Review

Latest developments in glaucoma

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Introduction

Glaucoma is a leading cause of irreversible blindness in the world affecting 12.5% of blind population. In addition to that, it is the cause of morbidity for 64.3 million of people among 40-80 years of age. World statistical predictions estimate it to be 118 million in 2040. Unpublished data in Sri Lanka reveals 6-9% of prevalence among people over 40 years with more predilections to Northern Province.

Glaucoma is a disease of optic nerve head with progressive ganglion cell loss resulting in loss of neuro-retinal rim and retinal nerve fiber layer. It is characterized by structural changes in optic nerve head and retinal nerve fiber layer and functional loss depicted as visual field loss.

Asymptomatic nature of the disease causes a delay in diagnosis. On the other hand, the early diagnosis and treatment will minimize the physical, psychological and social impact of the illness. The diagnosis of glaucoma is a complicated and expensive effort that is heavily dependent on the experience and expertise of a clinician. Therefore, the awareness on latest discoveries on pathophysiology, diagnostic evaluations and therapeutic interventions in the field of glaucoma will help to face the challenges in patient care.

Diagnostic approach

Glaucoma was diagnosed in the past with standard history taking and clinical examination supported by conventional peremetry. Nowadays large numbers of cases are accidentally detected and sometimes the diagnosis is not straight forward even for an ophthalmologist. Therefore, additional tools are required to overcome these diagnostic dilemmas to prevent over or under diagnosis.

Optical coherence tomography (OCT)

OCT revolutionized the diagnosis and monitoring of glaucoma providing structural analysis optic nerve head, retinal nerve fiber layer of peripapillary region and ganglion cell layer of macula. Usage of this further extended by anterior segment analysis of iridocorneal angle, anterior chamber depth and iris configurations also. Glaucoma diagnosis was more strengthened with analysis of optic nerve head vasculature and perfusion by OCT angiogram.

OCT creates high resolution cross sectional images of ocular structures by measuring echo time delay and magnitude of back scattered light. Statistical analysis comparative to normative database provides details with diagnostic values. OCT angiography works by analyzing not only the intensity of the reflected signal, but also the time changes in the reflection caused by the motion of red blood cells in blood vessels. OCT should be performed more frequently when glaucoma is suspected at examination and early stage of the disease to ascertain rates of progression.

