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The Ten Year Challenge


Dr. (Prof.) Subhash C. Dadeya

Dear colleagues and friends!!

If glaucoma was to take the ten year challenge as on Facebook, most of us will be surprised at how little the principles of glaucoma management have changed over the last decade. Despite the introduction of striking imaging techniques and dramatically intricate stents, the mainstay of patient care remains the old fashioned clinical examination, and patient communication.
Which is why this issue of DOS Times, dedicated to glaucoma, will feel like an amalgam of both: the most basic techniques that you learn as a resident: optic nerve examination, visual field interpretation and gonioscopy; juxtaposed against the brilliance of technological innovations: microstents and newer drugs in therapeutics, and OCT-Angio in the diagnostics section. It has been our endeavour to bring to you the mainstays of current glaucoma practice, with experts discussing the clinical decision making in complex surgical scenarios involving glaucoma shunts and combined cataract and glaucoma, secondary pediatric glaucomas, as well as the protocol for taking a patient off glaucoma medications.

It is with great joy that we bring to you this glaucoma edition in the New Year, and hope that it gives you enough food for thought, and helps you when you make decisions for your glaucoma patients in your clinic, and your operation theatre.

I would also like to extand a very warm invitation to each member of DOS family for the Annual Conference to be held at the Hotel Ashok, New Delhi on 12th to 14th April, 2019.

Last but not least, I must take this opportunity to express my utmost gratitude again to all the contributing experts for their enthusiastic support and my team for making this world-class speciality issue possible.

Happy New Year!

Thanks

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Considerations During Glaucoma Drainage Implant Procedure


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The decision to choose between various glaucoma surgical procedures involves weighing the risks and benefits to the patient. Although preferred practice patterns vary among glaucoma specialists, evidence based medicine in the form of several multi-center clinical trials helps guide glaucoma surgeons to make the best possible decision for their patients. The landmark trial of Tube versus Trabeculectomy (TVT) study compared the two most commonly performed glaucoma filtration procedures in patients with previous intraocular surgery. This trial helped glaucoma specialists to understand the effectiveness and safety concerns of either procedure and take a better informed decision. At 5 years, although both procedures were associated with similar intraocular pressure (IOP) reduction and use of supplemental medical therapy, additional glaucoma surgery was needed more frequently after trabeculectomy with MMC than tube shunt placement. The latest Primary TVT study is a way forward in the same direction and will provide valuable information regarding these two procedure in patients with medically uncontrolled glaucoma and no previous intraocular surgery. In PTVT at one year, trabeculectomy with MMC has been reported to have a higher surgical success rate but more frequent serious complications producing vision loss or requiring reoperation than tube shunt surgery. Similarly, trials between the valved Ahmed glaucoma implant and the non-valved Baerveldt implant have given valuable data about surgical success and safety concerns of each device. In India, the advent of Aurolab Aqueous Drainage Implant (AADI) which is a based on the prototype Baerveldt 350mm^2 implant, has widened the options that we can offer to our patients. As we look at the results of these trials and see what's new on the horizon, it is essential to understand how these clinically impact our patient care and decision process. We asked a panel of imminent glaucoma specialists about their decision-making process, as regards glaucoma drainage implants (GDI) in the various subtypes of glaucoma and the operative considerations with each device.

(PAS): Dr. Paul A. Sidoti, *MD, Professor of Ophthalmology,* Icahn School of Medicine at Mount Sinai; Site Chair, Department of Ophthalmology, New York Eye and Ear Infirmary of Mount Sinai; Director, Glaucoma Service, Mount Sinai Health System, New York City, NY, USA.
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(DG): Dr. Davinder S. Grover, *MD, MPH, Attending Surgeon and Clinician*, Glaucoma Associates of Texas Dallas, Texas, USA.
(JFP): Dr. Joseph F. Panarelli *MD, Associate Professor of Ophthalmology,* Icahn School of Medicine at Mount Sinai, Associate Residency Program Director, Glaucoma Fellowship Director, New York Eye and Ear Infirmary of Mount Sinai, New York City, NY, USA.
(AS): Dr. Arsham Sheybani *MD, Assistant Professor of Ophthalmology,* Advanced Anterior Segment and Glaucoma Surgery, Washington University School of Medicine, St. Louis, Missouri, USA.
(SD): Dr. Sonal Dangda *MS, DNB, FICO. Research Fellow (Glaucoma)*, New York Eye and Ear Infirmary of Mount Sinai, Icahn School of Medicine, New York City, NY, USA.

SD: How often in your clinical practice do you perform a GDI procedure?

PAS: This is the most common surgical procedure performed in my glaucoma specialty practice. Many of my referred patients have advanced glaucoma and have often undergone prior surgical procedures for glaucoma and other ophthalmic conditions.

SG: Placement of a GDI is one of the most common surgical procedures I perform in my tertiary referral glaucoma practice.

SS: I do 3-4 GDI procedures per week.

CT: I have a referral glaucoma practice, with many complex and advanced glaucoma cases. I would estimate that approximately 40% of my glaucoma surgeries involve a glaucoma tube implant.

DG: I typically perform GDI several times a week. However, the frequency that I need to depend on tube shunts have substantially decreased following the evolution of angle surgery and other minimally invasive subconjunctival filtration procedures.

JFP: 5-7 per week.

AS: 3-5 cases per week.

SD: What is the patient profile you prefer for GDI procedure over Trabeculectomy?

PAS: My choice between trabeculectomy and GDI has shifted in the direction of GDI during my 25 years in clinical practice. This has as much to do with my clinical experience as well as the results of several well-designed clinical trials. I still prefer trabeculectomy as a primary glaucoma procedure in phakic or pseudophakic patients who require a very low postoperative IOP such as those with advanced disc damage or low-tension glaucoma (LTG). Additionally, phakic patients with an anterior chamber angle that is compromised by peripheral anterior synechiae (PAS) (leaving inadequate room for safe tube placement) and without a visually significant cataract are often better candidates for a trabeculectomy than a GDI.

SG: I prefer to use a GDI over trabeculectomy in those patients who are at increased risk of filtration failure. This includes patients with high risk secondary glaucoma, (i.e., neovascular glaucoma (NVG), uveitic glaucoma, iridocorneal endothelial syndrome (ICE), and fibrous/epithelial ingrowth) and eyes with conjunctival scarring from prior ocular surgery, trauma, or cicatrizing diseases (i.e., Stevens Johnson syndrome (SJS) and ocular cicatricial pemphigoid). I also favor GDI surgery in patients with severe posterior blepharitis and contact lens (CL) wear, because of the increased risk of bleb-related infection with filtering surgery in these groups. Additionally, the TVT Study provides strong evidence to support the use of GDIs in eyes with prior cataract extraction and/or failed filtering surgery, a lower risk population than has traditionally had GDI surgery.

SS: Majority of my indications for GDI are secondary glaucoma eyes, specially those with multiple previous intraocular surgeries or scarred conjunctiva. In eyes with primary glaucoma, failed primary trabeculectomy or failed repeat filtering surgery is an indication for GDI.

CT: There are various considerations for me in electing to perform GDI over trabeculectomy. I consider patient's age, ethnicity, glaucoma disease level, IOP, prior incisional surgery history, social situation, ability to take eye drops, ability to return for postoperative visits, distance residing from my office, etc. If the patient is elderly and lives independently, has difficulty coming for postoperative visits, or cannot instill eye drops, I may consider a GDI over a trabeculectomy. I try to tailor my decisions for each patient's situation, and make the best informed decision for them. Before choosing a surgery, I think, what would be the best for this patient?

DG: Despite the MIGS (minimally invasive glaucoma surgery) revolution, GDI and trabeculectomy surgeries are not going away. However, we are able to depend on these two surgeries less often to treat surgical glaucoma. There are a several patient profile where I believe GDI are essential. First, GDI are a tremendous help in patients with a pro-inflammatory environment, such as NVG, Uveitic glaucoma and traumatic glaucoma. Second, in patients with prior corneal transplant surgery (full or partial) ideally with the GDI in the sulcus or far away from the endothelium. Third, in patients that are younger where angle surgery has failed and I am concerned they will have a very active subconjunctival fibrotic reaction. Fourth, in patients who have failed a prior trabeculectomy. Fifth, in patients that are aphakic and at high risk for a suprachoroidal hemorrhage (SCH). In these patients, I will perform a GDI with a rip-cord to allow complete control over when I want the tube to start functioning. Sixth, in patients who do a lot of outdoor work or recreation with a lot of dirt or dust that would put them at high risk for a blebitis. Seventh, in patients who need to return to physical activity very quickly. Again, in these patients, I will perform a GDI with fenestrations and a ripcord. This approach will allow the patient to return to work within a week and then schedule time off in 2-3 months where we can open the tube in clinic. Eighth, in patients with ICE syndrome, posterior polymorphous dystrophy (PPMD) or epithelial down growth. In these group of patients, I am careful to keep the tube away from the cornea and keep the tube relatively long. This is not intended to be an all inclusive list of patient scenarios but more a general guide one when I feel GDI are best indicated.

JFP: Nearly all! I prefer trabeculectomy in patients who are in need of a very low IOP like, those progressing with Normal tension Glaucoma (NTG) or phakic patients with chronic angle closure glaucoma (CACG) who need a lower IOP and do not have a visually significant cataract.

AS: The patient profile I prefer for GDI is IOP > 21mmHg on maximum medications on presentation, prior failed trabeculectomy or tube, those travelling from long distance, and patients with poor compliance, uveitis and NVG.

SD: Do you consider primary GDI procedure as the first option in patients with primary glaucoma, both open (POAG) and closed angle (PACG) cases?

PAS: Primary GDI surgery is a consideration in patients with all varieties of primary and secondary open-angle glaucoma. I use this more commonly in patients who require low postoperative pressures because of moderate to advanced disease and have significant risk factors for failure of trabeculectomy due to episcleral scarring. Young patients, darkly pigmented patients, patients who have undergone prior intraocular or conjunctival-incising surgery, and those with complex secondary glaucoma such as neovascular and uveitic would be included in this group.

I also consider a GDI as a primary glaucoma surgical option in pseudophakic patients with CACG, assuming there is adequate anterior chamber depth for anterior chamber tube placement well away from the cornea. If high PAS preclude safe tube positioning in the anterior chamber, placement in the ciliary sulcus is a consideration in some patients. For phakic patients with CACG and no prior incisional ocular surgery, I prefer a trabeculectomy as an initial glaucoma surgical procedure.

SG: I generally prefer trabeculectomy over GDI surgery as an initial incisional glaucoma procedure in patients at low risk for surgical failure, including eyes with POAG and PACG. However, I favor initial GDI surgery in patients who are poorly compliant with medical therapy and follow-up, even if they have primary glaucoma. The success of trabeculectomy critically depends on the use of postoperative topical steroids and frequent follow-up visits in which laser suture lysis (LSL) and 5-FU injections are commonly performed. A patient who is unlikely to seek prompt medical attention in the setting of a bleb-related infection is a poor candidate for trabeculectomy. I will recommend placement of a GDI if the patient had a poor outcome with trabeculectomy in the fellow eye (e.g. bleb-related infection or hypotony maculopathy). I avoid trabeculectomy in patients who are dependent on CL because of the associated risk of bleb infection, and GDI surgery is a desirable alternative.

SS: I do not prefer GDI over trabeculectomy in eyes with primary glaucoma. In eyes with primary glaucoma with associated co-morbidities like severe ocular surface disease or lid pathology, I would avoid trabeculectomy, hence if there is a need for incisional surgery in these eyes, GDI would be the choice.

CT: I have certainly performed GDI as a first line option in many patients and do consider it to be an effective first line option. Given the many innovative and new options in performing glaucoma surgery, there are many considerations that have to be made when choosing a glaucoma surgery. One consideration is the level of disease. For a mild to moderate case, there may be better options than a GDI.

DG: In certain situations, yes. In angle closure, my first priority would be to remove the lens and open the patient's angle to see if we can enhance their native outflow pathways before creating a new one. If patients with both POAG and PACG have some of the features as the patients described above, I will consider a primary tube. However, the results of the 1-year PTVT study have really caused me to re-assess my surgical decision-making prior to placing a GDI in POAG patients without prior surgery.

JFP: I will perform a "primary" GDI in patients with all types of POAG, especially if they have a high starting IOP. For PACG patients who have not had primary incisional ocular surgery, I prefer to start with a trabeculectomy though I have recently begun using the Xen Gel Stent in select cases.

AS: I consider primary GDI in POAG cases if the IOP $\geq$ 21mmHg and PACG only if angle is still closed after phacoemulsification.

SD: Has the TVT study changed your acceptability of the GDI procedure as a primary surgery?

PAS: For me, the TVT study provided good evidence for the relative efficacy and safety of GDI surgery over trabeculectomy in patients who have undergone limited prior intraocular surgery. It confirmed my clinical impression regarding outcomes of GDI surgery versus repeat trabeculectomy in patients with prior failed trabeculectomy. It also provided good evidence for the relative safety and effectiveness of GDI surgery in pseudophakic patients who have not undergone prior glaucoma surgery. For both of these patient groups, the information provided by TVT has made me more likely to pursue GDI surgery over trabeculectomy.

SG: The TVT Study found that GDI surgery had a higher rate of surgical success compared with trabeculectomy with MMC in patients with previous cataract and/or failed filtering surgery. The TVT Study supports the use of GDIs in a less refractory population than had historically undergone this procedure. However, it is important to note that all patients in the TVT Study had undergone prior ocular surgery, and study results cannot be extrapolated to dissimilar patient groups (i.e. previously unoperated eyes). The Primary Tube Versus Trabeculectomy (PTVT) Study is an ongoing multicenter randomized clinical trial (RCT) that is similar in design to the TVT Study, but enrolled patients without prior incisional ocular surgery. In contrast to the TVT Study, the PTVT Study found a higher success rate with trabeculectomy with MMC compared with GDI after 1 year of follow-

up. However, trabeculectomy with MMC also had a higher rate of early postoperative complications and serious complications producing vision loss or requiring reoperation.

SS: The results of TVT Study have not changed my practice pattern in primary glaucomas or pseudophakes with no prior conjunctival surgeries. Trabeculectomy is still my preferred first surgery in these eyes. However, in eyes with primary glaucoma with early failure of trabeculectomy or pseudophakes with conjunctival scarring or disturbed anterior segment (synechiae, variable AC depth, misaligned IOL), I prefer GDI.

CT: TVT is an important study that demonstrated that tube shunt surgery with a Baerveldt had a higher success rate compared to trabeculectomy with MMC, in patients who had previous trabeculectomy and/or cataract extraction with IOL implant (CEIOL). In these subset of patients at 5 years of follow up, the IOP was similar, as were the number of glaucoma medications. The failure rate was higher in the trabeculectomy group as were the number of reoperations. While the TVT study did not directly study GDI as primary surgery, I feel it has had influence on the increase in the number of GDIs being performed in relation to trabeculectomy.

DG: I think both the TVT and the PTVT studies have had a major impact on how we treat surgical glaucoma patients with open angle glaucoma. Overall, we are less reluctant to place a GDI, as a primary procedure if we think the surgery is best for the patient. Prior to the results of the TVT and PTVT, many surgeons were reluctant to place a GDI unless the patient had failed multiple incisional glaucoma surgeries (multiple trabeculectomies in most cases). Now, thanks to the hard work and dedication of Dr. Steven Gedde and the entire TVT and PTVT research teams, surgeons can place these GDI in specific patients as a primary procedure with confidence in the long-term safety and efficacy of tube shunts.

JFP: The TVT study showed us that we can achieve lower IOPs in patients that are at lower risk for failure. The biggest change for me is with my pseudophakic patients who have not had prior glaucoma surgery. Though many would still perform a trabeculectomy here, the data shows that GDI is associated with greater success.

AS: It has not. PTVT has patients with IOP > 21mmHg and I favor GDI over trabeculectomy in these patients.

SD: Between the valved Ahmed glaucoma implant (AGV) and the non-valved Baerveldt glaucoma implant (BGI), which is your primary preference? What are the patient characteristics which tilt your decision in favour of one as compared to the other? Have the Ahmed-Baerveldt comparison studies influenced your decision in the above regard?

