupillary block. Additional iridotomies will not remedy this.

As laser iridotomy is sufficiently safe, a trial with laser iridotomy followed by medical therapy is generally quite appropriate before proceeding to more invasive trabeculectomy.

In some eyes the angle will open sufficiently following the laser iridotomy, but the intraocular pressure remains elevated. This is usually from trauma to the trabecular meshwork or where there is an inherently reduced aqueous outflow. Such cases would require additional medical therapy, before proceeding to a filtering procedure.

Prophylactive laser iridotomy

A laser iridotomy is always indicated in the fellow eye of a patient who has suffered an acute angle closure in the first eye. Other indications

include, an angle so narrow that a provocative test is dangerous and unnecessary (an angle which is narrowed to a slit or closed, or requires indentation gonioscopy to view the scleral spur (172). Other indications for a laser iridotomy are presence of PAS in an eye with a narrow angle, family history of angle closure glaucoma and need for frequent pupillary dilatation in patients with narrow angles (diabetes)

Like open angle glaucoma ACG is a bilateral disease. The fellow eye almost always has an occludable angle and should be treated with a laser iridotomy, once the first eye is stable. However an iridotomy in the fellow eye may not prevent the need for treatment. 50% of patients with PACG treated with bilateral peripheral iridectomies required additional treatment of some type in the involved eye. 25% needed treatment in the uninvolved eye post laser (173)

SURGICAL IRIDECTOMY

Given the current evidence, the sole indication for a surgical iridectomy is probably the lack of access to a laser. The risk of complications from intraocular surgery such as endophthalmitis and iris prolapse do not seem justified when a closed surgical technique is available. The technique may be of use in eyes in which a symptomatic rise in IOP which cannot be controlled by medical or laser therapy, especially those in whom corneal edema is a persistent problem.

Glaucomatous optic neuropathy in primary angle closure : Management and visual prognosis

When symptoms have settled and short term IOP control has been achieved, a full glaucoma work-up should be carried out. A detailed gonioscopic examination of both eyes, visual field assessment and recording of the optic disc status are essential to plan appropriate long-term management. If glaucomatous optic neuropathy is detected, the therapeutic options are as follows:-

Laser Peripheral iridotomy

Laser peripheral iridotomy is the treatment of choice for people with glaucomatous optic neuropathy in PAC. In one study 140 eyes of 104 people with PAC in Japan, treated by argon laser iridotomy found prior to treatment 73 / 109 (67%) of eyes had a cup: disc ratio of 0.7, the cup: disc ratio enlarged in 31 (28%) and was unchanged in 64 (59%), mean follow-up 1.7 and 2.7 years (in two groups), visual fields defects were minimal or absent in 96 / 118 (81%), moderate in 19 / 18 (16%) and advanced in 3 / 118 (3%). The defects

Table 12 : Side Effects of Glaucoma Medications

Medication Class	Mechanism of Action	Efficacy	Ocular Side Effects	Systemic Side Effects	Relative Contraindications
Parasymoathomimetics Pilocarpine HCL 1-4% Pilocarpine Nitrate 1,2, 4 %	Increased outflow through the trabecular meshwork	++(+)	Miosis, dim vision accommodative spasm, induced myopia, posterior synechiae, cataracts*, iris cysts* pseudopemphigoid*, retinal detachments	Headaches brow ache	Uveitis, neovascular glaucoma, retinal breaks, succinylcholine induced general anesthesia.
Non-Selective Adrenergic Agonists Dipivefrin HCl 0.1%	Increased outflow	+(+)	Hyperemia, blepharo-conjuctivitis, adrenochrome deposition, mydriasis, pseudopemphigoil, cystoid macular edema, stains, soft contacts lenses	Headache, anxiety, palpitations, elevated blood pressure incidence (fewer side effects with Dipivefrin)	Aphakia, pseudophakia, narrow angles, patients using resperine, MAO inhibitors or trycylic, antidepressant, labile hypertension. Cardiac arrhythmias thyrotoxicosis
α Adrenergic Agonists Aproclonodine 0.5 , 1% Brimonidine 0.15 , 0.2%	Decreased aqeous production Increased	++(+) ++	Toxic dermatitis, blepharoconjunctivitis, lid retraction+, conjunctival blanching+, hypotension	Dry mouth, lethargy	Babies and young children patients using MAO inhibitors or sedatives, significant cardiac, renal