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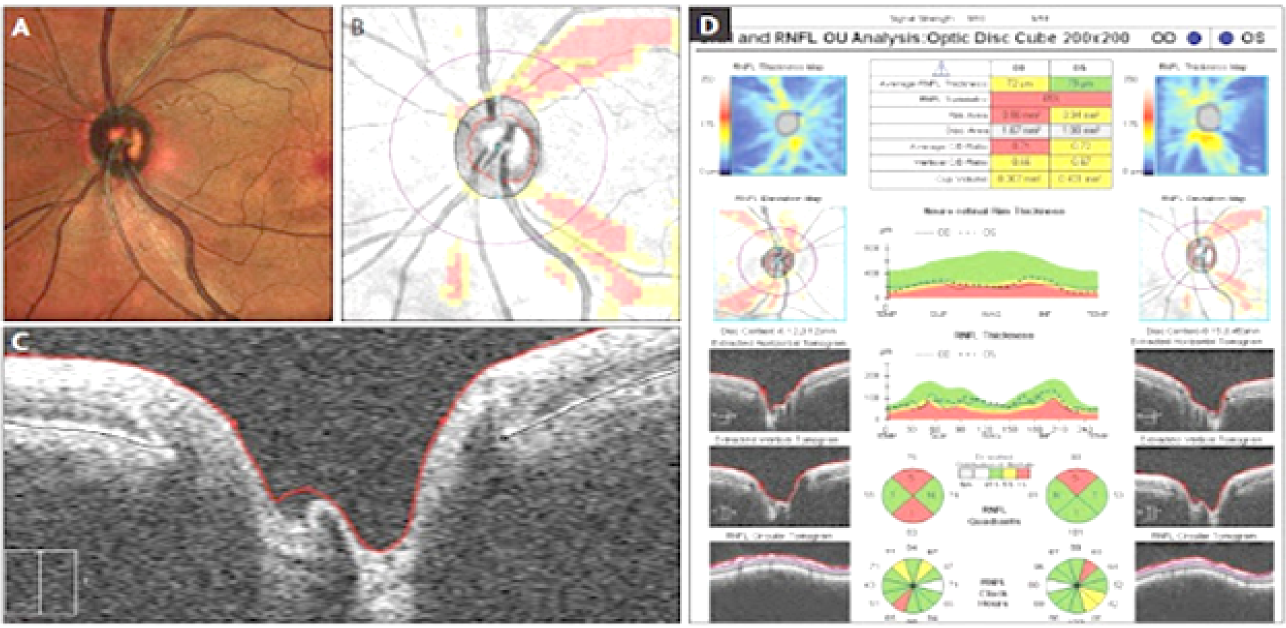
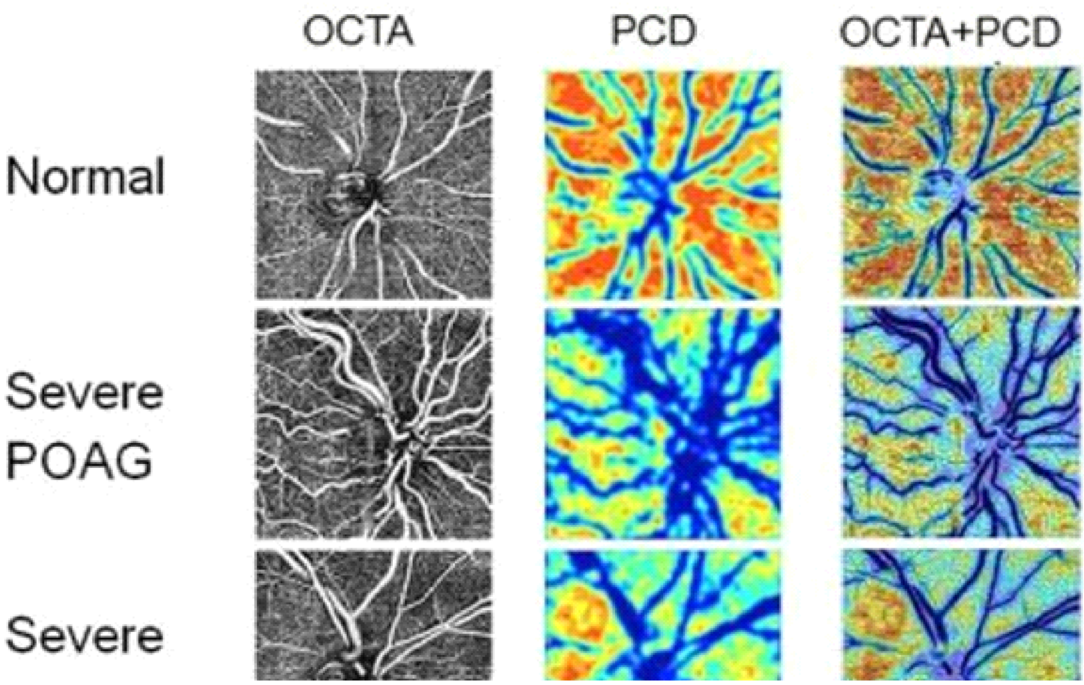