PAS: I prefer the AGV model FP-7 in a few select groups of patients who are at risk for chronic hypotony due to aqueous hyposecretion. Specifically, for patients over the age of 75 years with pseudoexfoliative glaucoma (PXG), NVG or Uveitic glaucoma, I now routinely use this device. I also use the AGV in most patients over the age of 80 years. For younger patients who may also be at risk for aqueous underproduction, I prefer to use a BGI with a relatively small end plate (model BG103-250; 250 mm^2). For most other patients in whom I am using a GDI, I prefer the 350-mm^2 BGI.

SG: The Ahmed Baerveldt Comparison (ABC) Study and Ahmed Versus Baerveldt (AVB) Study are landmark randomized clinical trials comparing the safety and efficacy of the AGV and BGI. These trials have provided valuable information to guide implant selection. The design and results from both trials are remarkably similar, allowing each study to validate the other. The BGI was more effective in lowering IOP, but the AGV had a more favorable safety profile. I prefer a 350-mm^2 BGI in patients with advanced glaucoma and those who are poorly compliant or intolerant of medical therapy, given its ability to achieve lower IOP with fewer medications. I favor the AGV in patients with marked IOP elevation, as the implant reliably produces immediate IOP reduction. I also select the AGV for patients with Uveitic glaucoma and eyes that have undergone prior cyclodestruction/ cyclophotocoagulation (CPC), as the valve helps to prevent postoperative hypotony in patients at higher risk for this complication.

SS: Valved shunts achieve an immediate IOP drop and have less risk of postoperative hypotony. However, they are associated with higher percentage of hypertensive phase, need for glaucoma medications and long-term failure. While, with non-valved implants, the postoperative course is slightly more complex. Initial high IOP needing medications in the early postop, hypotony after the ligature suture dissolves with its attendant complications if not recognized and treated appropriately, hence needing close and frequent follow ups. However, they have less hypertensive phase, less need for antiglaucoma medications and better long-term success. AGV is my preferred choice in most cases. Specifically, I would prefer AGV in eyes Post keratoplasty, vitrectomized eyes, high myopes, very old patients, uveitic patients, PXF, poor follow up, if other eye had hypotony with non-valved device, nanophthalmos, post Keratoprosthesis (K-Pro) eyes and those needing early IOP control. Baerveldt implant was not available in India and hence our experience with non-valved implants is limited. Since the availability of the Aurolab Aqueous Drainage Implant (AADI) which is similar to the BGI, over 4 years, our indications for non-valved implants have slowly evolved from eyes with failed AGV to considering them more often in refractory childhood glaucomas and adult glaucomas. Apart from the indications mentioned, I would prefer a non-valved implant only if postoperative follow-

up is possible for the patient with us or any other local glaucoma specialist and in those eyes with severe allergy to anti-glaucoma medications (as post-AGV we may still need medications in the long term which they may not be able to use). The other consideration is definitely the cost, as the AADI is available at close to ¼ the cost of AGV.

CT: There are many nuances to both valved and non-valved surgeries. I have been using the valved implants more often. The decision depends on similar characteristics as I mention above, such as pathology of disease, IOP, social situation, etc. If a patient lives far away or live independently, I typically choose a valved implant because I find that there may be fewer postoperative interventions needed. These patients may not be able to come for frequent follow ups, and the techniques used in non-valved implants to restrict flow typically would involve more visits to tailor the IOP. These could involve pulling a ripcord, lasering a ligating stitch, or waiting for the ligating suture to dissolve. Once one of these steps is performed, the patient may follow up visit a few days later to check the result. In a non-valved implant, hypotony is a serious consideration that I make sure to follow up on once the tube is opened. For valved implants, no manipulations are needed, though patients may be more susceptible to hypertensive phase, where there is a rise in IOP, and may need to be on glaucoma medications during that time. I have been fortunate to participate in humanitarian projects, and in these settings, if a patient needs a glaucoma implant, I perform a valved implant, because there may not be adequate follow up, and I can be more confident in an early term uncomplicated course. ABC study showed that the BGI may have a lower failure rate, and lower mean IOP in the long run, but had a higher risk of hypotony.

DG: I think the Ahmed-Baerveldt studies were a great addition to the literature and further gave doctors evidence regarding decision making in glaucoma surgery. I applaud and am grateful to all the authors involved in both of these studies (ABC and AVB as well as the combined study) for providing us high quality evidence to help us make better decisions for our patients. We are seeing more and more tube associated hypotony, especially in older patients. My tube of preference, if I can control the IOP for a reasonable amount of time in my young patients would be a 350 BGI and in my patients over 75 years old would be a 250 BGI. If the IOP is very elevated and I know that I cannot watch the IOP for the next 4-6 weeks, I will then place an AGI FP7. In patients that need an AGI FP7 (eg. NVG patients who typically have a very high IOP), I will tell them that they may need another surgery to control their IOP once the eye is more stable. I depend heavily on low energy CPC/Diode laser after a first tube to provide better IOP control. Since I have incorporated this approach into my practice over the past 5 years, it has dramatically decreased the number of second tube shunts that I place in an eye.

JFP: I prefer the AGI in patients with NVG, PXG, and Uveitic glaucoma. For all other cases I prefer a BGI, either with a 250mm^2 or 350mm^2 endplate, depending upon the age of the patient. For older patients, I prefer the smaller implant.

AS: I perform a Molteno implant. Our data show similar IOP and medication reduction compared to BGI-350, which we are publishing soon. I choose AGV in patients with increased chances of hypotony though my preference is non-valved implants.

SD: What are the operative considerations during placement of the GDI plate?

PAS: Posterior placement of the GDI plate is critical to optimal functioning of the device and limiting complications. I prefer to place the plate at least 10 mm posterior to the limbus in the superotemporal and inferotemporal quadrants and 9 mm posterior to the limbus inferonasally. This positions the plate well posterior to the rectus muscle insertions. Placement of the end plate in this location enhances function by allowing for better capsule development and aqueous flow and minimizes complications associated with anterior plate positioning such as strabismus, discomfort and conjunctival erosion.

SG: The quadrant for GDI placement is generally made preoperatively, but occasionally intraoperative findings (e.g. extensive conjunctival scarring or scleral ectasia) may direct the surgeon to a different quadrant. I generally prefer the superotemporal quadrant for GDI implantation, but the inferonasal quadrant is my second choice. However, in eyes with silicone oil, I will place the tube inferiorly in case oil migrates into the anterior chamber. In the presence of scleral thinning, the end plate can be attached with tissue glue or sutured to the rectus muscle insertions to avoid scleral sutures. The tube should be positioned away from the corneal endothelium. If I'm not satisfied with the tube position intraoperatively, it's easy to create a new needle track adjacent to the first one.

SS: Based on the indication and the condition of the eye, I choose the type and location of implant placement. I prefer superotemporal mostly followed by inferotemporal location. I prefer limbal based conjunctival incision, 5-6 mm behind the limbus; this allows smaller conjunctival incision size of 5-6 mm, helps easy identification of the muscles, easy insertion and fixation of the implant, less dependent on an assistant for exposure and allows quick and easy conjunctival closure. I prefer plate fixation 9-10 mm from the limbus with 9-0 prolene suture. I prefer a scleral tunnel 3-4 mm from the limbus for tube insertion. The tube length if in AC is around 2 mm. If in sulcus it is longer and depends on the pupil size. If in the anterior chamber, I prefer the tube placement parallel to the limbus. However with sulcus placement, I prefer the tube perpendicular to the limbus so that the tube tip

is visible beyond the pupillary margin. The entire tube length is covered by the scleral patch graft. I use fibrin glue and additional 10-0 nylon sutures sometimes. The closure of conjunctiva is with 8-0 vicryl in a continuous fashion (I use 8-0 vicryl on a round bodied needle).

CT: Adequate dissection is important. I like to identify the muscle edges, which serve as a landmark for me to suture the plate. If doing a large plate that sits underneath the muscles, there must be good dissection, and the muscles must be isolated with a muscle hook. My placement of the plate is roughly 7-8mm posterior to the limbus, which is essentially at the edge of the muscle insertions. This allows for needling of the plate if needed later on. If the plate it too far back, it may be more difficult to access. Additionally, if the patient has a thick tenon's capsule, I will perform a tenonectomy, which I find will decrease the thickness of the capsule that forms over the plate.

DG: There are several considerations. The first, which has been previously answered above, is tube or no tube. Once we decide that a GDI is the best for the patient, the next immediate question is which one. The GDI's I currently use routinely are Ahmed valve (FP7 and FP8), Baerveldt 250mm^2 and 350mm^2, as well as the Molteno implant 185mm^2 and 245mm^2. If the IOP is very high and I do not think I can wait 4-6 weeks for the tube to open, I will consider an FP7. If I am concerned about long-term hypotony, I aim to use the smallest plate size possible (FP8 if IOP very high, BGI 250 or Molteno 185 if the IOP not too high). If I do not want to (or cannot) isolate the muscles during the surgery, for example in a patient with a previously placed scleral buckle, then I will use an implant that does not require muscle isolation (Molteno or Ahmed valve). Lastly, the patient's age is a key factor. We know that with age, the aqueous production slowly decreases and we are starting to see more and more tube associated hypotony (as stated above). I therefore will err on the side of the smallest plate possible in patients who are in their 80's or 90's.

JFP: I prefer that the muscles are cleanly dissected (with either implant) and the implant secured 10 mm posterior to the limbus. This encourages better flow and I believe decreases the incidence of strabismus.

AS: I make the traction suture centered along the planned peritomy. Ensure that you make the peritomy large enough to where you don't tear tissue. If placing a BGI 350, which goes under muscle at least 8mm back, the front of the plate should run parallel to the tangent of the limbus so that tube inserts without a significant bend.

SD: What are the operative considerations during tube placement in the anterior chamber (AC), sulcus and pars plana? What special precautions do you consider in post-corneal transplant patients?

PAS: For AC tube, placement just anterior to and parallel with the iris is ideal. While some contact with the iris is generally well tolerated, this should be avoided if possible. The tube should have an anterior bevel at its proximal tip and should lie between the pupillary margin and the limbus. Sulcus tubes should be positioned just anterior to and parallel with the intraocular lens (IOL). The proximal ostium should be beveled posteriorly to avoid iris incarceration and the tip should be seen at the time of insertion to ensure proper placement (above the IOL) and following pupillary dilation. Pars plana tubes should also be visualized at the time of surgery to ensure that there is complete insertion into the vitreous cavity and that the proximal ostium is not obstructed by residual vitreous gel. I prefer to bevel the tip posteriorly with pars plana tubes. For patients who have undergone prior PK, I prefer to place the tube deep in the AC making sure that the trajectory of the tube is parallel with the plane of the iris or angled slightly posterior. I prefer to keep the tube relatively short, with the tip extending no more than 2 to 3 mm from the limbus as visualized through the cornea. Sulcus placement is also a good option for some patients, although there is little evidence supporting the benefit of a sulcus tube over a well-positioned AC tube. Pars plana placement should be considered when concurrent pars plana vitrectomy (PPV) is required for other reasons or there is inadequate room or other contraindications to AC or sulcus positioning.

SG: I will generally insert the tube into the AC, as long as there is adequate space. If there are concerns that the tube may be positioned too close to the cornea in a phakic eye, concurrent lens extraction (especially with a visually significant cataract) will provide more AC space. In eyes with endothelial dysfunction or prior corneal transplantation, I position the tube as far away from the cornea as possible. This commonly involves sulcus placement in pseudophakic eyes. The tube is cut with an anterior bevel when inserted into the AC and with a posterior bevel when placed in the sulcus, which serves to prevent obstruction by iris. Alternatively, the tube may be inserted through the pars plana. However, a complete PPV with trimming of the vitreous base is required if the tube is placed in the vitreous cavity.

SS: I prefer the tunnel and tube entry with a 24 G needle, in few eyes with thin and stretched sclera (specially in children) I prefer 26 G needle entry. This prevents peri-tubular leak and snugly fits the tube entry hence preventing postoperative hypotony. I trim the tube after the needle entry and always trim bevel up. When tube entry is difficult, I tend to reverse the tube tip (bevel down) which helps in easy entry, once inside the eye I rotate it bevel up. Always do this only in vitrectomized eyes or else plan PPV with pars plana tube entry. In Post-PK/DSEK eyes, if the AC depth is good, I place the tube in the AC, prefer a shorter tube taking precautions not to place it closer to the graft. In virectomized eyes or eyes with with extensive

PAS or very shallow AC, a sulcus placement or pars plana tube is preferred.

CT: For AC, the angle of entry is important. The tube entry needs to be parallel to the iris, and not touching the iris or cornea. I teach my fellows to identify the entry point of the sclerostomy with the 23G needle, then look away from the microscope and at the surgical field, at a macro level view, in order to visualize the angle of entry. Due to rotation of the globe, the needle could be over or under tilted, and this may not be apparent when looking though the microscope. If this is the case, I ask them to make an adjustment to the angle of entry, and once the angle is noted to be parallel to the iris, then I instruct them to make the sclerostomy. For pars plana placement, I instruct fellows to not point the needle too radial. The entry should be slightly directed posterior but not radial. This is to ensure that after the surgery, the tube may be visualized readily at the slit lamp, so the doctor can check for patency and to ensure it is not plugged with vitreous. In corneal transplant patients, the tube would ideally be as far away from the cornea as possible. If the patient has had a corneal transplant and is pseudophakic, ideally the tube will be placed in the sulcus. Alternatively, a PPV may be performed and the tube may be placed in the pars plana.

DG: I do my best to keep the tube slightly long so that the tip is near the iris border. I also aim to try and place the tube as close to the iris (and as parallel to the iris) as possible. If I place the tube in the sulcus, I will often leave the tube in the visual axis and have never had a patient report that they can see the tube. In my patients with a PKP, I am very careful to keep the tube as far away from the cornea as possible and will often place the tube in the sulcus. In patients with corneal surgery, I also like to keep the tube slightly longer in case it is inadvertently cut during a repeat PKP or in case it needs to be redirected. Again, my first priority would be to keep the tube as far away from the cornea as possible. Unless there is a specific reason for me to place a tube combined with my retina colleagues (in the setting of a K-pro for example), I will not usually place the tube in the pars plana. In patients with NVG, I purposefully keep the tube long. These patients tend to have PAS and the iris is often traumatized during tube placement. If the tube is too short or just in the angle, one can often get a blood clot over the tube and a severely elevated IOP on postoperative day #1.

JFP: For AC tubes, I prefer the tube deep in the AC, resting just above the iris. For sulcus and pars plana placement, I always make sure I can see the tip clearly before I close the conjunctiva. In fact, for sulcus placement, I prefer to touch the tube tip with a cannula to be sure it is in the proper spot (Not the pars plana!). For post PK patients, I prefer sulcus placement of a GDI. Whether I place an AGV or BGI, I try to leave the eye fairly well pressurized at the conclusion of the case to avoid postoperative bleeding. Often a precipitous drop in IOP will lead to significant bleeding from the needle track and this can result in early tube occlusion and obstruction. Pars plana placement is a reasonable option for these patients but it does require more surgery and if the patient becomes hypotonous, it is much harder to manage given the posterior location of the tube. Injections of viscoelastic to re-pressurize the eye are not as helpful in these cases.

AS: We still place it in the AC but the goal is to be posterior. Sulcus placement is not as consistent as some report and there is a risk of bleeding if you hit the ciliary body.

SD: What are the special considerations with GDI procedure in glaucoma post-vitreoretinal (VR)? How do you plan the shunt placement in cases with a scleral band/buckle (SB)?