Medication Class	Mechanism of Action	Efficacy	Ocular Side Effects	Systemic Side Effects	Relative Contraindications
	unveoscleral outflow		and apnea in babies and children		hepatic, or cerebrovascular disease, Raynaud's disease, thromboangiitis obliterans
β Adrenergic Antagonists Selective Betaxolol HCL 0.25, 0.5% Non selective Timolol Maleate 0.25, 0.5% Levobunolol 0.5% Carteolol 1% Metipranolol 0.3%	Decreased aqueous production	+++ ++ betaxalol	Corneal anesthesia, blepharoconjunctivitis, delayed choroidal detachments	Broncho-construction, bradycardia, exacerbates heart block and congestive heart failure, fatigue, malaise, depression, dizziness, impotency, memory loss (fewer side effects with betaxolol)	Asthma, chronic obstructive pulmonary disease, bradycardia second or third degree heart block, congestive heart failure brittle diabetes, thyrotoxicosis, myasthemia gravis. Use with aution in patients taking resperine, guarnethidine quinidine (Contraindications of greater concern with non-selective b-blockers)
Prostaglandins Latanoprost 0.005 Bimatoprost 0.03% Travoprost 0.004%	Increases Unveoscleral outflow	++++	Iris color change (hazel and mixed green/brown irides), conjunctival hyperemia, uveitis,	Myalgias	

Medication Class	Mechanism of Action	Efficacy	Ocular Side Effects	Systemic Side Effects	Relative Contraindications
Unoprostone			cystoid, macular edema, hypertrichosis		
CAIs	Decreases aqueous production	+++	Transient myopia, delayed choroidal detachments	Metallic taste to food, malaise, depression, weight loss, anorexia, chronic diarrhea, kidney stones, stevens -Johnson syndrome, aplastic anemia, metabolic acidosis, hypokalemia, acidosis with chronic aspirin use	Sulfa allergy, Kidney stones, diabetic ketoacidosis, chronic respiratory acidosis, hypokalemia, patients using thiazide diuretics or phenytoin sodium, sickle cell anemia, hepatic disease
Oral Acetazolamide 125, 250mg					
Topical Dorzolamide 2% Brinzolamide 1%		++(+)	Burning on instillation (dorzolamide)	Metallic taste, theoretical potential for same side effects as oral CAIs but no definitive evidence to date	Significant sulfa allergy

progressed in only 3 patients (all with initially mild changes). **IOP < 21 mmHg (with or without medication) after PI was achieved in 94% (174).** IOP control was more likely to be successful if there were less than 180 degree PAS. There was no significant change in the amount of PAS during the follow-up period. Loss of visual acuity by more than 3 lines occurred in 19%, due to progression of lens opacities.

Another retrospective analysis of 57 Singaporeans with symptomatic PAC found that more than 24 hours delay in presentation, or the need for a laser iridoplasty to achieve short-term pressure control, was associated with worse pressure control after laser iridotomy (mean follow – up period 20 months) (175). Another retrospective study in South Africa of 52 asymptomatic patients (78 eyes) followed for a mean period of 22 months reported that IOP was controlled (< 21 mmHg) without medication in 9%, and with medication in 51% of eyes, trabeculectomy was required in 29% of eyes, risk factors for needing trabeculectomy were: IOP on presentation > 35 mm Hg, 3 quadrants of synechial angle closure, and cup: disc ratio of >0.6.36% of these eyes with these risk factors needing trabeculectomy were controlled by PI with or without medication (176).

The likelihood that a non-invasive procedure will control IOP and arrest progression of optic neuropathy justifies the use of laser PI as first line treatment in all but the most severe cases.

Medical Therapy

If satisfactory pressure control cannot be achieved with a laser iridotomy alone, topical medical therapy can be used in a manner similar as for POAG. A target pressure should be set according to the degree of nerve damage and field loss. If the iris contour has been satisfactorily changed by iridotomy (implying that pupil block was the predominant mechanism), then a first line drug as felt appropriate may be used. If the iris profile has not changed after the laser iridotomy (suggesting peripheral iris crowding is the predominant mechanism), Pilocarpine 1-2% is a more appropriate choice. An μ_2-agonist is an appropriate second-line therapy.

Trabeculectomy

Trabeculetomy is indicated in cases of PAC with glaucoma that cannot be controlled by laser iridotomy and medication. There is often concern that aqueous (ciliolenticular block) misdirection may complicated trabeculetomy in cases with PAC, although published data and anecdotal experience do not support this (177). Despite the finding that eyes with PAC do not seem to suffer especially high rates of malignant glaucoma, cases of

this problematic complication do occur. The condition may be recognized by progressive asymmetrical axial shallowing of the anterior chamber.The disorder stems from misdirection of aqueous flow by closure of the ciliolenticular space. Dilating the ciliary ring is probably the best preventive measure and the agents of choice being either cyclopentolate or homatropine.

Primary trabeculectomy is an option for cases of PAC in which immediate pressure control cannot be achieved. Patients with very advanced PAS, optic nerve damage, and visual field loss, are often considered for primary trabeculectomy. A trial of laser iridotomy in all cases, although if synechial angle closure for more than 180 is identified after laser treatment, the patient should be considered at high risk of needing a trabeculectomy to achieve control.