OCT optic nerve head



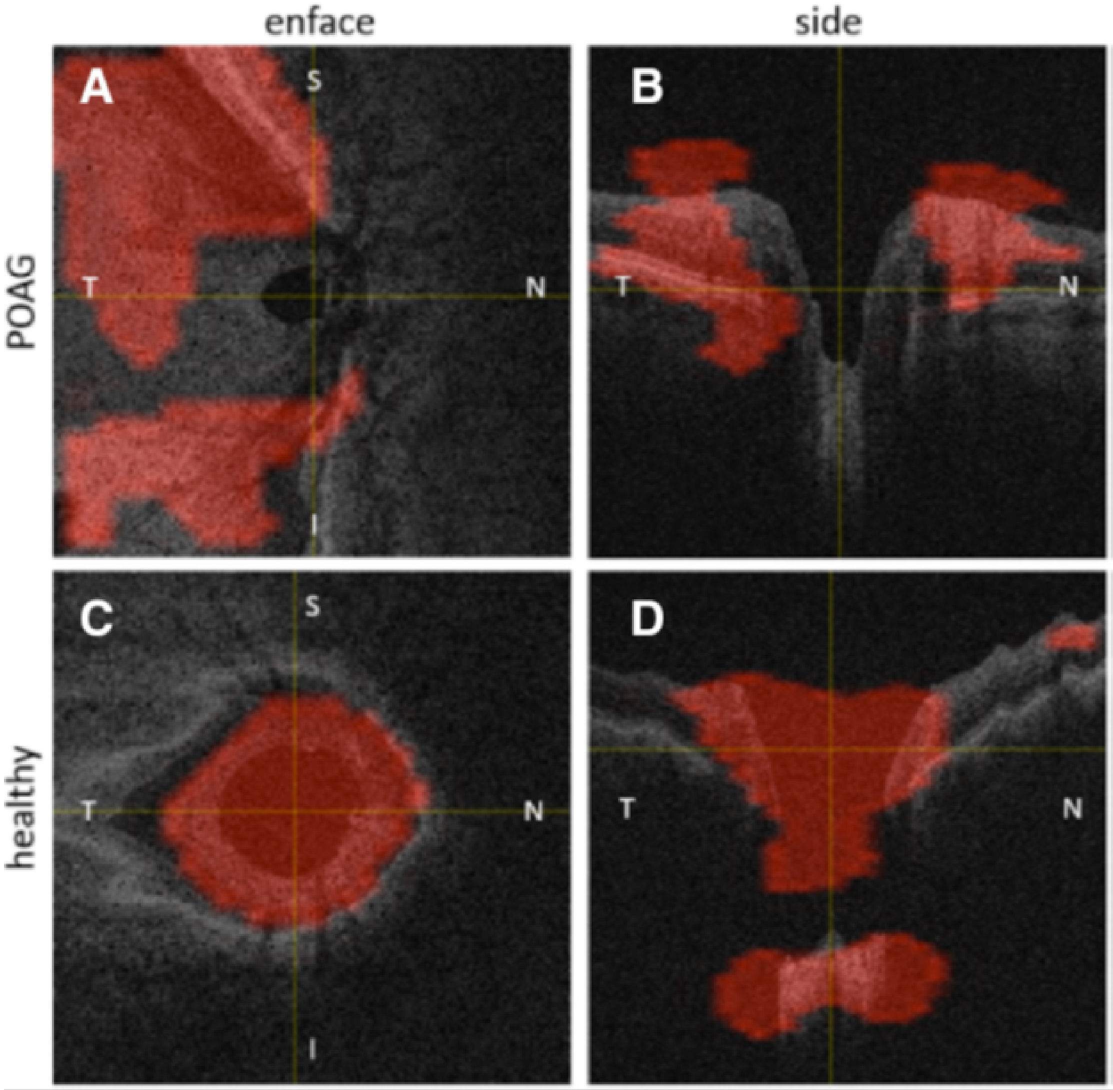
OCT Angiogram

Artificial intelligence (AI) algorithms

Since there is no single diagnostic test for glaucoma it has become a complicated process with profound analysis of clinical findings and series of investigation reports. The applications of artificial intelligence (AI) algorithms in glaucoma facilitate evaluation as well as prediction. Several AI techniques have been proposed to help detect glaucoma by analysis of functional and structural evaluations of the eye.