PAS: For eyes that have undergone prior PPV, placement of the tube through a pars plana scleral fistula is a reasonable option. If the prior PPV was not performed with the intent to place a tube in this location at a later date, careful preoperative evaluation should be performed to determine whether additional vitrectomy is required at the time of tube insertion. Removal of the posterior hyaloid membrane (which often detaches following PPV) and additional trimming of the anterior vitreous base may be required to prevent postoperative occlusion of the tube. Ocular hypotony (as often occurs following tube ligature release with non-valved GDIs) can be more difficult to manage with a tube placed in the posterior segment. Injections of viscoelastic to re-pressurize the eye are less effective in these patients as the viscoelastic does not have direct access to the tube tip and adds less to tamponade of the tip and resistance to aqueous flow as it does with AC tubes. For eyes that have an encircling band, I position the end plate over the band and secure it directly to the band with 8-0 nylon sutures as the band generally sits 10-12mm posterior to the limbus. I use a BGI in these situations as the lower profile of this device (compared with the AGV) facilitates insertion and conjunctival closure with less risk of postoperative erosion. When using a 350-mm^2 BGI, I attempt to dissect scar tissue and place the wings of the device beneath the muscles. If this is not possible (as is more common with wider encircling bands), I place the wings over the muscles. For patients where silicone oil cannot be removed, AC placement of the tube is required. If the pupil is large and the eye is aphakic, it is best to place the tube inferiorly to minimize the risk of contact with the anterior silicone meniscus. In pseudophakic patients with a relatively intact iris diaphragm and small pupil, the tube can be placed superotemporally, leaving the intraocular portion long to reduce the risk of emulsified silicone oil draining into the tube.

SG: Eyes that have undergone a PPV may have tube insertion though the pars plana. However, a complete vitrectomy is needed because any residual

vitreous may lead to tube obstruction. I prefer the BGI in eyes with a retinal band/buckle, given the low profile of the device. If a radial element is present, this quadrant should be avoided. Sufficient posterior dissection is performed between the sclera and Tenon's capsule to allow the implant to seat comfortably over the rectus muscles. In cases where the band is located anteriorly, the end plate can be sutured to the band. If the band is positioned more posteriorly, the implant is placed over the band. I excise the capsule overlying the band in the quadrant of GDI implantation. This may allow contiguous encapsulation of both the encircling band and Baerveldt plate. Studies suggest that the degree of IOP reduction is proportional to the surface area of the capsule.

SS: Special considerations in these eyes are conjunctival scarring, thin sclera, limited space, silicon oil in eye and predisposition to recurrent retinal detachment (RD). In eyes with multiple previous VR surgeries and scarred conjunctiva, trabeculectomy may not be possible and GDI with posterior subconjunctival drainage have a definite role to play. Placing an implant in these eyes is technically challenging due to the space constraint. The preoperative planning includes choosing the location for the implant placement and selection of implant type. The extent, position and height of the buckle need to be identified to decide the site of placement of the GDI. It is ideal to avoid the quadrant where the buckle is anteriorly placed due to the difficulties in fixing the plate. In an anteriorly located belt buckle, GDI can be fixed 8 mm from the limbus, behind the buckle. In posterior buckle, the implant can be placed over the encircling band and sutured to the capsule or directly to the buckle. In the presence of segmental buckle, it is better to choose a quadrant where the scleral band is absent. If the conjunctival scarring is extensive, a pediatric implant is chosen or an adult implant can be trimmed appropriately to ensure adequate and free conjunctival closure. It is better to avoid dissection in areas with thin sclera and also to avoid excising the buckle or disturbing the buckle. Also preoperatively, adequate IOP control is mandatory to avoid sudden decompression. In cases of silicone oil filled eyes, inferior implant placement would be preferred. In case of eyes post-silicone oil removal, or floating bubbles, one can choose any site as appropriate. In these eyes I prefer a pediatric AGV (FP8) which is safer in a space constrained situation to avoid implant exposure and its related complications.

CT: In a patient with a scleral buckle, the plate can typically be sutured to the encircling element, which serves as a nice suturing platform. One consideration is to check to be sure the patient does not have lagophthalmos prior to the GDI placement, because putting a plate over an encircling element could worsen it and lead the patient to have cornea exposure. If the patient has some lagophthalmos, then I recommend an inferonasal placement of the GDI. If a patient with silicone oil in the eye has elevated IOP and the oil is unable to be removed, then I recommend inferior placement of the tube. This is because if the oil migrates from the pars plana into the AC, it will rise, and if the tube is placed in the superior position, it may become blocked with oil. If the tube is inferior, the oil will rise within the AC and the tube will not get occluded.

DG: Eyes with prior PPV are at increased risk for SCH when the tube opens. I therefore tend to change my technique in these eyes when performing non-valved implants and place a rip cord (4-0 nylon through the tube, tucked in the inferior subconjunctival space and tied off near the plate with a 7-0 prolene suture). This technique allows me to use fenestrations to temporarily lower the IOP but more importantly, it allows me to have complete control over when I open the tube. The tube opens when I want it to open. I can therefore open the tube in clinic, place a drop of atropine in the eye and have the patient sit in the waiting area for an hour. I sometimes inject viscoelastic into the AC at the slit lamp if the IOP is too low and I am very concerned about developing a SCH. I also make sure the patient limits their activity strictly for the first week once the tube opens. This approach theoretically allows me to further decrease the chance of a SCH and maximize safety outcomes. In eyes with a prior scleral buckle, I suture the plate to the buckle and do not attempt to isolate the muscles. I usually place a Molteno implant (the largest possible, depending on the anatomy) knowing that if I need further pressure lowering, I can always follow up with a low energy CPC/Diode.

JFP: For eyes that have an encircling band, I prefer to use a BGI (often 250 mm^2 due to tight space) and I will routinely secure the implant to the SB if it sits 10-12mm from the limbus. This requires extensive dissection but often leads to better long-term results with less chances of erosion. Due to the high profile of the AGV, I find it challenging to place above the SB and safely close the conjunctiva. I also find the AGV tend not be as successful in these patients due to the higher risk of encapsulation with additional hardware on the eye. For eyes with or without a SB that have silicone oil which cannot be removed, I will use an AGV. To ensure that the oil stays back, I will fill the eye with Healon GV and I prefer the AGV in these cases as it will filter the viscoelastic more easily than a BGI that relies on a wick or fenestrations to lower the IOP in the early postoperative period.

AS: With a buckle, we use a BGI-250 and sometimes cut the plate to size. If there is significant scarring, consider placing the tube from a tube extender into the fibrotic band around the buckle.

SD: What are the special considerations in patients with Uveitic and Neovascular glaucoma?

PAS: Given the concern with compromised ciliary body function in ischemic eyes with NVG or in eyes with chronic uveitis, my preference is to use a 250-mm^2

BGI. In patients with more severe disease or over the age of 75 years, an AGV may be preferable due to the presence of a flow-restricting mechanism at the distal end of the tube and the smaller surface area of the end plate. These features provide additional protection against hypotony in the early and late postoperative periods, respectively. Good control of the underlying disease is important in these patients. For patients with NVG, adequate panretinal photocoagulation (PRP) and treatment with anti-VEGF agents prior to GDI surgery is recommended. Control of uveitis with topical, intraocular and systemic steroids and other immune-modulating agents prior to glaucoma surgery is critical. Ongoing postoperative management of ischemic retinal disease and uveitis in appropriate patients is essential.

SG: I prefer to use an AGV in patients with Uveitic glaucoma and NVG. Patients with uveitis are more prone to hypotony, and the flow restrictor in this valved implant minimizes the risk of postoperative hypotony. NVG is frequently associated with marked IOP elevation, and a valved implant reliably provides immediate IOP reduction. The rate of progression to No Light Perception (NLP) vision was twice as high in the Baerveldt group compared with the Ahmed group in the ABC Study, providing compelling evidence to support the use of an AGV in patients with NVG.

SS: Valved implants are preferred in these cases. There are no other special precautions. Meticulous surgery is needed to avoid trauma to the iris and to avoid bleeding and inflammation.

CT: I frequently see patients with NVG. Often, they also have advanced cataracts. In these situations, I almost always perform a cataract surgery and valved implant. At the end of these cases, I leave a moderate amount of viscoelastic in the AC to guard against potential hypotony and potential for hemorrhage. In these cases, when the IOP goes from a preoperative very high level to postoperative low level, there is a possibility of choroidal effusions and potential for hemorrhage. I find that retaining viscoelastic in the AC guards against this. In uveitic cases, I favor valved implants to guard against the possibility of hypotony in the long term.

DG: These patients tend to have severely high IOP and are at very high risk of developing hypotony afterwards. I typically will place either an AGI FP7 or a small non-valved implant (Molteno 185) if I can, depending on the preoperative IOP. In some patients with aggressive inflammation, I may consider even placing an AGI FP8.

JFP: For both of these cases I prefer an AGV. For uveitic, the only consideration I have is to ensure that they are on the proper steroid regimen as dictated by their uveitis specialist. For NVG patients, I try to have their retina specialist inject an anti-VEGF agent 3 days prior to tube shunt placement. During the surgery, I am especially careful to keep the tube off the iris and preform a more anterior placement if necessary. Any contact with the iris, whether it is with the 23G needle used to create the tube entry site or the tube itself, can result in bleeding. I will leave the eye with a full viscoelastic fill at the completion of the case and inject Kenalog (triamcinolone) into the sub-tenon's space to limit the amount of postoperative inflammation.

AS: Caution should be taken in a patient with active neovascularisation or a hyphema, we prefer diode CPC here as there is a significant risk of a larger hyphema if the IOP drops after a tube shunt. In uveitis, we inject dexamethasone in the sub-conjunctival space.

SD: Do you routinely use patch grafts to cover the tube? If so, what is your preferred choice of graft material and how much portion of the tube do you cover?

PAS: I routinely use a patch graft to cover the anterior portion of a GDI tube and the limbal (or pars plana) insertion site. This is done to minimize the risk of conjunctival erosion with exposure of the tube. My preferred patch graft material is VisionGraft human corneal allograft (Tissue Banks International) oriented with its long axis parallel with the path of the tube to cover the anterior 5 to 6 mm of the tube. The clarity of this tissue permits visualization of the underlying tube and allows LSL of the tube ligature if positioned beneath the graft.

SG: A low incidence of tube exposure has been reported with tube insertion through a long scleral tunnel without a patch graft. I insert the tube through a 4-5 mm scleral tunnel, but I also place a patch graft over the limbal portion of the tube to further minimize the risk of tube exposure. I generally use cornea as the patch graft material because it is transparent and cosmetically superior to sclera or pericardium. It is particularly important to use a corneal patch graft with inferior GDI placement, as the lower lid covers less of the graft compared to the upper lid with superior GDI implantation.

SS: Yes, I do use patch graft in all cases. I prefer preserved donor sclera. I use it cover the entire subconjunctival tube length including anterior to the tube entry up to the limbus. I use fibrin glue to fix it and also supplement with 10-0 nylon suture anteriorly, if needed. In all children supplemental sutures are given. I use half thickness corneal patch graft in very limited cases like, in young patients if they have a cosmetic requirement.

CT: I routinely use a cornea patch graft to cover the tube. I use a half portion of cornea to cover the tube and it typically covers about 5mm of the tube course.

DG: I routinely use partial thickness corneal tissue to help avoid tube erosions as I feel it is very durable and also is much more cosmetically appropriate than sclera or pericardium. There are more and more studies showing very good success when placing the tube through a long scleral tunnel and under a scleral flap, thus avoiding the need and

expense of a patch graft. I think patch free approach is very attractive but have not incorporated it into my practice as I still feel that in the United States, using a patch graft is considered the standard of practice. Moreover, I know that it is helpful and is very unlikely to be harmful. Additionally, I still place the tube through a 3mm scleral tunnel and aim to enter the AC as close as I can get to the 12 o'clock position. I feel lid coverage helps decrease the risk of tube exposure.

JFP: I use VisionGraft to cover all of my tubes and orient it in a "D" fashion to cover as much of the tube as possible.

AS: Yes, I use tutoplast sclera. We cover the portion from the limbus to just beyond the insertion into sclera.

SD: What is your preferred technique for tube occlusion during the early postoperative period in non-valved (BGI) implants? What measures do you consider for IOP control during that time? Would you prefer to add oral carbonic anhydrase inhibitors (CAIs) for IOP control postoperatively in these patients?

PAS: My preference for tube occlusion at the time of BGI implantation is a single, external, 7-0 polyglactin suture. I position this ligature 5 to 6 mm anterior to the front edge of the end plate so that it is easily visualized for release postoperatively (following encapsulation of the end plate), using an argon or green diode (532 nm) laser. In my hands, a single fenestration through both walls of the tube using a 10-0 polyglactin suture needle and leaving a segment of suture through the fenestration to act as a stent has proven to be the most consistent technique for achieving some aqueous egress and IOP reduction in the immediate postoperative period. Topical medications are generally used to supplement IOP reduction while the tube is ligated. Oral CAIs are sometimes used, despite their side effects, to optimize for IOP control during this period.

SG: Unlike valved implants, non-valved implants require a temporary restriction of aqueous flow with tube ligation or occlusion until encapsulation of the end plate occurs. This serves to minimize the risk of postoperative hypotony. I ligate the tube with a 7-0 polyglactin suture near the tube-plate junction, and I place 1-3 fenestrations just anterior to the tube ligature using a TG-140 needle (Ethicon). I have found that tube fenestration is an effective way of providing IOP reduction in the early postoperative period. However, fenestrations generally begin failing a few weeks after surgery, and I frequently will need to add glaucoma medications prior to opening of the tube. An oral CAI is a viable option if topical glaucoma medications are not sufficient, although there is an added risk of significant hypotony with tube opening. An orphan trabeculectomy at the time of GDI placement is an alternative approach for early IOP control. If I need reliable, immediate IOP lowering in the setting of markedly elevated IOP, I will generally choose a valved implant.

SS: Double ligature with 6-0 vicryl suture and ensuring complete tube blockade is my preferred technique. I use postoperative anti-glaucoma medications (AGM) including oral CAIs for IOP control (if they can tolerate). I also use tube fenestrations proximal to the tube ligation for early postoperative IOP control in non-valved devices.

CT: For BGI, I use a tube ligation with a 7-0 vicryl. I fenestrate the tube with 3-4 passes with the 7-0 needle to provide a slow flow until the suture dissolves, typically in 5-6 weeks. If the IOP is elevated during the period before suture dissolution, I find that topical glaucoma medications work sufficiently. In rare cases, an oral CAI may be needed. Occasionally, I will ligate the tube with a 7-0 prolene, which can be lasered at the slit lamp. This enables a more controlled opening of the tube that the doctor can dictate. Prior to lasering the suture, I place 1 drop of atropine. Using a Ritch lens and an argon laser, the prolene can be lasered. One consideration in doing this is that it is important to tie the suture knot on the underside of the tube. This can be achieved by turning the implant upside down, then tying the suture. This will ensure that the argon laser goes through a single line of prolene, rather than a dense knot. Additionally, if the IOP is too low after the laser opening, viscoelastic may be injected at the slit lamp, to protect against hypotony.

DG: In my routine cases, I tie the tube off near the plate with a 7-0 vicryl suture. I then perform 3-6 fenestrations with the needle on the 7-0 vicryl suture. In patients who are on blood thinners, have undergone a PPV, come from a long distance away, or those that need to get back to work as soon as possible, I will consider using the ripcord technique that I have described above. Using a rip cord approach gives me complete control over when the tube opens and maximizes safety in this high risk group of patients. If needed, I will use an oral CAI, however, my goal is to avoid starting my patients on oral medications. If the patient has a severely elevated IOP and I am concerned that I may not be able to keep the IOP controlled with aggressive fenestrations during the immediate post-op period, I am much more likely to consider a valved implant.

JFP: I occlude the BGI with a 7-0 polyglactin suture. For early IOP control, I use a 10-0 polyglactin suture on a cutting needle to make a fenestration and leave a strip of suture material going through the fenestration to act as a stent to allow for aqueous to egress out.

AS: I use a vicryl suture. We do prefer 1-2 slits but this is not very titratable as others describe. Around 4-5 weeks if the IOP is dangerously high despite all medications we can consider LSL. For early severe IOP elevations we can create slits through the tube at the slit lamp using 7-0 vicryl needles.

SD: What measures do you consider during tube opening in BGI? How often do you encounter hypotony post-tube release and how do you prefer to manage it?