Lens extraction: Since the position of the lens determines the iris profile, and therefore the angle configuration, lens extraction is a logical choice for surgical management of raised IOP in cases of PAC with visual impairment due to cataract. Extracapsular cataract extraction was used in the management of PAC in 21 eyes of 20 patients (2 with raised IOP alone, 5 symptomatic, and 14 asymptomatic). In 14 cases lens extraction was performed in place of filtering surgery, where peripheral iridectomy or precious filtering surgery had failed (178). Mean IOP reduced from 31 to 16 mm Hg after surgery, 16/21 eyes did not require further medication (follow up:6-42 months), IOP was reduced even if there were extensive previous PAS, in 6 patients with previous failed filtering surgery, lens extraction gave a median IOP reduction of 17.5 mmHg (range 5-30).

Management of the asymptomatic narrow angle

In a multi-centre study of 129 asymptomatic patients with anterior chamber depth < 2 mm, or drainage angles that were potentially occludable, only 6% developed signs or symptoms consistent with PAC over a mean period of 2.7 years (maximum follow up 6 years) it would therefore appear that an individual risk of developing visually threatening sequelae is low on a year-to-year basis. However, **it is now an accepted practice to perform a laser iridotomy on patients with early gonioscopic evidence of angle closure, reflecting the perceived (although unproven) high benefit/risk ratio for this procedure.** This view is probably justified when one considers the potential for late-presentation or misdiagnosis under non-ophthalmic care, and low incidence of sight-threatening complications of laser iridotomy.

The management of an eye contralateral to one that had an episode of symptomatic PAC is open to less conjecture. Follow up of 200 such "fellow" eyes found 113 were managed by observation or with topical Pilocarpine

(129). Of this number 58 developed symptomatic PAC (half within a five year period), 26 of the 58 were using topical Pilocarpine. In a further 250 patients with PAC, 72 did not have prophylactic peripheral iridectomy. Forty three developed PAC (33 symptomatic, 10 asymptomatic or unknown), 33 of these were affected within 6 years. This is overwhelming evidence in favour of prophylactic peripheral iridotomy by laser, or surgical iridectomy if no laser is available.

The Indian Perspective:

In the glaucoma clinic of an eye hospital, 45.9% of all primary adult glaucomas were of angle closure glaucoma (179). Of these 24.8% had acute angle closure glaucoma, 31.2% had subacute and 44% had chronic glaucoma. More than 80% of the chronic eyes had no significant symptoms. Nd Yag laser iridotomy alone or with topical medication controlled the IOP in 48.3% of acute angle closure glaucomas, 78.8% of subacute and 30% of chronic eyes. Similar data from another tertiary setting reported 15.88% acute, 19.26% subacute and 64.86 % chronic angle closure amongst the 888 patients with Primary angle closure glaucoma (180). Over a period of five years, 22% of occludable angles progressed to primary angle closure glaucoma (none progressed to glaucoma) and 28.5% of the primary angle closure developed optic disc and visual field changes. (181)

Light and electron microscopic studies (182) have revealed accumulation of pigment in the widened trabecular spaces and Schlemm's canal (acute PACG). The endothelial cells were attenuated and devoid of subcellular components. Chronic angle closure was associated with loss of the trabecular architecture with narrower trabecular spaces and fusion of the trabecular beams. Loss of endothelial cells and reactive repair was visible in areas away from peripheral anterior synechiae.

Extent of peripheral anterior synechiae on gonioscopy does not reflect the extent of trabecular meshwork dysfunction in PACG.

Following an acute attack of PACG, long term followup is needed despite a laser iridotomy as the IOP may rise later due to progressive compromise of the outflow facility.

Conclusion: **Primary Open Angle Glaucoma** is characterized by a typically progressive glaucomatous optic neuropathy with correlating visual field loss. IOP is one of the risk factors responsible for this damage to the

optic nerve. However even though factors other than IOP are involved in the pathogenesis of glaucoma, IOP is the only factor that can be modulated to date. The decision to treat is individualized depending on the whether the level of IOP will lead to progressive nerve damage. Available treatment algorithms rely on medical management to achieve the target IOP, failing which filtering surgery can be resorted to. In the Indian context, early filtering surgery to achieve the desired target pressure is a viable alternative. Laser trabeculoplasty is an intermediate step. The role of neuroprotection is not yet established clinically.

Primary Angle Closure Glaucoma : There is a significant change in the perception of PACG. The definition of PACG has undergone a change. Angle closure is now described as an anatomical disorder where symptomatology does not specify the involved mechanism. Screening for angle closure glaucoma appears tempting, but is still not a viable option. Improved detection with simple tests (flashlight test and von Herrick's test) and confirmation on gonioscopy plays a key role in diagnosis. Provocative testing is likely to provide a supportive role in asymptomatic occludable angles. Asymptomatic, chronic angle closure glaucoma mimicking POAG is common. Gonioscopy is the confirmatory test. After the definitive treatment, laser iridotomy, angle closure is treated medically or surgically in the same manner as open angle glaucoma.Treatment of the fellow eye with a laser iridotomy is mandatory.

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