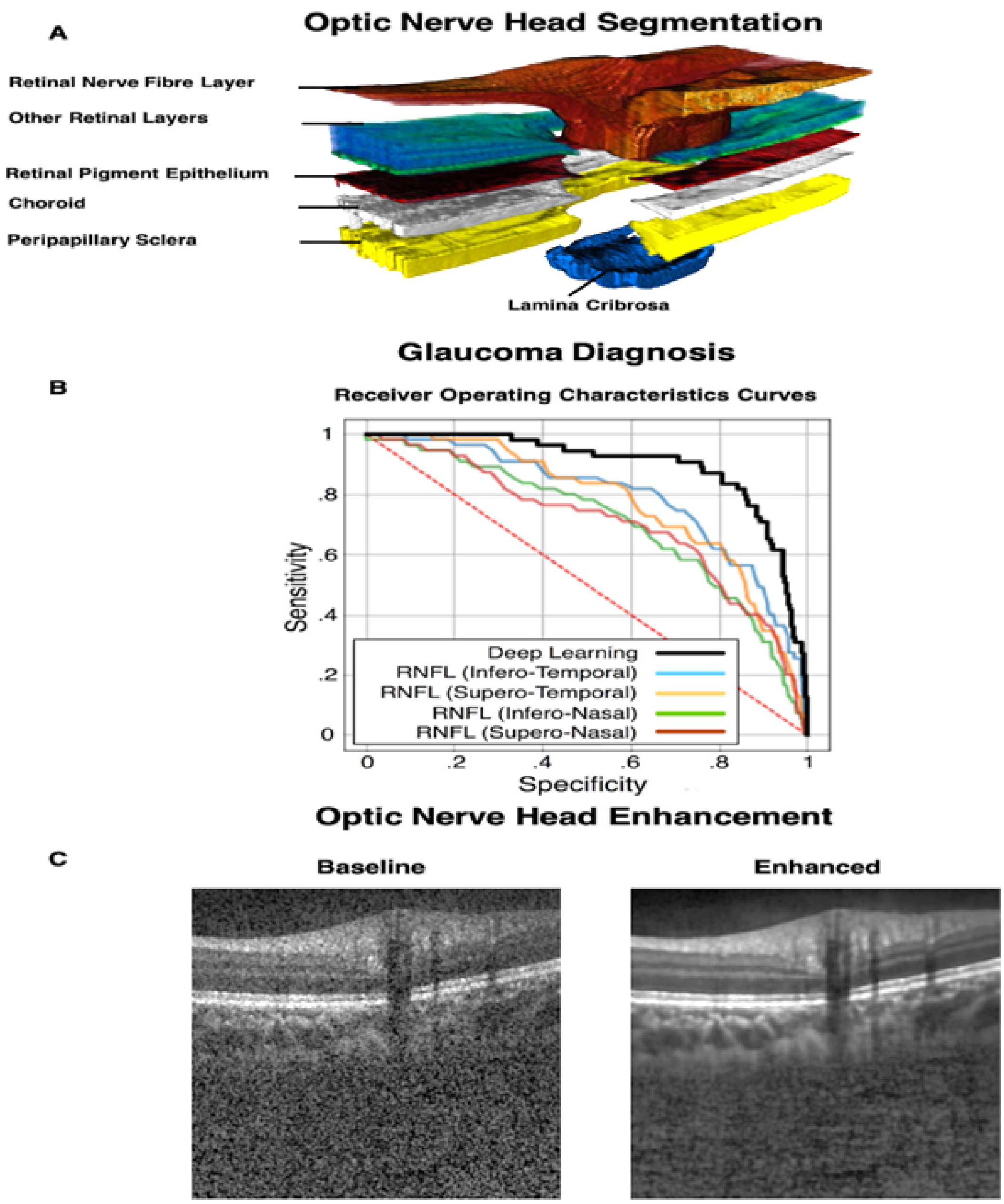
Structural analysis AI algorithms are based on OCT findings such as optic disc parameters, neuroretinal rim, retinal nerve fiber layer thickness and thickness of ganglion cell layer. Functional analysis AI algorithms are based on visual field parameters. Hybrid AI algorithms consisting both structural and functional data have been developed with higher level of diagnostic accuracy.

Deep learning (DL) is recently invented more advanced and powerful AI approach in the field of medical imaging for segmentation, enhancement and diagnostic applications.