PAS: I feel that it is best to release the tube ligature in a planned fashion so that measures can be taken to minimize the occurrence of hypotony and its related complications that frequently follow initiation of flow into the drainage reservoir. It is generally safe to release the ligature between the 3rd and 4th postoperative week as adequate capsule formation has occurred by that time. If the IOP is well controlled, I will frequently wait until the 5th postoperative week to release the ligature. After week 5, the risk of spontaneous release of the 7-0 polyglactin ligature increases significantly. Depending on the IOP level, I ask the patient to discontinue some or all of their glaucoma medications 2 to 3 days prior to ligature release so that the aqueous suppressant effect begins to dissipate before the tube is opened. Immediate, profound reduction of the IOP frequently occurs following ligature release as fluid from within the eye fills the reservoir of the BGI. If the IOP drops below 8 mm Hg, especially in patients at high risk for SCH, I prepare the eye with 5% betadine and administer an AC injection of a cohesive viscoelastic agent via a 30 gauge needle at the slit lamp. This viscoelastic maintains the AC depth, elevates the intraocular pressure and provides some temporary resistance to aqueous flow through the tube. All glaucoma medications are discontinued and, in phakic patients, 1% atropine is added twice daily. I also increase the frequency of topical corticosteroid as an increase in intraocular inflammation, sometimes with fibrin formation, generally accompanies ligature release. The patient is asked to return to the office within 48 hours. Occasionally, the viscoelastic injection needs to be repeated to allow the eye more time to equilibrate at a lower IOP level.

SG: I have found that a 7-0 polyglactin suture ligating a tube will reliably lyse about 5-6 weeks postoperatively. A sudden drop in IOP increases the risk of SCH, and I instruct the patient to avoid bending, lifting, and straining during this period. I follow patients closely around the time a tube is expected to open. I will occasionally open a tube with argon LSL (laser settings: 50 microns, 500 mW, 0.02 seconds) when the IOP is significantly elevated and/or the patient is using multiple glaucoma medications, as it is beneficial to know the exact time of tube opening. A visible separation of the suture is not seen (as with LSL of a nylon flap suture following trabeculectomy), but the eye will become noticeably softer when the suture is successfully cut and a bleb will form over the end plate.

SS: Close follow up in the early postoperative period until about 3 months. I stop oral Diamox by 5 weeks and topical AGM by 5-6 weeks based on the level of IOP. I also step up the topical steroids and cycloplegics during the time the ligature is likely to open (by 5-6 weeks) to treat the inflammation and prevent hypotony and its associated complications. Hypotony is common but not all develop hypotony related problems. I see this in close to 30% of eyes and majority resolve with topical medications. I have had to intervene for prolonged hypotony in about 5% of eyes with tube stenting using 3-0 or 4-0 nylon. Hypotony induces inflammation which further worsens hypotony, hence that vicious cycle needs to be broken.

CT: Hypotony certainly may occur after suture dissolution. I prepare the patient for this by having them stop the IOP drops at week 5, and I tell them that they may feel a sensation in the eye, indicating the tube opening. I have them come back at week 6, and if the tube is open and the IOP is in the low single digits, then I may start cycloplegics to protect the eye from developing choroidals. If there is a shallow AC with or without choroidals, then I will consider anterior chamber reformation at the slit lamp with viscoelastic.

DG: My goal is to keep the tube closed for as long as possible, especially when using the rip-cord technique. When I tie off the tube with a vicryl suture, I see the patient around the time that I think the tube will open and place a drop of atropine in the eye. I also will taper and eventually stop all glaucoma drops around the time that I expect the tube to open. During this phase, I still have the patients on topical steroids at least 4 times a day. In the case of persistent hypotony after the tube opens, I usually put the patient on atropine at least BID. I also keep the patient on topical steroids 4-6 times/day. If the patient has significant hypotony with large choroidal detachment (CD) or tube corneal touch or lens-corneal touch, I will reform the eye, at the slit lamp, with a viscoelastic. If the choroidals are persistent despite this conservative treatment, I will consider draining the choroidals in the operating room. In extremely rare cases, I have to revise or remove the tube shunt.

JFP: I will release the polyglactin ligature in the office at postoperative week 4-5 for high-risk cases (previous hypotony in the other eye, high myopia, aphakia, etc.) and fill the eye with a cohesive viscoelastic right after to ensure that the IOP does not drop and remain too low. For all other cases, I follow the patient weekly after week 4 and will begin to remove any topical IOP medications that the patient is on if the IOP allows. For certain phakic patients, I will begin Atropine as well. If the IOP is low but the eye is stable, I will not intervene. When the IOP is low and either the AC shallows or choroidal effusions begin to develop, I will inject viscoelastic into the AC to slow the flow though the tube (works better for AC or sulcus tubes). If the IOP remains low and the effusions worsen despite multiple viscoelastic injections, I will return to the operating room to drain the effusions. Re-ligation

of the tube with downsizing of the implant is rarely needed but I will do this if the patient does not appear to have adequate encapsulation as evidence by B-scan ultrasonography.

AS: Hypotony can be transient in most cases but 5% can have a prolonged course. Treatment is usually conservative with atropine unless there is lens endothelial touch. In those cases we fill with cohesive viscoelastic, the amount varies based on the hypotony and AC depth.

SD: How can we identify and manage the hypertensive phase? Is it seen with both valved and non-valved implants?

PAS: The "hypertensive phase" commonly occurs with both flow-restricted and non-flow-restricted devices. It is defined by elevation of the IOP despite aqueous flow into the capsule of the GDI. B-mode echography can be useful in distinguishing this phenomenon from IOP elevation due to occlusion of the tube. I have found that the hypertensive phase tends to be more frequent and greater in magnitude with the AGV as compared with the BGI. Regardless of the device, management should be directed at aqueous suppression to reduce the IOP, thereby reducing surface tension on the fibrous capsule surrounding the end plate which is an important stimulus to increased fibrosis, capsule thickening and reduced permeability to aqueous outflow. In fact, I have found that early aqueous suppression following endplate encapsulation and ligature release is helpful in minimizing the occurrence and magnitude of hypertensive phase IOP elevations. I will start topical aqueous suppressant therapy when the IOP rises to between 12 and 14 mm Hg after ligature release in patients with a BGI, especially if they have advanced disc damage. I maintain topical corticosteroid therapy.

SG: A hypertensive phase is commonly seen after GDI surgery and usually develops a few weeks postoperatively. In this condition, the capsule surrounding the end plate is less permeable to aqueous humor resulting in IOP elevation despite tube patency. The hypertensive phase after GDI surgery is felt to be analogous to the encapsulated bleb phase often observed after trabeculectomy; both are treated with aqueous suppressants and frequently resolve over time due to tissue remodeling as part of the wound healing process. Early initiation of treatment with aqueous suppressants has been shown to reduce the likelihood of a hypertensive phase and improve surgical success with GDI surgery. A hypertensive phase may occur with valved or non-valved implants, although the incidence appears to be higher with valved implants. Aqueous humor rich in inflammatory mediators is delivered to the end plate immediately after surgery with valved implants, while non-valved implants have a delayed drainage of aqueous humor to the end plate after ocular inflammation has subsided. This has been offered as an explanation for the higher rate of hypertensive phase with valved implants compared with non-valved implants.

SS: Hypertensive phase is more commonly seen with valved implant in 50-60% eyes (in my cases). This problem can be significantly decreased by starting topical aqueous suppressants in the early postoperative period. We typically start aqueous suppressants when the IOP is around 8-10 mmHg. Hypertensive phase is not common with non-valved implants and in our experience it is seen in around 27-30% eyes. We do not use prophylactic AGM in non-valved implants, as it is short lived, and treat cautiously with aqueous suppressants for limited time of 3-4 weeks during which time the hypertensive phase resolves. In my experience, I have seen delayed hypotony when hypertensive phase is treated aggressively in eyes with non-valved implants, hence shorter duration AGM along with topical steroids are preferred with close monitoring of IOP. I prefer to stop the glaucoma medication once the hypertensive phase resolves except in less than 10% eyes where it may need to be continued.

CT: Hypertensive phase may be seen in both types of implants. Typically, the IOP rises above goal, in which IOP lowering drops should be started to blunt the increase. The etiology may be continued wound modulation at the plate. This phase will typically pass once the patient is restarted on IOP lowering drops. If the IOP is elevated and sustained, then a plate needling with 5-FU injection can be performed at the slit lamp.

DG: The hypertensive phase is definitely seen in both valved and non-valved implants. In valved implants, I start the patient on timolol 0.25% usually around the 2-3 weeks point, which typically coincides, with the point in time when the IOP is slowly starting to increase. In non-valved implants, I will start timolol typically 2 weeks after the tube opens. I think the hypertensive phase is related to aggressive steroid use but feel that steroids are essentially to control inflammation and allow the eye to recover appropriately from surgery. I only consider tapering the steroids when the AC is completely quiet after the tube has opened.

JFP: This is commonly seen with both AGV and BGI implants. Once the IOP goes above 16 mm Hg, I will begin topical IOP lowering medications. I do not alter my steroid regimen but treat depending upon the degree of inflammation present.

AS: I treat IOP > 12mm Hg with medications. After tubes open, they can still have a hypertensive phase. Both implant types can get it.

SD: What is the routine postoperative medication regimen you consider? Is the duration of anti-inflammatory medications same in both procedures?

PAS: Following GDI surgery, I start my patients on 1%

prednisolone acetate 8 times/day or difluprednate 6 times/day and maintain this through the period of ligature release (for BGIs) or plate encapsulation (for AGVs). I then taper these medications based on the degree of intraocular inflammation with the goal of discontinuing by 3 months after the surgery. For patients in whom I am concerned about the possibility of excessive inflammation or the ability to comply with the postoperative eye drop regimen, I administer a posterior sub-Tenon's injection of 40 mg of triamcinolone acetate at the conclusion of the surgery. I also use a topical antibiotic for the first 3 postoperative weeks. In phakic patients and those at high risk for hypotony-related complications, I use 1% atropine eye drops until the tube is functional and the IOP has stabilized.

SG: My standard postoperative medical regimen after GDI surgery consists of a topical antibiotic 4 times daily for 1 week and a topical steroid 4 times daily for approximately 2 months, followed by a steroid taper over the subsequent month. An increased AC reaction is universally seen when a non-valved implant opens, so I usually do not begin a steroid taper until after tube opening. Glaucoma medications are used depending on the postoperative IOP level, and the frequency of steroid administration may be modified based upon the inflammatory reaction observed.

SS: For AGV, I give topical steroids for 3-4 weeks, cycloplegics for 2-3 weeks, AGM (aqueous suppressants) after 1st week. I step up the AGM during hypertensive phase. For AADI, early postoperative AGM need to be continued based on the IOP. Mostly low dose steroids and cycloplegics are needed. As the ligature opens up in AADI/ BGI around 5th to 6th week, the steroids are stepped up, cycloplegics are restarted (to treat the inflammation) and anti-glaucoma medications are stopped to avoid hypotony. Steroids are slowly tapered in eyes with non-valved implants over 2-3 months.

CT: I use prednisolone 4 times a day for at least 1 month; I begin to taper it off after then. Occasionally, for patients that may develop aggressive scarring, I may leave them on Prednisolone 1 drop a day for the long term. I use the same regimen in both valved and non-valved implants. I use cycloplegics as needed, and will use difluprednate if the the inflammation is severe.

DG: In valved implants, I leave a small amount of viscoelastic in the eye and place a drop of atropine on the eye after the surgery to protect against immediate postoperative hypotony. I aggressively treat with predisolone acetate 4-6 times a day depending on the case. I will sometimes give a subtenon's injection of 40mg of kenalog in the operating room as well. In non-valved implants, I fenestrate as much as I think is safe to help control the IOP until the tube opens. I place the patient on prednisolone acetate 4 times a day until almost a month after the tube opens. During this time, I treat the IOP as indicated. Around the time that I suspect the tube to open, I will place a drop of atropine in the patient's eye. I will usually taper the prednisolone down to once a day and may keep my patients on a topical steroid drop once a day for 3-6 months.

JFP: I often will give a sub-tenon's injection of kenalog at the time if surgery and begin difluprednate on postoperative day #1. I continue this 4 times a day for 3 weeks and then drop to 2 times a day for another 3 weeks. I will taper off over the next month depending upon the inflammation noted.

AS: I treat with steroids QID until the tube opens since it can cause a robust inflammatory reaction. Otherwise, I taper steroids after the vicryl sutures on the conjunctival closure absorb.

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SECONDARY ACQUIRED GLAUCOMA IN CHILDHOOD

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Childhood glaucoma is a heterogenous group of diseases, which all share the final common pathway of ocular hypertension, and pressure related damage to the ocular structures in form of optic neuropathy, and progressive visual field loss. It is estimated to cause significant percentage of blindness in children, from 1.2% in UK to 3-7% in India[1-3].

Being a heterogenous group of disorders, it was classified by overlapping and variably defined nomenclature, which denoted an age of onset rather than the underlying mechanism until an international collaboration on childhood glaucoma for the World Glaucoma Association (WGA) meeting in July 2013, gave the definitions of childhood glaucoma, glaucoma suspect, and a new childhood glaucoma classification system which is the most widely followed at present (Figure 1)[4]. The Childhood Glaucoma Research Network (CGRN) is an international consortium of clinicians and scientists who specialize in treating children with glaucoma.

According to CGRN classification, Childhood age is based on national criteria:

US: younger than 18 years

EU, UK, UNICEF: 16 years or younger

GLAUCOMA

IOP related damage to the eye; at least 2 criteria are required for the diagnosis:

1. IOP > 21 mm Hg; however, investigator discretion is required if there is data of examination under anesthesia alone due to variable effects of anesthesia on all methods of IOP assessment.
2. Optic disc cupping: progressive increase in cup-disc ratio.
3. Cup disc asymmetry of ≥ 0.2 when the optic discs are of similar size, or there is focal rim thinning.

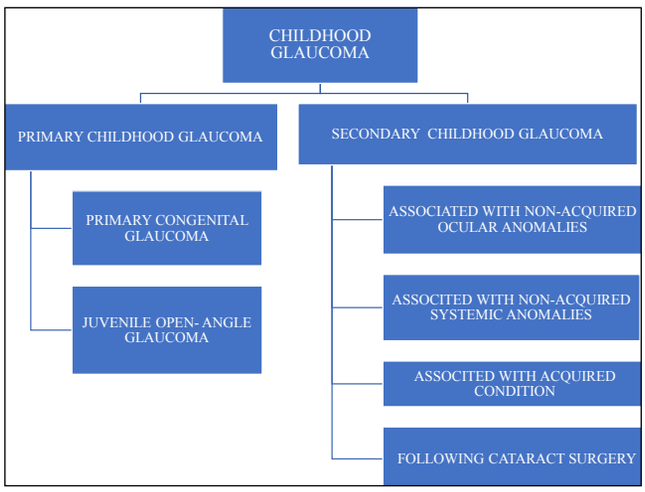

Figure 1: *Childhood Glaucoma Research Network (CGRN) classification*

4. Corneal findings: Haab's striae or diameter ≥ 11 mm in newborn, > 12 mm in a child < 1 year, or > 13 mm at any age
5. Progressive myopia, myopic shift, or an increase in ocular dimensions out of keeping with normal growth.
6. Reproducible visual field defect consistent with glaucomatous optic neuropathy with no other observable reason for the defect.

GLAUCOMA SUSPECT

No IOP related damage; at least 1 criteria is required for the diagnosis:

1. IOP > 21 mm Hg on 2 separate occasions.
2. Suspicious optic disc appearance for glaucoma, i.e., increased cup disc ratio for size of optic disc.
3. Suspicious visual field for glaucoma.
4. Increased corneal diameter or axial length in the setting of normal IOP.

Primary congenital glaucoma is the most common form of childhood glaucoma. However, secondary glaucoma also forms a significant proportion of childhood glaucoma. Various studies have given variable prevalence of secondary childhood glaucoma ranging from 20-52%[5-7].

In this write-up, we shall be discussing about secondary acquired glaucoma which includes glaucoma secondary to uveitis, trauma, steroid induced, tumours (benign/malignant, ocular/orbital), retinopathy of prematurity (ROP), prior ocular surgery other than cataract surgery. Trauma, uveitis and steroids are the most common ones amongst all these causes.

TRAUMATIC GLAUCOMA

Trauma is a very important cause of secondary glaucoma in children. School going children are most commonly affected due to unsupervised activities among active peers. Mode of trauma can be blunt trauma with toys, household appliances, ball games, gullidanda, sports activities; or penetrating eye injuries with sharp objects, bow and arrow; firecracker related injuries or chemical burns.