Heat maps (or class activation maps) are used to better understand the decision-making process of the 3D deep learning (DL) network. The first column represents the en face view for a glaucoma (A) and healthy (C) optical coherence tomography (OCT) scan; while the second column represents their respective side views (B and D). The red maps correspond to the regions that have influenced the DL network the most for the classification of healthy/glaucoma eyes. POAG, primary open-angle glaucoma.

It shows higher diagnostic accuracy (87.6%) than glaucoma experts (62.6%) and traditional diagnostic criteria in Advanced Glaucoma Intervention Study (45.9%).



Recent deep learning (DL)-based networks for the segmentation (A), diagnosis (B) and enhancement (C) of the optical coherence tomography (OCT) images of the optic nerve head (ONH). A 'Co-Training' DL network proposed by Girard et al for the simultaneous segmentation of neural and connective tissues, and diagnosis of glaucoma (A and B). Devalla et al developed a DL algorithm to enhance the quality of ONH images (C). RNFL, retinal nerve fiber layer.

This can be used as a clinical tool to supplement the diagnosis of glaucoma but never to replace the expert capacity. It is helpful as triage process to handle work load of clinicians to minimize diagnostic errors. In addition to that AI algorithms can be a screening tool for large populations. There are limitations of using them because of variations depend on factors such as region, ethnicity, gender etc.

Pathophysiology

Aqueous humour flow along conventional and uveoscleral pathways regulates intraocular pressure. Conventional flow crosses trabecular meshwork consists of corneoscleral trabecular meshwork and juxta canalicular connective tissue that covers endothelial lining of Schlemms canal. Resistance to aqueous outflow within trabecular meshwork plays a role in controlling intra ocular pressure. Latest in depth analysis has revealed certain aspects of pathophysiology leading to newer therapeutic and diagnostic strategies.

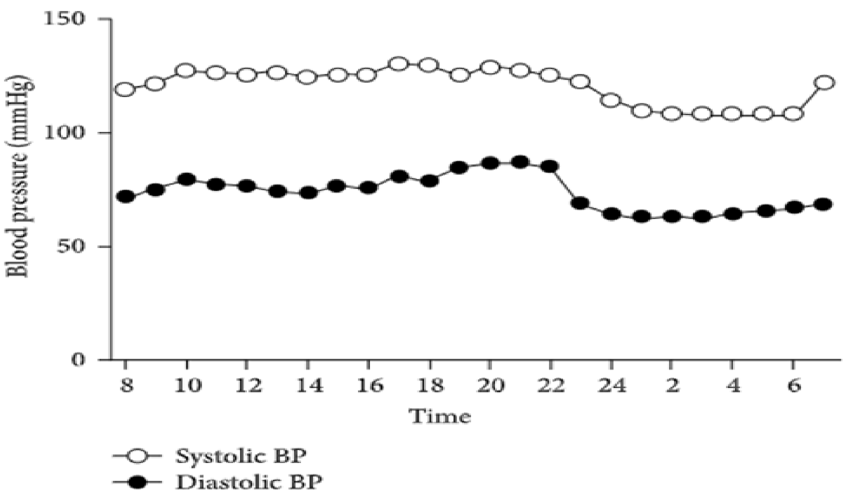
Molecular biology

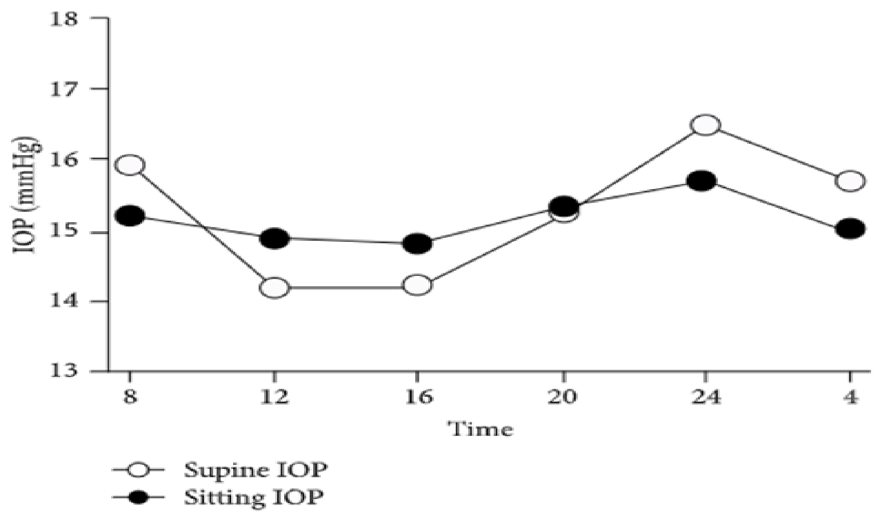
Modern molecular biological studies have exposed factors interfere with conventional outflow pathway. Increased extracellular matrix (ECM) deposition and cell stiffness due to imbalance of transforming growth factor-b2 (TGF-b2), connective tissue growth factor (CTGF), integrins (avb3 and avb5), Rho-associated kinase (ROCK) and nitric oxide (NO) considered to result in glaucoma. This knowledge has opened the path to newer drugs in glaucoma treatment.

Systemic blood pressure and intra ocular pressure

Normal ocular perfusion pressure nourishes optic nerve head. Poor perfusion can cause axonal loss of optic nerve. Nocturnal hypotension coincides with IOP spike and reduces ocular perfusion pressure exacerbating the progression of visual field loss in patients with glaucoma. These intermittent insults will increase the risk of disease progression.

Studies have suggested that nocturnal BP could be a modifiable risk factor for glaucoma severity and progression. Therefore, Diastolic OPP (DOPP= DBP- IOP) is considered to be an independent risk factor for glaucoma progression.





This makes ambulatory blood pressure monitoring a useful tool to identify patients at greatest risk for progression. General physicians and ophthalmologists should be aware about relationship between glaucoma and systemic blood pressure when treating concomitant disease to avoid excessive lowering of night time blood pressure.

Melatonin, Circadian rhythm and glaucoma

There is evidence for a progressive loss of intrinsically photosensitive retinal ganglion cells (ipRGC) due to oxidative stress in glaucoma.

As ipRGC are responsible for the photic transduction to the circadian system and subsequent melatonin secretion. Melatonin is involved in the pathophysiology of circadian desynchronization, sleep disorder, and depression. Impairment of photo-dependent melatonergic signaling may be a common pathway connecting glaucoma with these comorbidities.

There is a proven retinal neuroprotective role of melatonin, suggesting that melatonergic drugs provide a potentially promising treatment strategy supplementing the management of intraocular pressure by pharmacological and surgical measures.

Additionally, multidisciplinary treatment focusing on depression and normalization of circadian rhythms might be beneficial for glaucoma patients.

Furthermore, glaucoma might be a useful model for studying the pathophysiological interactions between the melatonergic, circadian, and mood systems.

Trans-lamina cribrosa pressure gradient (TLCPG)

There is significant evidence suggesting that the trans-lamina cribrosa pressure gradient (TLCPG) contributes to the glaucomatous optic neuropathy in primary open-angle glaucoma.

Moreover, many studies have confirmed that the circulation of cerebrospinal fluid (CSF) can be affected by the increase of the TLCPG, such as compartment syndrome which may play crucial roles in nutrient delivery and clearance of metabolic waste of the optic nerve.

Prof. Yücel et al., demonstrated that the CSF circulating around the optic nerve is not just in the subarachnoid space, but also enters the optic nerve itself via spaces surrounding blood vessels. Using a mouse model, they also found that CSF entry into the optic nerve is impaired in glaucoma.

Emerging medical treatment

Novel therapeutic approaches comprise medical and surgical options. Inventions of medical aspect are directed towards newer therapeutic agents, therapeutic targets, neuro protective drugs and drug delivery mechanisms.

Novel therapeutic agents

1) Rho-kinase inhibitors

   This is a topical agent containing an inhibitor to Rho-kinase enzyme that regulates the calcium-dependent smooth muscle contraction. Structural modification of trabeular meshwork cause reduction of IOP by increasing aqueous humour outflow

Novel therapeutic targets

1) Cytoskeletal agents

   Compounds cause cytoskeletal alterations are found to effectively lower IOP. Cytochalasin, prevent the elongation of actin filaments, distend trabecular meshwork and rupture the inner walls of the Schlemm's.