Seven rings of trauma include:

1. Sphincter tear
2. Iridodialysis
3. Angle recession
4. Separation of ciliary body attachment to scleral spur-cyclodialysis.
5. Trabecular meshwork (TM) tear.
6. Zonular dialysis resulting in subluxation of the crystalline lens.
7. Retinal dialysis

Post-traumatic glaucoma can be

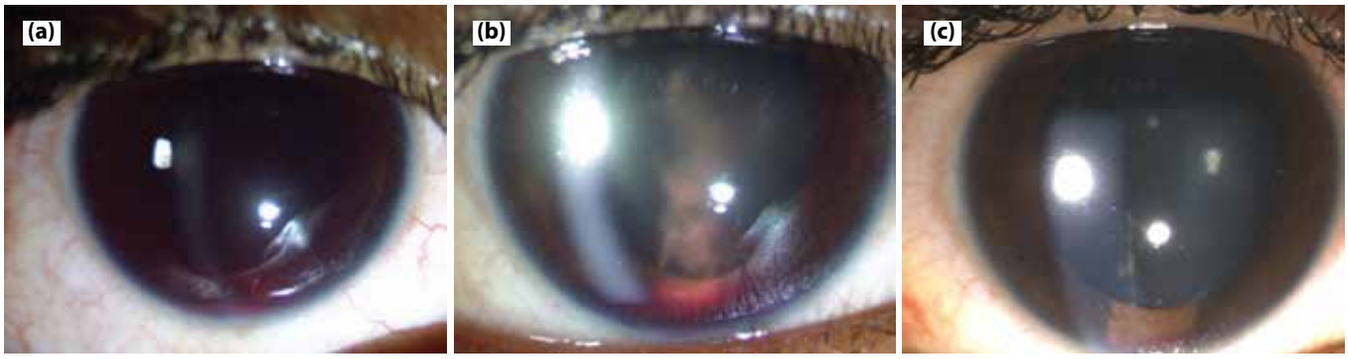

Figure 2: A: *Diffuse hyphaema in a 8 year old child following blunt trauma.* ***B:*** *After 2 days of head end elevation and conservative treatment, hyphaema was resolving and fibrin in pupillary area.* ***C:*** *Near complete resolution of hyphaema and disappearance of fibrin on 5 th day*

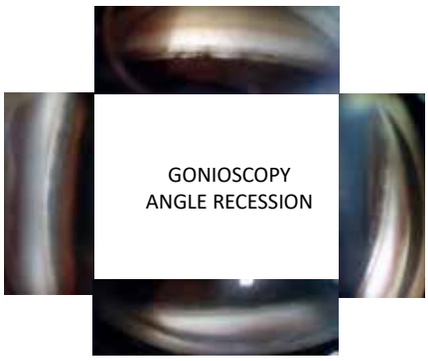

Figure 3: *Angle recession in >270 degrees visible as widened ciliary body band with synechiae and pigmentation in inferior angle.*

- Early onset due to hyphaema (Figure 2), lens related due to cataractous lens/lens subluxation/dislocation leading to angle closure or pupillary block or anterior capsular rupture leading to lens particle glaucoma.
- Late onset due to angle recession (Figure 3), peripheral anterior synechiae, ghost cell glaucoma or post surgical after surgical intervention for traumatic cataract or retinal detachment.

In a case of hyphaema, raised intraocular pressure (IOP) occurs due to inflammation and trabeculitis or blockage of trabecular meshwork with red blood cells/ inflammatory cells.

A large blood clot can cause raised IOP due to pupillary block.

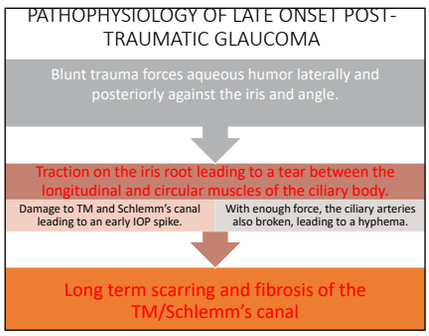

Figure 4: *Flow-chart depicting the pathophysiology of post-traumatic glaucoma.*

Approximately one-third of all hyphema patients exhibit increased intraocular pressure in early period which increases to 2/3rd in cases of rebleed[8,9]. In every case of blunt trauma, gonioscopy and indirect ophthalmoscopy with peripheral scleral depression is very important to rule out angle recession or retinal dialysis so as to prognosticate the disease and treat at the earliest. Scleral depression and dynamic gonioscopy should be avoided for about 4 weeks[10].

IOP elevation in angle recession usually presents with two peaks of onset, first around 3 months post injury and second after an interval of 10 years[11]. Angle recession is defined as separation of longitudinal and circular ciliary muscles. On gonioscopy, it is visible as wide irregular ciliary body band (Figure 3) and it should always be confirmed by comparing with the fellow normal eye. Although angle recession can be seen with blunt trauma without hyphaema, but the incidence increases in cases of hyphaema (about 60-100%). About 6-7% of the patients with angle recession go on to develop glaucoma[12,13]. Angle recession in itself is not responsible for glaucoma, but it is an indirect measure of the severity of trauma which must have caused damage to the trabecular meshwork (TM) (Figure 4). Late onset glaucoma in cases of angle recession also suggests patient predisposition to open angle glaucoma as IOP rise and glaucoma onset has been noted in 50% of the contralateral eyes years after the IOP rise in traumatic eye. It has been hypothesized that angle recession might be accelerating the process of manifestation of glaucoma in traumatic eye of these individuals[14].

In cases of penetrating trauma, IOP is usually low, but it can be high in cases with flat anterior chamber and peripheral anterior synechiae due to self-sealed corneal laceration or anterior capsule rupture leading to lens particle glaucoma.

- Following factors have been found to be the predictors for post-traumatic glaucoma:
  1. Presence of increased angle pigmentation
  2. Elevated baseline IOP
  3. Hyphema

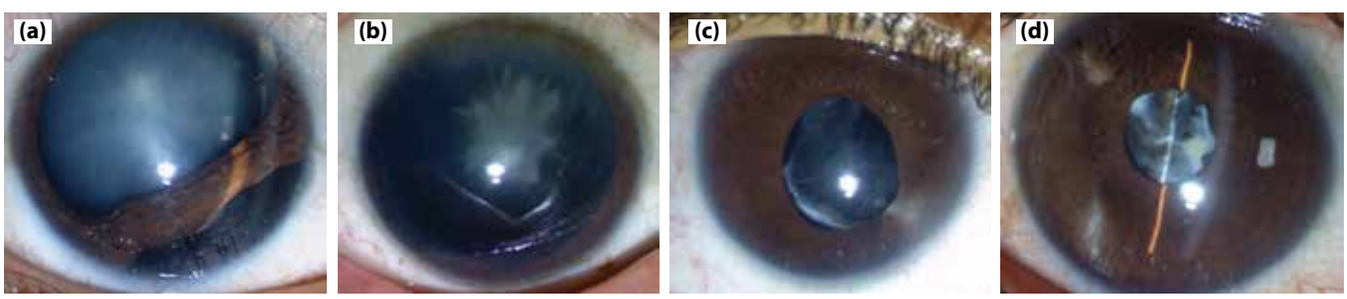

Figure 5: *Different presentations of trauma.* ***A:*** *Iridodialysis and cataract.* ***B:*** *Rosette cataract.* ***C:*** *Absorbed cataract with advanced glaucomatous cupping in a patient with old history of trauma.* ***D:*** *Siderotic cataract with raised IOP, corneal scar and iris hole with foreign body in vitreous cavity and optic nerve head cupping on ultrasonography in a patent with old trauma which was neglected.*

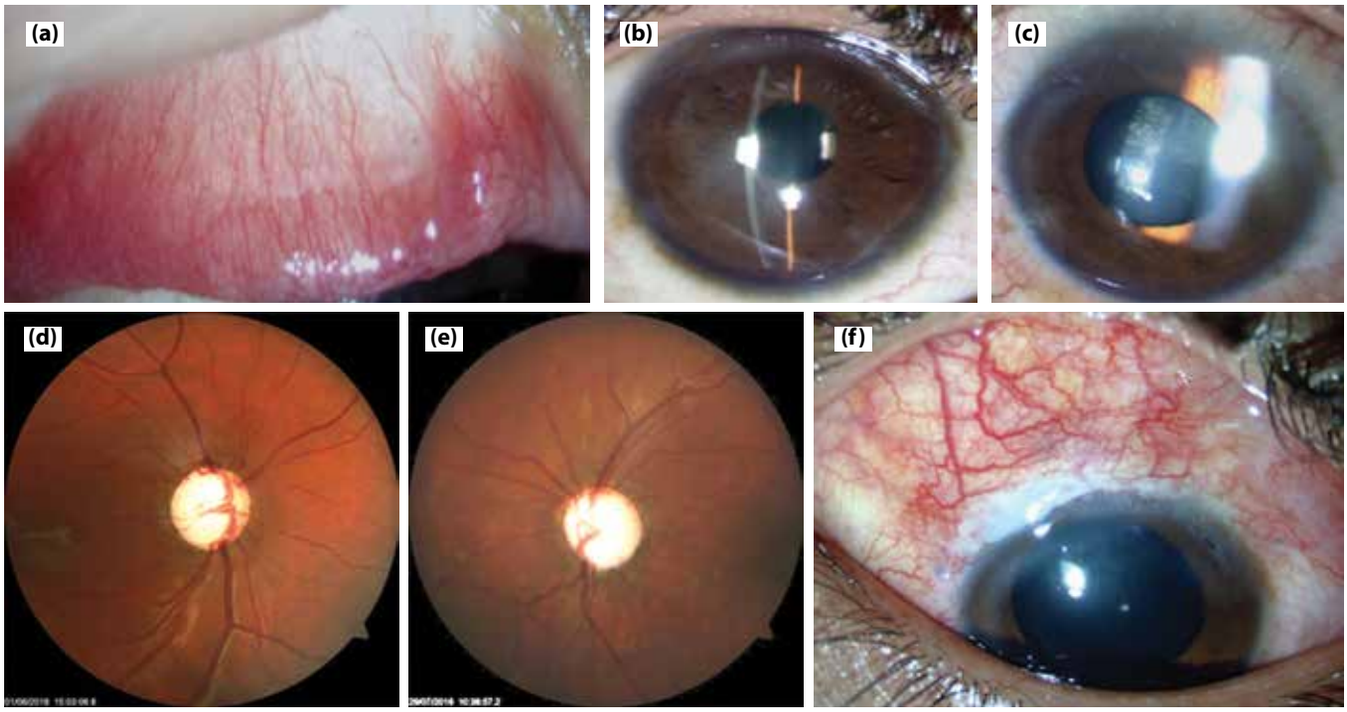

Figure 6: *Steroid induced glaucoma in a 14 year old patient suffering from vernal keratoconjunctivitis.* ***A:*** *Papillae in superior palpebral conjunctiva.* ***B:*** *Pseudogerontoxon and pseudophakia in right eye.* ***C:*** *Pseudogerontoxon and steroid induced posterior subcapsular cataract in left eye.* ***D and E:*** *Advanced glaucomatous cupping in both eyes.* ***F:*** *Left eye required trabeculectomy, Right eye IOP is controlled with medical treatment.*

4. Lens displacement
5. Angle recession more than 180 degrees[15]

Figure 5 shows the variable presentations of traumatic glaucoma with traumatic cataract.

MANAGEMENT

Treatment for hyphaema includes conservative management in majority of the cases (Figure 2):

- Propped up posture in a hyphaema patient helps by following mechanisms:

a. Allows circulating RBCs to settle inferiorly
b. Faster drainage of hyphaema
c. Limits corneal endothelial blood staining.
d. Early evaluation of posterior segment
e. Faster improvement in vision

- Topical steroids and cycloplegics- to reduce anterior chamber inflammation and to minimize the discomfort related to traumatic iritis
- To avoid aspirin/ non-steroidal anti-inflammatory drugs
- Antifibrinolytic agents can be given in high risk cases to reduce rebleed. Aminocaproic acid- 50mg/kg every 4 hrs (max 30g/day) for 5 days. Side effects can be nausea, vomiting, postural hypotension, rarely lethargy, skin rash.

Surgical management is required in about 5% of the hyphema cases[16] and the indications for surgery include:

1. IOP >50 mm Hg for 5 days, >35 mm Hg for 7 days, >60 mm Hg for 24-48 hours
2. Total hyphema not resolving by day 5
3. Grade 3 hyphemas (>50% of anterior chamber) with IOP>25 mm Hg for 5 days.
4. Appearance of corneal blood staining.
5. IOP >25-30 mm Hg for >24 hours in patients with sickle-cell trait[16]

If possible, evacuation of blood should be delayed until the fourth day because at this time, the clot is somewhat retracted and less adherent to the surrounding tissues. Techniques include paracentesis and anterior chamber washout and in cases of clot, clot expression using viscoelastic through an adequate sized incision or by a vitrectomy cutter.

STEROIDS

These are a group of anti-inflammatory drugs, used to treat many ocular and systemic inflammatory conditions, but unmonitored use can lead to cataract and glaucoma formation. Ocular hypertensive response to steroids depends upon the mode of use, potency of steroid, individual variability (depending on low, intermediate or high responders) etc. Patients with primary open angle glaucoma, high myopia, very young age (<10 years), pigment dispersion syndrome, traumatic angle recession are more prone for high steroid responsiveness and the hypothesis is that with already compromised trabecular meshwork, outflow in these cases is further attenuated because of steroid induced trabecular meshwork swelling and damage[17-21]. Steroid hypertensive response is more common with topical use as drops or ointments applied directly to the eye or around the eyelids, periocular injections like posterior subtenon kenacort, intravitreal steroid therapy, inhalational route etc.[22,23] Oral use is less likely to cause steroid responsiveness. Steroid responsiveness usually occurs within first few weeks of use, however, it may occur even after years of use, so it's very important to detect the steroid responsiveness in a particular patient in first 2 weeks after steroid use and then at regular intervals. In cases with only IOP rise and without disc damage or early damage, only discontinuation of steroids can bring down the IOP to normal, however, with long-term use and advanced disc damage, medical and/or surgical treatment might be required because of irreversible trabecular meshwork damage (Figure 6,7). In children, the most common cases to present with steroid responsiveness are vernal keratoconjunctivitis, nephrotic syndrome, chronic uveitis (Juvenile