2) iNOS inhibition

   Nitric oxide synthases (NOSs) are enzymes that synthesis nitric oxide. An elevated level of Inos

   (inducible-NOS 2) is observed in the glaucomatous population suggest accumulation of toxic amounts of NO which is capable to induce inflammations neuronal damage. Inhibition of Inos is believed to reduce inflammation and neural damage.

Neuroprotective drugs

1) N-acetylcysteine (NAC)

   NAC is cell permeable, serves as a precursor of cysteine and stimulates the synthesis of glutathione in neural cells. Glutathion is an anti-oxidant that suppresses oxidative stress. Therefore it may be an effective therapeutic strategy for the prevention ganglion cell loss.

2) Gingko biloba

   Gingko biloba is a native chinese tree. Extracts of it composed of flavonoids and terpenoids reported to possess antioxidant properties. Additionaly it cause vasodilation, thereby improve the blood flow to safeguard mitochondrial metabolic process. Quaranta et al performed a double-masked randomized crossover trial that revealed improvement of visual fields.

3) Ubiquinone/Coenzyme Q 10 (CoQ10)

Ubiquinone is a cofactor in the mitochondrial electron transport chain. Mitochondrial dysfunction is reported to cause apoptosis of neurons and ubiquinone can counteract these effects. Certain studies have shown decreased ganglion cell death on topical application of CoQ10 in an experimental model of glaucoma, suggested it as a promising candidate for use in glaucoma.

Novel drug delivery mechanisms

1) Mucoadhesive polymers

The ocular barriers and the defense mechanism of the human eye prevent the passage and retention of drug solutions. These ocular barriers lead to low ocular permeability of drugs and also their absorption in the eye. Drug delivery system that facilitates retention of drug on the surface of the eye for a longer duration after installation is needed to overcome these problems. Hyaluronic acid (HA) is a naturally occurring biopolymer. Other mucoadhesive polymers include carboxymethylcellulose, polyacrylic acid derivatives and Chitosan etc. These are liquid at room temperature and transform into gel after application to ocular surface due to changes in temperature, pH or ionic strength. Polymers can increase ocular drug residence period and bioavailability of the drug. These substances possess good viscosity, adherence and a reduction in the drug drainage rate. Attachment of drug carrier with the mucin coat covering the ocular surface increase absorption time and higher drug concentration at site of action.

2) Contact lenses

Increase of drug retention time can be achieved with sustained release medicated contact lenses. Nanoparticle laden lenses and imprinted contact lenses with layered structures might have extended drug delivery with improved ocular availability and reduced side effects. Significant IOP reduction has achieved with Dorzolamide and Timolol impregnated lenses.

3) Liposomes

Liposomes are the vesicles made up of natural or synthetic lipid materials comprising of phospholipid bilayers containing inner core and outer lipid layer. After few decades, the research on liposomes made it one of the preferred choice of drug carrier due to higher bioavailability and ability to carry both hydrophobic and hydrophilic agents.

4) Nanoformulations

Varieties of nanoformulations with size of less than 1000nm are introduced to improve drug efficacy. These will enhance bioavailability, controlled release and drug retention time thereby lowering dosage and frequency which improves patient compliance.

Nanomicelles

Nanomicelles are amphiphillic agents with 10-100nm in size molecules which consist hydrophobic core and hydrophilic tail protrudes to the outside environment. Drug particles are retained within hydrophobic core.

Nanoemulsions

Nanoemulsions are thermodynamically stable drug carriers containing interfacial surfactant layer separating the oil and water environments. These drug carriers are identified as oil in water, water in oil and bicontinuous nanoemulsions. Nanoemulsions provide better bioavailability, improved drug absorption and rapid drug penetration. Nanoemulsions allow the entrapment of hydrophilic and lipophilic drug particles. Dorzolamide and acetazolamide preparations as nanoemulsions have shown acceptable efficacy.