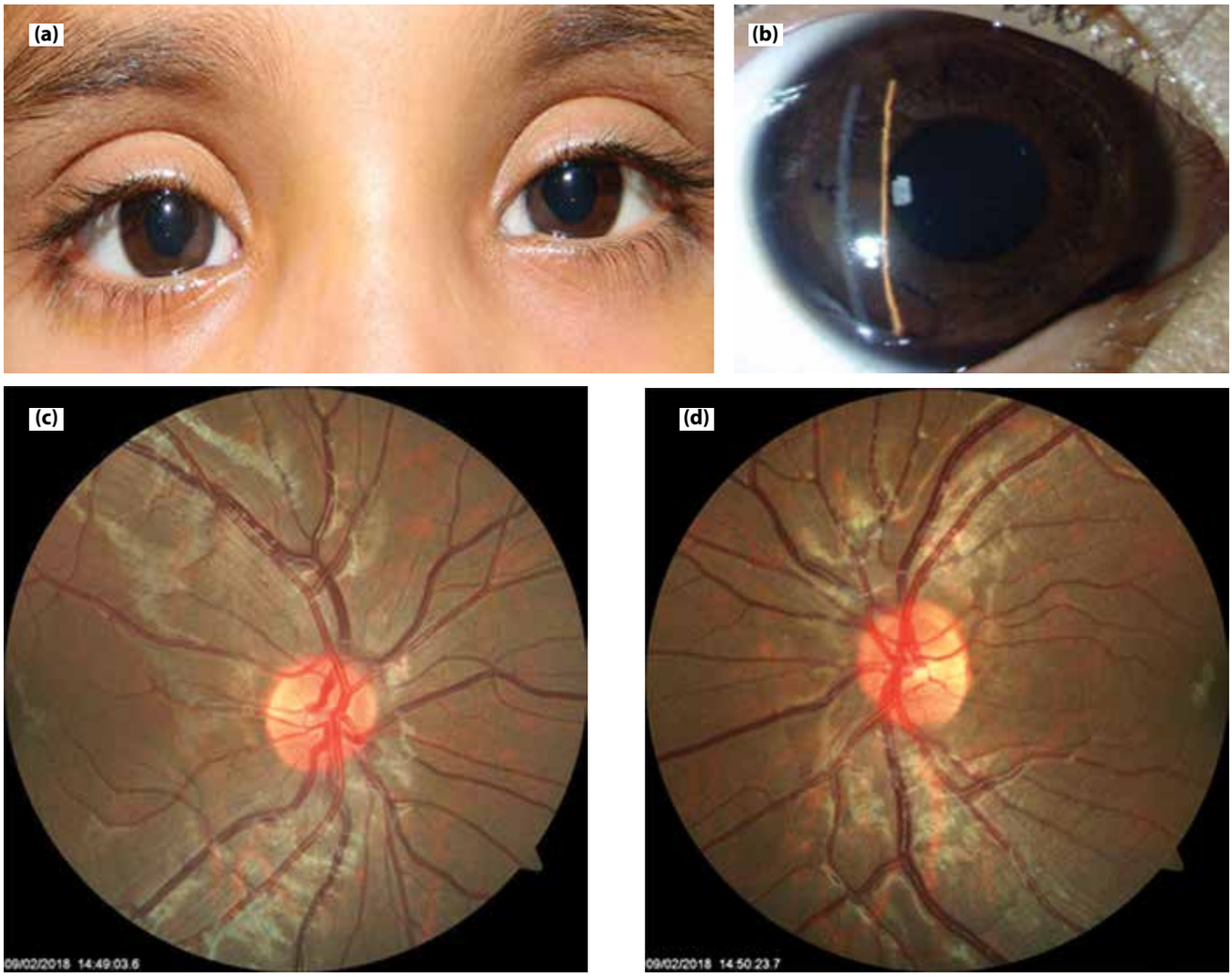

Figure 7: *Steroid induced ocular hypertension in a 7 year old girl due to steroid use after bilateral squint surgery.* ***A:*** *Residual esotropia.* ***B:*** *Normal anterior segment with clear crystalline lens.* ***C and D:*** *Healthy optic discs in both eyes. Patient had high IOP of 40 and 46 mm Hg in right and left eyes respectively and on discontinutaion of steroids only, IOP returned back to 16 and 18 mm Hg within 2 weeks.*

idiopathic arthritis). In such cases, it's very important to monitor these patients regularly and to replace high potency steroids like betamethasone, prednisolone, and dexamethasone with nonadrenal steroids like rimexolone, loteprednol etabonate, fluorometholone and one should consider steroid sparing agents to prevent cataract formation or irreversible glaucomatous disc damage. In a study, 24% of secondary glaucoma cases were due to steroid induced out of which 44% cases were managed by stopping steroids only, 36% were controlled by medical therapy and 19.4% required surgical intervention[24].

UVEITIS

Prevalence of glaucoma in uveitis patients is variable ranging from 5-25%[25-27]. Juvenile idiopathic arthritis (with ANA positivity) has been found to be the most common cause[28]. Severity of glaucoma in uveitis depends upon the type of uveitis, response to treatment, duration of the disease, steroid therapy. The mechanism of increased IOP is complex in uveitis patients. It can be because of chronic trabeculitis leading to sclerosis of trabecular meshwork canals or it can be steroid induced. Acute exacerbation of uveitis can present with low IOP because of ciliary body shutdown and with treatment, as ciliary body function starts, IOP can rise because of compromised trabecular meshwork with longstanding uveitis or steroid responsiveness[29]. It can be an open angle or a closed angle glaucoma. Angle closure glaucoma can occur because of peripheral anterior synechiae or seclusio pupillae leading to iris bombe formation.

Management of uveitic glaucoma is difficult because of the various mechanisms involved in its pathogenesis.

Prostaglandin analogues are usually contraindicated due to increase of inflammation with their use. Iris bombe formation due to seclusio pupillae requires urgent laser iridotomy (Figure 8A&B). In such cases, laser iridotomies need to be more (≥2) and larger in size as they have propensity to close because of inflammation and it's difficult sometimes to make big iridotomy, as there are high chances of bleed with inflamed tissues. Refractory glaucoma requires surgical management. Trabeculectomy with mitomycin-C (MMC) is more likely to fail in such cases because of inflammation, thus glaucoma drainage devices might be considered as a primary procedure (Figure 8C&D)[30]. Goniotomy has also been tried in such cases with studies reporting good outcome in upto 70% of the cases and poor prognostic factors for failure have been found to be older age at surgery, longer duration of glaucoma, greater clock hours of peripheral anterior synechiae and aphakia[31].

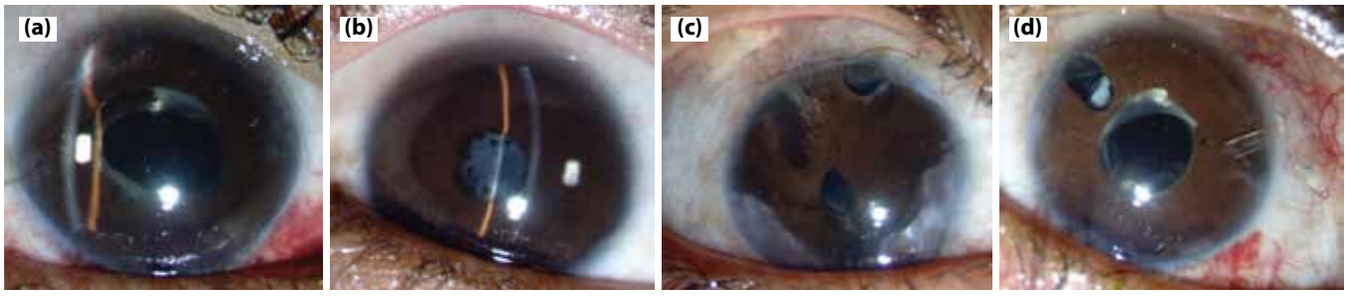

Figure 8: A and B: *A young patient of 16 year age with a known case of Juvenile idiopathic arthritis (JIA) having iris bombe in the right eye after cataract surgery (A), other eye with posterior synechiae and complicated cataract (B). Right eye IOP was 28 mm Hg, iris bombe was treated by laser iridotomy with control of IOP on one topical drug for short-term use.* ***C: and D:*** *Another uveitis patient 16 year old suffering from JIA with refractory glaucoma which was managed by glaucoma drainage devices in both eyes.*

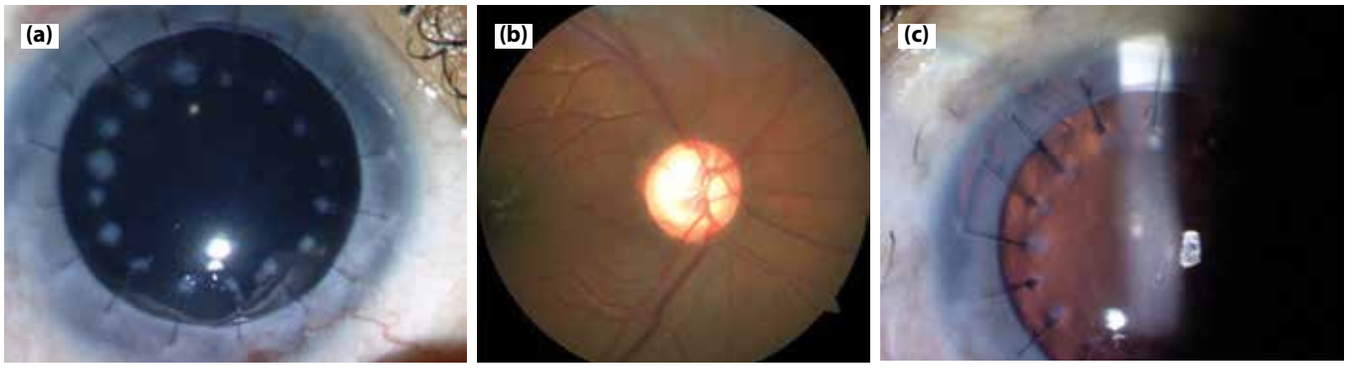

Figure 9: *A 8 year old patient with history of corneal laceration repair presented with raised IOP which was controlled on medical treatment, underwent optical penetrating keratoplasty for corneal opacity.* ***A:*** *Clear corneal graft.* ***B:*** *Advanced glaucomatous optic disc cupping.* ***C:*** *Patient required surgical management for post-keratoplasty uncontrolled IOP (Glaucoma drainage device in anterior chamber visible on retroillumination).*

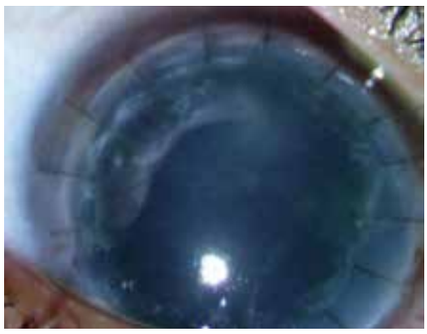

Figure 10: *This patient, 10 year old male child underwent therapeutic penetrating keratoplasty for perforated corneal ulcer. Anterior chamber was shallow with peripheral flat AC and peripheral anterior synechiae with high IOP in range of 50 mm Hg. IOP was controlled on medical treatment first followed by diode laser cyclophotocoagulation in view of decompenstaed graft with visual acuity limited to perception of light inaccurate projection of rays and poor visual potential.*

POST-SURGERY OTHER THAN CATARACT SURGERY

Penetrating keratoplasty: Pediatric penetrating keratoplasty is required for corneal opacity secondary to congenital cause (sclerocornea, corneal opacity in congenital glaucoma, Peters anomaly, aniridia etc), acquired traumatic (post-corneal laceration repair, corneal blood staining) (Figure 9) or non-traumatic corneal opacities (infectious keratitis, keratoconus etc). Peters anomaly and aniridia are more likely to have associated glaucoma and the IOP control gets disturbed after keratoplasty because of surgical trauma and inflammation as well as long-term steroid use after keratoplasty and keratoplasty success rates are also lesser in these cases[32]. Various other factors responsible for post-keratoplasty glaucoma can be: angle closure because of pupillary block by an intact hyaloid phase or peripheral anterior synechiae formation (more common with perforated corneal ulcer cases), (Figure 8) distortion of angle anatomy due to tight sutures or trabecular meshwork collapse in aphakic cases due to loss of ciliary body and lens support[33].

Management includes prophylactic measures before surgery including good control of IOP in pre-existing glaucoma cases and intraoperative precautions like adequate tightness of sutures, intraoperative synechiolysis and careful wound closure to prevent post-operative shallow anterior chamber. Treatment includes medical treatment first and the options include β-blockers, alpha-agonists systemic carbonic anhydrase inhibitors (for short-term use after surgery). The carbonic anhydrase inhibitors should be used with caution as they can inhibit carbonic anhydrase enzyme in corneal endothelium and disturb the endothelial function. Prostaglandins can increase the inflammation and can cause cystoid macular edema or reactivation of herpetic keratitis, so should be used with caution after acute inflammatory period is over. Miotics should be avoided as they can increase inflammation and there is risk of graft rejection. Topical steroid use should also be monitored and steroid sparing agents like cyclosporine or tacrolimus should be preferred in cases with steroid responsiveness. Surgical treatment options include trabeculectomy with MMC, glaucoma drainage devices and caution is required in such cases to prevent anterior chamber shallowing so as to prevent endothelial cell loss and glaucoma drainage device should be placed as far as possible from the graft. Cyclodestructive procedures might be required for recalcitrant cases with poor visual potential (Figure 10).

After retinal detachment surgery: Intraocular pressure can rise both after scleral buckling or vitrectomy. Scleral buckle leads to secondary angle closure due to obstruction to the drainage of vortex veins leading to swelling and anterior rotation of ciliary body which pushes the lens-iris diaphragm forward. It usually improves spontaneously over several days-weeks and requires short-term use of antiglaucoma medications.

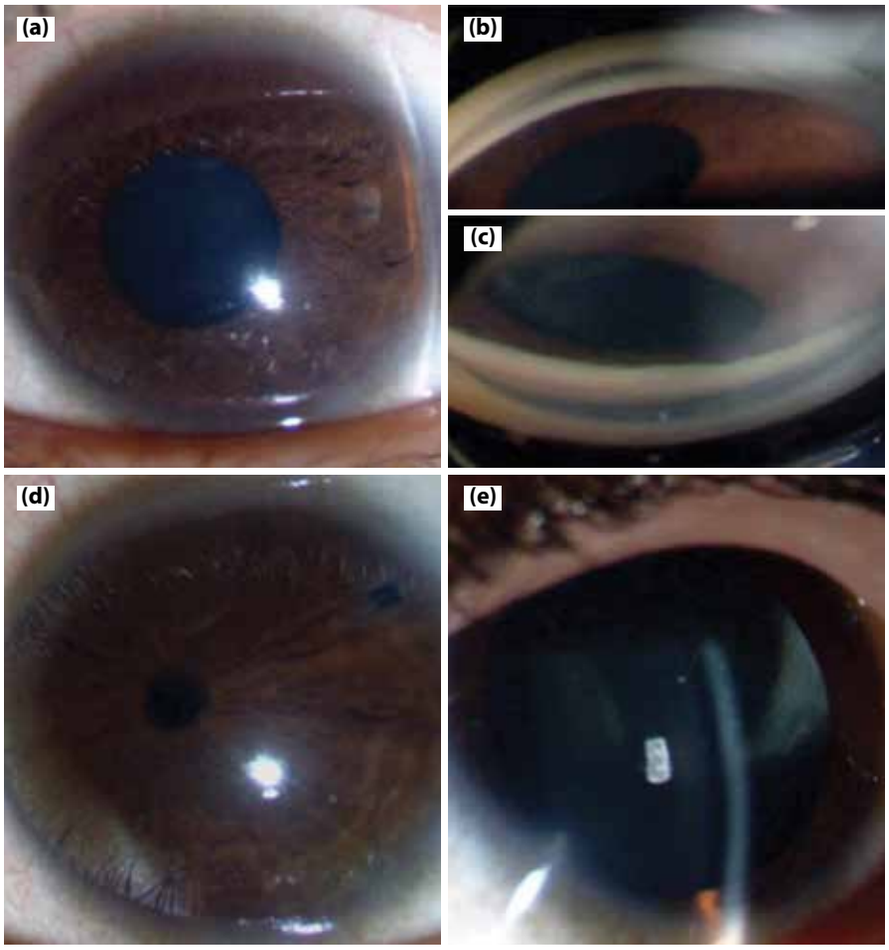

Figure 11: *A 18 year male patient with old history of retinopathy of prematurity and laser treatment for the same, presented with diminution of vision and ocular pain.* ***A:*** *Patient had shallow anterior chamber with IOP of 60 mm Hg.* ***B: and C:*** *Gonioscopy showed closed angles* ***D:*** *After controlling the IOP with medical treatment, laser iridotomy was done with control of IOP with gradual discontinuation of antiglaucoma drugs.* ***E:*** *Dilated examination showing a retrolental glial mass and shallow central AC with thick crystalline lens; lens thickness could not be measured with A-scan.*

RETINOPATHY OF PREMATURITY

Glaucoma after retinopathy of prematurity can occur in about 2% cases of high-risk prethreshold/threshold ROP and is most likely due to angle closure because of retrolental membrane or swollen lens or ciliochoroidal detachment following laser treatment which can lead to forward movement of lens-iris diaphragm[35,36]. In some cases, it can be open angle type because of inflammation post laser treatment or vitrectomy surgery. It can develop months or years after ROP development or treatment or may also occur in adulthood[37]. A case series has described neovascular/non-neovascular angle closure glaucoma because of neovascularization of angle, retrolental mass or swollen lens. These patients have been found to have longer axial length with shallow anterior chamber and swollen lens (Figure 11). Management includes medical treatment, laser iridotomy, lensectomy in cases of intumescent lens, trabeculectomy, glaucoma drainage devices. Cyclodestructive procedures are done in eyes with poor visual potential.