Nanocapsule

Nanocapsule has drug enclosed inside a polymeric membrane or protective matrix. It is an efficient drug delivery system and advantageous than the other free drug counterparts. Nanocapsule offers maximum therapeutic efficacy with drug content. This minimizes the side effects as well. Pilocarpine in nanocapsule formulation has been successfully used in studies to control IOP.

Niosomes and proniosomes

Niosomes are hydrated non-ionic surfactant molecules forming bilayers. The medication is encapsulated inside this bilayer. Proniosomes are free-flowing, dry formulations of surfactant coated which forms multilamellar niosomes following hydration. It provides better stability for the drug than niosomes on storage, handling, and transportation. Some studies have proved the efficacy of this preparation with brimonidine and dorzolamide.

Dendrimers

The dendrimeric structure consists three parts as initiator core, interior layers and exterior functionality with particle size between 1-100 nm. It's reactive end group forms an internal cavity encapsulating the drug molecules. Dendrimers deliver drugs by either enclosing a lipophilic moiety within a hydrophobic cavity or by attaching drugs onto the surface. Dendrimers are an advantage, is more targeted drug delivery than other molecules.

Hydrogel

These cross linked polymers are highly absorbable three-dimensional network. The three-dimensional crosslinks make these structures insoluble in water because of anionic interactions and hydrogen bonds. Porosity of the gel allows the timely release of the drug from the matrix. Hydrogels swell when exposed to an aqueous environment. It's muco-adhesiveness provide more ocular residence time and enhanced action.

Latest surgical interventions

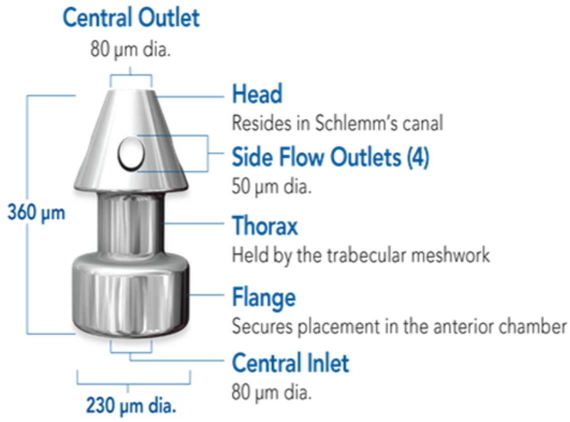
As a whole, surgical treatment options for glaucoma are as follows:

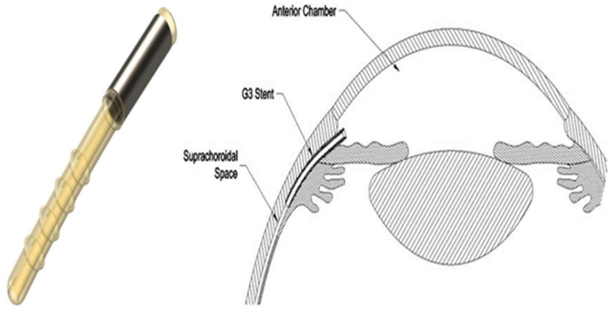
1) Filtration surgery – trabeculectomy
2) Glaucoma drainage devices
3) Minimally invasive glaucoma surgery (MIGS)

Out of these, minimally invasive glaucoma surgery is the latest discovery. Different varieties of mini shunts have been developed to be used in different levels.

- 3G stens
- I-stent

Several MIGS studies have demonstrated successful outcomes in patient groups with a mean preoperative IOP less than 22 mmHg. But, MIGS procedures will have limited success in achieving this treatment goal for patients with target IOP less than 10 mmHg. Trabeculectomy is more effective procedure in that scenario.





However, most MIGS procedures have not been studied exclusively in an NTG population thus far. Based on the mean postoperative IOP levels in a largely POAG population, clinicians can infer a final IOP in the range of 12-16 mmHg is likely to be achieved.

Glaucoma is a global health problem which has imposed a significant impact on productive population in Sri Lanka also. Therefore, early diagnosis and optimum treatment for the disease is becoming a national level requisite. Consequently, awareness about latest developments of glaucoma management will be a great advantage in facing this global challenge in the future.