RETINOBLASTOMA

Retinoblastoma can be a cause of secondary buphthalmos and the mechanisms for IOP elevation in cases of retinoblastoma includes neovascularization of iris, anterior

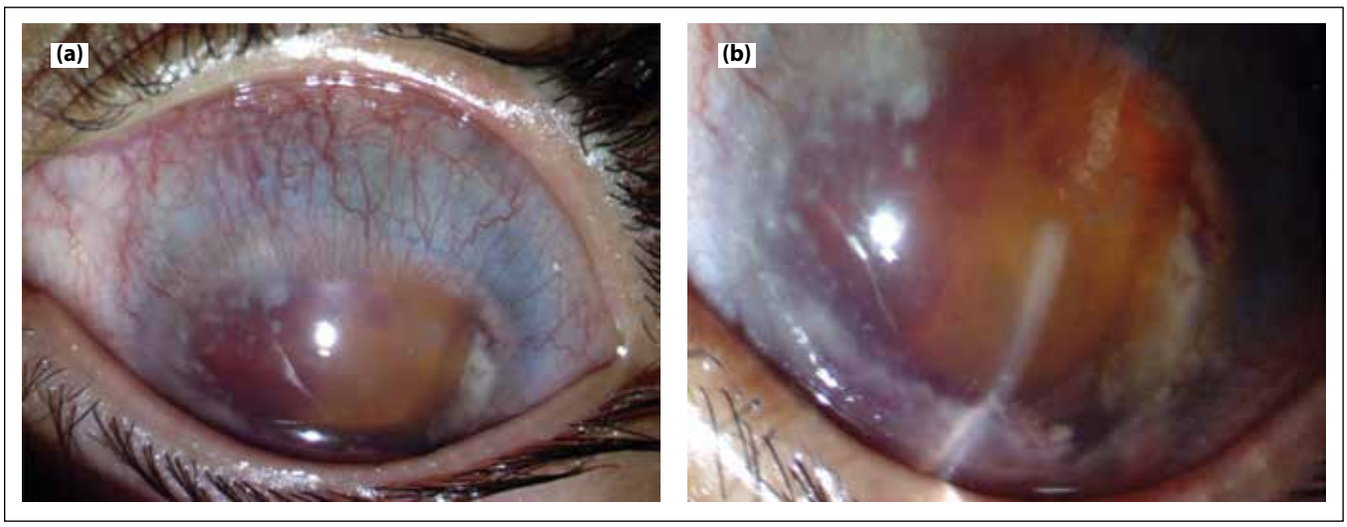

Figure 12: *A 2 year male child of retinoblastoma with secondary buphthalmos and limbal stretching* ***(A)*** *and anterior chamber showing white tumour cells* ***(B)****. CT scan revealed extensive calcification of intraocular mass with optic nerve thickening and spread to the brain.*

After vitrectomy, glaucoma can occur with the use of gas or silicone oil tamponade and the mechanism can be angle closure because of pupillary block by oil/gas bubble or open angle because of gas expansion or overfill by silicone oil or inflammation or steroid use. Angle recession/ trabecular meshwork damage due to previous trauma can also predispose to increased IOP post retinal detachment or macular hole or cataract surgery in traumatic cases[34].

displacement of lens-iris diaphragm or by tumour seeding of trabecular meshwork (Figure 12)[38]. Neovascularization can occur because of angiogenic factors produced by tumour itself or vascular endothelial growth factor produced by

hypoxic retinal cells[39]. Seeding of tumour cells can be seen as pseudohypopyon. Presence of pseudohypopyon suggests extraocular spread of tumour because of drainage through angle of anterior chamber. Patients usually present with pain, photophobia, watering and vomiting in extreme cases. Thorough examination under anaesthesia, ancillary investigations including ultrasonography is must to rule out intraocular mass. CT scan to detect the calcification or MRI orbit and brain are required to detect optic nerve or brain involvement in advanced cases. It's very important to be aware of the association and need of collaborated work between glaucoma specialist and oculoplastic/ retinoblastoma specialists to take care of this potentially life-threatening disease. It's very important to rule out retinoblastoma in every case of congenital glaucoma by ultrasonography before going ahead with the surgery.

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Accurate Clinical Examination in Glaucoma is Key: Disc Features

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Intraocular pressure (IOP) is a crucial component in the diagnosis of Glaucoma, but as our understanding of Glaucoma has grown it has become evident that IOP is just one of the components in the diagnostic puzzle and great caution has to be exercised so that due focus is given to the other elements required to make a comprehensive diagnosis. Several population-based studies done in different parts of the world suggest that one-third or more of patients diagnosed with glaucoma in the community will present without elevated IOP levels[1,2,3]. In fact, in an epidemiological study published by Iwase et al in Tajimi, Japan the authors noted that IOP was 21 mmHg or less in 92 percent of patients identified with open angle glaucoma[3].

In a population-based cross-sectional study published by Wong et al titled "Detection of undiagnosed glaucoma by eye health professionals" the authors concluded that raised IOP should not be relied upon as the only triggering factor for glaucoma evaluation[4].

Apart from intraocular pressure, gonioscopy plays a very crucial role in the evaluation of a glaucoma patient. It has a role in the diagnosis and classification of a patient and also sheds some light into the prognostic aspect depending upon the gonioscopic findings.

Besides the above two crucial tests the optic nerve head (ONH) evaluation is perhaps the most important clinical test in the evaluation of a glaucoma patient. The ONH is composed of neural tissue, glial and collagenous supportive tissue and blood vessels. Glaucoma as it is understood today is an optic neuropathy characterized by progressive injury to retinal ganglion cells and their axons leading to changes in the intrapapillary and parapapillary regions of the optic disc (OD) and the surrounding retinal nerve fiber layer. Despite technological advances, clinical identification of optic nerve head and retinal nerve fiber layer changes remains one of the main tools in the diagnosis of glaucoma.

Careful examination of the disc parameters including disc shape, size, neuroretinal rim width, size of the optic cup in relation to the area of the disc, the cup -disc ratio , configuration and depth of the optic cup, presence and location of splinter hemorrhages, occurrence, size, configuration, and location of peripapillary chorioretinal atrophy, and changes in the retinal nerve fiber layer (RNFL) are important to differentiate between glaucomatous and nonglaucomatous optic neuropathy.

The evaluation of the optic disc (OD) is helpful in detecting glaucomatous ONH damage. Even cases of early rim thinning or notching can be picked up with the help of careful ONH evaluation. Once a case has been detected, periodical evaluation of the OD can be helpful to note any form of progressive damage. The careful evaluation of a glaucomatous disc may also help to differentiate certain types of glaucomas and it may also give us an idea about the prognosis of a particular patient.

NORMAL ANATOMY OF THE OPTIC NERVE

Ganglion cell axons make up the vast majority of the neuroretinal rim tissue of the optic disc. One to 1.5 million axons leave via the optic nerve head through the scleral canal, while the remainder of the neuroretinal rim is composed of capillaries and astrocytes[5,6].

There are four distinct layers of the optic nerve head, including the surface, prelaminar, laminar, and retrolaminar layers[6]. The surface layer is the anterior limit of the optic nerve and is the point of contact with the vitreous. Its peripheral edge is defined by the anterior limits of the scleral ring, and its posterior limit is where the axon bundles have completed a 90-degree turn from the plane of the retina and reached the level of the choroid[6]. The prelaminar optic nerve is an indistinct segment of axons surrounded by outer retina, choriocapillaris, and choroid. Within the laminar optic nerve, the ganglion cell axon bundles are wrapped in glial cells and confined in the rigid pores of the lamina cribrosa. The retrolaminar optic nerve thickness is doubled by the presence of myelinating oligodendrocytes[6].

The lamina cribrosa is a part of the scleral tissue through which ganglion cell axons exit as they leave the globe. It is composed of several sheets of connective tissue that is fenestrated to allow the passage of the nerve fiber bundles[7,8]. The superior and inferior poles have the largest pores, thus providing less structural support for the axon bundles leaving the nerve in these two areas[8,9]. This may explain why there is typically greater damage to the retinal ganglion cell axons in the superior and inferior poles of the optic nerve that we see clinically[7]. Furthermore, as ganglion cell axons are lost, the laminar dots become more exposed, which can also be visualized clinically. While laminar dots may certainly be present in healthy non-glaucomatous eyes, their presence should alert the clinician to look for other signs of glaucoma. The lamina is also susceptible to thinning and bowing backward due to effects of the intraocular pressure, which results in a clinically visible deeper cup in glaucomatous eyes[10].

The surface optic nerve receives its blood supply from small branches of the central retinal artery[6,7]. The pre-laminar optic nerve is supplied by the short posterior ciliary arteries (SPCA), and their integrity is responsible for the reddish hue that is observed clinically in healthy optic nerves[5,6,7]. The

laminar optic nerve is supplied by the Circle of Zinn-Haller, which is composed of anastomoses from adjacent SPCA's[6,7]. The retro-laminar optic nerve head is supplied by axial vasculature from the central retinal artery, the pial vascular plexus, and the SPCA's. Knowing the vasculature of the optic nerve is critical when evaluating the health and integrity of the neuroretinal rim as it is necessary to remember that glaucoma is cupping without pallor[10,11]. If pallor of the optic nerve is observed, it indicates insult to the prelaminar vasculature and should always alert the clinician that a different or an additional optic neuropathy is present.

Venous drainage of the optic nerve occurs via the central retinal vein[6,7]. In chronic glaucoma, optociliary shunt vessels may appear due to disturbed retinal circulation. These vessels are pre-existing venules that become more visible as they dilate to re-route blood around an area of obstruction[6]. They can be differentiated from neovascular vessels as optociliary shunt vessels will not leak on fluorescein angiography, while neovascular vessels will always leak fluorescein dye.

OD EVALUATION

The evaluation of the disc is to be done methodically with emphasis given to each and every point. The evaluation should be done under the following headings:

1. Disc size
2. Disc shape
3. The Neuroretinal Rim
4. Cup Disc ratio
5. Disc Haemorrhages
6. Retinal Nerve Fiber Layer changes
7. Peripapillary changes
8. Vascular changes

The early changes which can be detected on careful evaluation of the OD are focal or generalized loss of the neuroretinal rim (NRR) (cup enlargement), superficial splinter hemorrhages, nerve fibre layer (NFL) defects and thinning and translucency of the neuroretinal rim.

The glaucomatous changes of the ONH may present as one or a combination of the following - structural changes, contour changes and colour changes. The changes of the ONH in glaucoma can also be classified as either quantitative changes or qualitative changes. The quantitative changes include optic disc size, cup- disc ratio (vertical or horizontal) and the rim/disc ratio. The qualitative changes include changes in the contour of the NRR (thinning , notching etc.), OD haemorrhages, peripapillary changes, the baring of circumlinear vessels (BCLV) and RNFL defects.

For the proper evaluation of the OD a stereoscopic view with magnification for proper evaluation of the neuroretinal rim changes and an estimation of the optic nerve head size are extremely important. Stereoscopic view of the optic nerve head is best achieved with the help of a Volk or Ocular + 90D, + 78D,+60 D or a superfield NC lens. The +78D lens give a good magnified view of the disc and the peripapillary region and also provides a decent field of view and is preferred by a lot of glaucoma specialists but the 90D lens is also preferred by many as it has excellent optics and gives a great view of the disc and also gives a wider field of view. Some of the other methods which may be used to give a stereoscopic view of the disc are indirect ophthalmoscopy, Hruby lens and the central part of a goniolens. Apart from the OD assessment the RNFL assessment is also extremely important. A slit lamp with red free light along with any one of the above lenses may be used for this purpose.

It is better to evaluate the ONH through a dialated pupil. In a study done by Kirwan et al the authors found that there was better interobserver agreement in size determined through a dilated pupil[12]. Disc diameter can be measured by adjusting the slitlamp beam height to the edges of the disc while viewing the disc with a +60D lens. As a +60D lens has a correction factor of approximately x 1, it is the optimal lens for the measurement of optic disc size. A similar measurement of the vertical and horizontal disc diameter can be obtained with other lenses by multiplying the measured value with the appropriate magnification factor: Goldmann contact lens (1.26) and Volk superfield lens (1.5), Volk +90 D (1.33), Volk + 78D (1.2) and Volk + 60D (0.88)[13,14,15].

Optic Disc size

There is a lot of inter individual variability when it comes to the size of the optic disc. In the various studies done on Indian eyes the results reflect this variability in the disc size. In the Andhra Pradesh Eye Disease Study (APEDS)[16], the mean optic disc area was 3.37 mm^2. This was larger than that found in the other studies. The Vellore Eye Study (VES)[17] showed a mean area of 2.58 mm^2. The Central India Eye and Medical study (CIEMS)[18] reported a mean optic disk area measured 2.25 ± 0.51 mm^2. As is evident from the figures above, there was a difference in the mean OD size which can be explained by the fact that different techniques were used to determine the disc size in the above studies.

The average vertical height of the healthy optic nerve ranges from 1.8 to 2.0 millimeters[19,20]. A small disc is referred to as one where the vertical diameter is equal to or less than 1.5 millimeters; similarly a disc is referred to as a large disc if the vertical diameter is greater than 2.2 millimeters[20].

The size of the OD/optic cup can vary due to the following factors

a) Hereditary factors: Individuals may have similar disc size(small or large) as their parents and/or siblings.
b) Age: Some studies have shown that although the disc size approximately remains the same there is an increase in the size of cup and pallor with increase in age[11,13].
c) Race: Individuals of African descent have larger disc size and thus larger cup disc ratios compared to whites[1,2].
d) Refractive errors: Myopes are more prone to develop primary open angle glaucoma (POAG). The disc size is highly variable in myopes ranging from very small optic discs to very large ones with extensive zones of peripapillary atrophy[18]. Hypermetropic eyes on the other hand present with small discs and these eyes are a risk factor for development of primary angle closure glaucoma(PACG).

The boundaries of the optic disc conform to the edges of the scleral canal, which appears as a whitish circular band. In the other words, the size of the scleral canal determines the optic disc size. Eyes with small scleral canals have small optic discs (high hyperopia) and eyes with large scleral canals have large discs (high myopia). The borders of the optic disc are defined as the innermost border of reflective tissue that is internal to any pigmented tissue and within which only neuroretinal tissue is present. It can be difficult to determine the borders of the optic disc in individuals with high myopia and eyes with significant PPA[10,21].

The ONH diameter can be calculated using the formula:

ONH diameter (mm) = (X/H) x D x C

(X = height of beam (mm); H = height

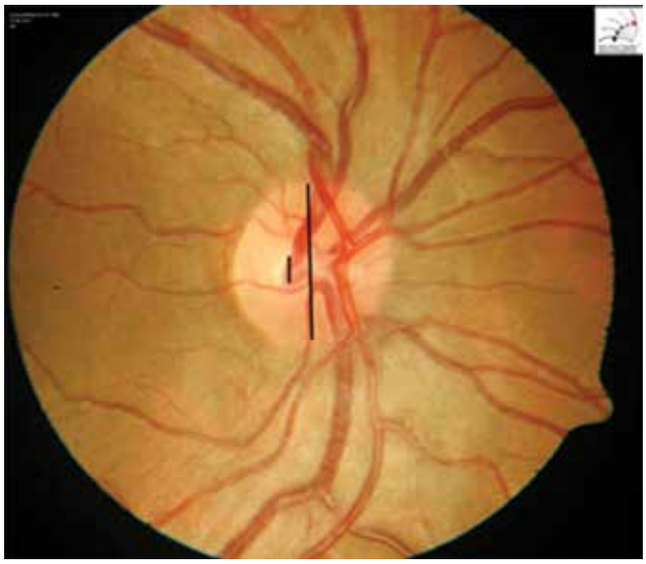

Figure 1a: *Normal small disc with a very small cup.*

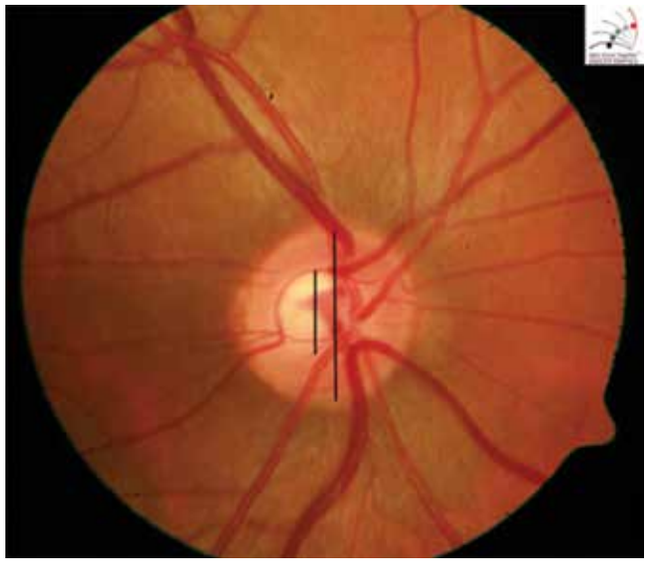

Figure 1b: *Normal small disc with a small cup.*

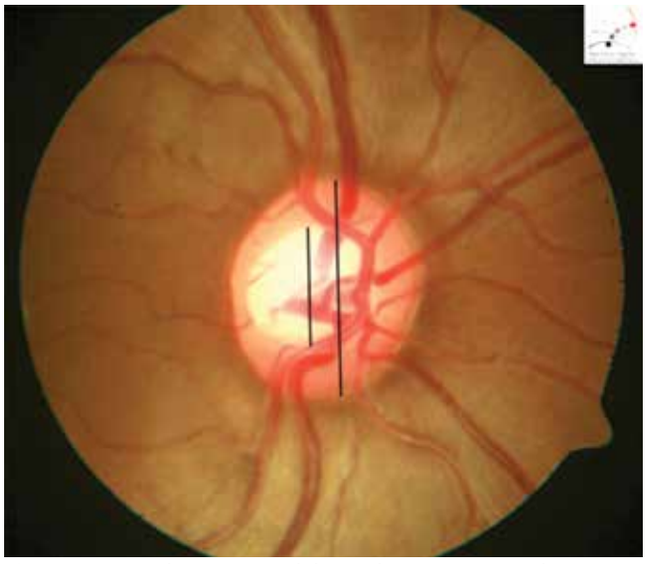

Figure 1c: *Normal average sized disc with an average sized cup.*

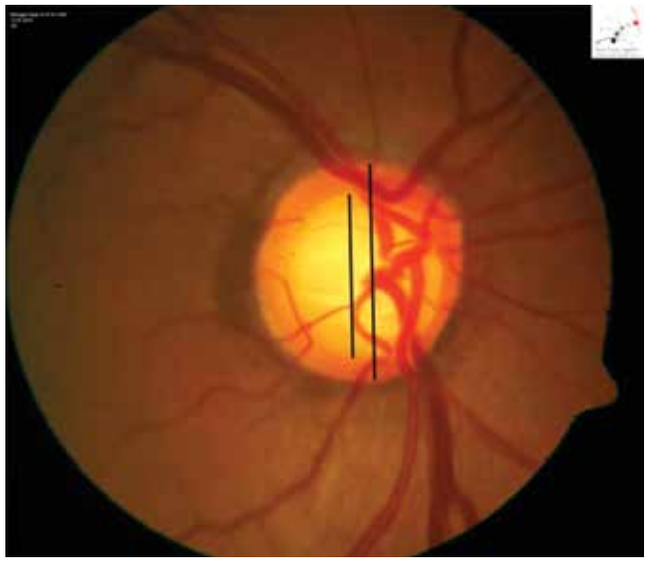

Figure 1d: *Normal large sized disc with a large cup.*

setting on the beam height indicator (mm); D = diameter of the optic disc measured by the beam height indicator (mm); C = correction factor)[19].

Additionally, the area of the ONH can be calculated using a modified formula: ONH area (mm): r/4 X horizontal disc diameter X vertical disc diameter (r = the correction factor based on used lens diopter)[19].

The distance between the optic disc and the fovea as disc diameters can be used for the evaluation of the optic disc size. This distance as measured from the temporal edge of the optic disc to the center of the fovea is approximately two to three disc diameters in eyes with normal size and axial length. A shorter distance indicates a larger disc, and a longer one signifies a smaller optic disc[21].

Clinical estimation of optic nerve head size is possible with a Welch Allyn Ophthalmoscope or with Volk 60D lens. The smallest white round spot of the Welch Allyn ophthalmoscope usually illuminates a cone angle of 5° and casts a light of 1.5 mm in diameter and an area of 1.77 mm^2 which is slightly smaller than the size of the average disc on the retina[22]. With this one can determine if the disc is small, average or large in size. This retinal spot size remains constant in phakic eyes with refractive errors between -5.00 D and + 4.00 D.

The location of the originating point of the light cone does not significantly affect the retinal spot size as long as it is ± 3mm from the anterior focal point of the patient's eye. Since 1.5 mm is the usual size of the optic nerve head, this can be used as a yard stick for measuring disc size. Simplistically, in eyes with large physiological cups due to large discs the area illuminated is less than the area occupied by the cup.

The thickness of the central retinal vein (CRV) can also be used to help estimate optic disc size. The average thickness or diameter of CRV is approximately 125 µm at the region where the CRV crosses the inferior NRR. If the optic disc has a width of about 12–14 CRV diameters, it can be considered that ONH is normal in size. A higher number of CRV diameters points out a larger ONH, whereas a smaller number of CRV diameters refers a smaller ONH[7,10].

At the onset it is very important to determine if the optic disc is of an average size, or it is smaller or larger than the average for the given population. The size of the disc is not a predictor of glaucoma by itself. A normal disc can be small, average or large in terms of size. However the size is relevant because it is the disc size which determines the cup disc

rato (CDR) (the vertical and horizontal cup/disc ratios), the neuroretinal rim thickness and the parameters like the cup/disc area ratio and the rim/disc area ratio. Thus a smaller disc is expected to have a smaller cup and a larger disc is expected to have a larger cup. This assessment becomes essential in order to avoid over-testing and over-diagnosis in large nerves due to the instantaneous reaction that any CDR greater than 0.4 is immediately suspicious for glaucoma. It is very important to examine a small disc very closely too as an early nothing or thinning may be missed due to the small size of the cup and the disc itself. Larger discs however may be more susceptible to glaucomatous damage. Jonas et al reported higher susceptibility of neuroretinal rim loss in area farthest from the exit of the central retinal vessel trunk, which is greater in a large disc[23] (Figures: 1a,1b,1c ,1d).

The disc size of the two eyes in the same individual are to be compared and any asymmetry is to be noted. If there is any asymmetry in the size of the disc between the two eyes of an individual then it is to be kept in mind that this may lead to an asymmetry in the other parameters like the thickness of the NRR and the CDR. However certain factors like a difference in the axial length between the two eyes or a difference in the refractive status of the eyes may lead to disc size asymmetry between the two eyes in the same individual.

OD shape

The shape of the optic disc is variable just like the size. However an optic disc is usually vertically oval with the vertical diameter being greater than the horizontal diameter. In the Vellore Eye Study (VES) done in a south Indian population the vertical diameter of the optic disc was found to be 6% longer than the horizontal one[17]. Infact in the VES, in 81.4% of the studied population the vertical diameter was longer than the horizontal one. In a study done by Jonas et al the authors reported the vertical optic disc diameter to be about 6%–10% longer than the horizontal one in whites[21]. However in quite a few glaucomatous patients as well as normal individuals the disc may be horizontally oval or round. In 14.3% of the eyes studied in the VES, the horizontal disc diameter was longer than the vertical and in 4.2% the vertical and horizontal diameters were equal[17].

In a study done by Jonas et al to assess the correlation between optic disc shape, corneal astigmatism and amblyopia the authors concluded that an abnormal optic disc shape is significantly correlated with corneal astigmatism[24]. The authors stated that if an abnormal optic disc shape is found on routine ophthalmoscopy, specially in children, refractometry should be performed to rule out corneal astigmatism and to prevent amblyopia. The study also suggested that the direction of the longest optic disc diameter could indicate the axis of corneal astigmatism[24].

The ISNT Rule

By analyzing the neuroretinal rim in disc photographs of normal subjects, Jonas and associates found that the rim width typically exhibited a specific pattern[25]. They used rim area measurements of normal eyes, calculated from projected optic disc photographs. Later, retinal nerve fiber layer thickness was measured at the optic disc borders histomorphometrically and was found to follow the same pattern[26]. They found that in normal individuals the neuroretinal rim was thickest inferiorly and thinnest temporally (Thickness of the NRR: Inferior >Superior > Nasal>Temporal). This specific neuroretinal rim pattern was later coined by Elliot Werner as the ''ISNT rule''[27].

Because neuroretinal rim loss is a hallmark feature of glaucoma, patients who deviate from the ISNT rule may need to be watched more closely for glaucoma. The RNFL, on the other hand, has also been shown in histologic studies in normal, nonglaucomatous eyes to exhibit a similar pattern of the inferior quadrant being the thickest, followed by the superior, nasal, and then temporal quadrant[26]. Because RNFL thinning, particularly in the superior and inferior quadrants, is also a characteristic structural change in glaucoma, deviation from the ISNT rule for RNFL thickness may also be an early indicator of glaucomatous structural change[28]. In a patient of glaucoma there occurs vertical thinning, with atrophy along the inferior and superior rims. Thus, when the optic nerve doesn't follow the ISNT rule, they may be undergoing glaucomatous damage.

In contrast, RNFL ISNT rule studies based on OCT findings are in uniform agreement, stating that the ISNT rule and its variants were not helpful in the diagnosis of glaucoma[29,30]. Some have hypothesized that the ISNT rule is not easily generalizable to the individual, because the initial studies were derived from mean values[25,26]. Therefore, some of the limitations of the ISNT rule may stem from the fact that it is unclear what percentage of individual normal eyes follow the ISNT rule. Other limitations may arise from the fact that perhaps other rules may be more common in the normal population.

In earlier studies based on disc photographs 52-79% of the individuals studied were found to obey the ISNT rule[31,32]. However later studies have revealed that the percentage of individuals obeying the ISNT rule was much lower. In a study done by Poon et al the percentage of individuals obeying the ISNT rule was found to be 37%[33]. One of the main reasons that the ISNT rule was not valid for a huge percentage of the population was because of considerable variation in the rim order of the nasal quadrant. In a large percentage of the population the rim width was wider nasally than inferiorly. In a normal population of 92 Chinese subjects, Wang and associates found that 9 out of 92 subjects (10%) had a nasal rim that was the widest compared to all the other rims, while Harizman and associates also reported in their study that 5 out of 66 normal subjects (7.6%) had a nasal rim that was thicker than the inferior rim[31,34].

A possible reason for the high variability in nasal rim order and hence the low fulfilment rate of the ISNT rule is that, although the central retinal vessel is not considered as part of the neuroretinal rim during disc assessments, there often is partial obscuration of the nasal rim by these large retinal vessels, which would make evaluation of the nasal rim width ranking more variable. Therefore, it is important to take into consideration the large variation that exists for the nasal rim order in the normal population when using the ISNT rule for determining whether a patient's optic nerve has glaucoma or not[31,33].

Thus our current understanding from various studies point to the fact that the ISNT rule may not be valid for a large percentage of the population and probably it is time to shift to a different rule or form of assessment. Some authors have stated that if the nasal quadrant is left out from the evaluation and the IST rule is followed or if both the nasal and the temporal quadrants are left out and the IS rule is followed then it would be more appropriate as more than 70% of

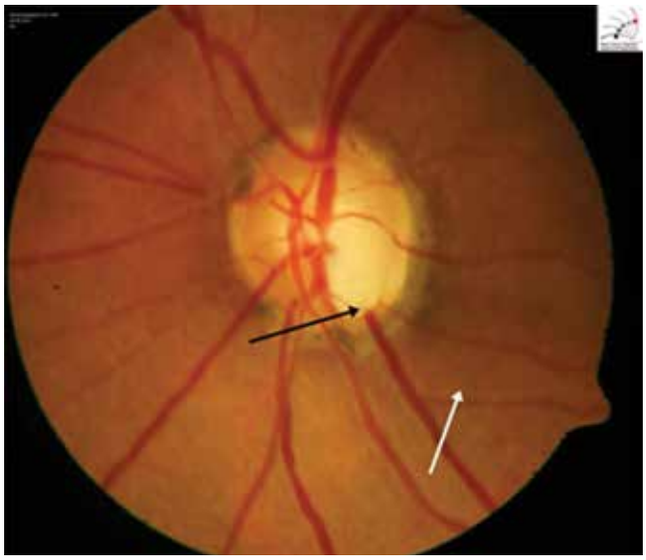

Figure 2a: *Figure showing a disc with a deep inferior notch (black arrow) with an NFLD (white arrow).*

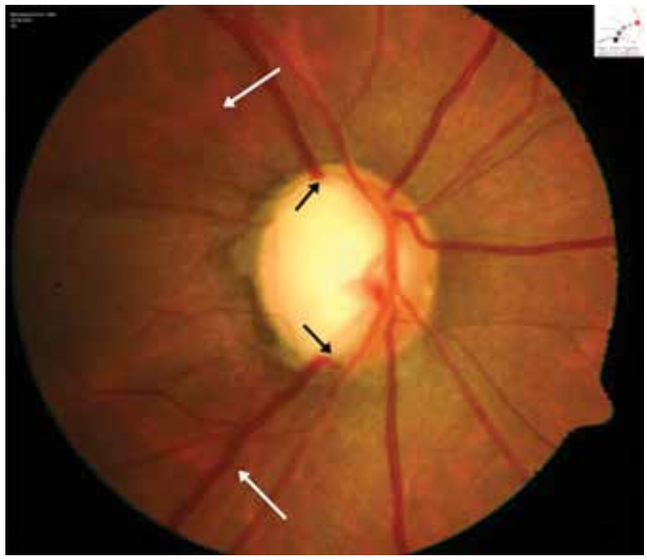

Figure 2b: *Figure showing a disc with bipolar notching with focal rim loss (black arrows) with NFLD (white arrows).*

normal eyes would follow the IST and the IS rule for both disc photographs and OCT RNFL thickness measurements[33].

The clinical significance of the shape also lies in the fact that it influences the distance between NRR at the disk border and the central retinal vessel trunk exit. It is important to document the shape of the disc if it is unusual as it is very difficult to assess the rim area in these discs. For these discs with unusual shapes it is very important to document them for future comparisons. Also the ISNT rule is not applicable in discs which are not vertically oval. It is very difficult to assess myopic discs because these discs may have may have a variation in disc shape, and they usually have a zone of peripapillary atrophy. Due to these it is very difficult to determine the margin of the disc. Careful attention should be paid while evaluating these discs as the unusual shape and the presence of a PPA may cause difficulty in the determination of the disc margin and thus the assessment of the disc as a whole.

The Neuroretinal Rim

The neuroretinal rim (NRR) is the intrapapillary equivalent of the optic nerve fibers. The NRR will reflect selective loss of the ganglion cell axons and is the primary location of pathologic changes seen in glaucoma[35]. Because the cup-disc ration ratio is often a poor indicator of early glaucoma, close attention should be paid to the width and health of the neuroretinal rim instead[36]. In fact the assessment of the NRR is probably the most important parameter in the optic disc evaluation of a patient. When assessing the neuroretinal rim tissue, its size, shape, and color must be taken into consideration[37]. As stated above the ISNT rule (or the IST or IS rule) should be kept in mind while evaluating the NRR as it correlates with the distribution of the nerve fiber bundles as they leave the scleral canal but there may be a huge percentage of anatomical variations which should also be kept in mind[33].

The mean NRR area was reported to be 1.97 ± 0.5 mm^2 by Jonas et al[21]. This study was done in a Caucasian subject population. Indian population based studies have however reported a larger disc area. The mean disc area was reported to be 2.8 ± 0.53 mm^2 in the participants of the Andhra Pradesh Eye Disease Study (APEDS) and 2.29 ± 0.39 mm^2 by the Chennai Glaucoma Study (CGS) group[38,39]. The Vellore Eye Study (VES) however reported a smaller rim area of 1.6 ± 0.37 mm^2, in a south Indian population[21].

The neuroretinal rim should be observed carefully to evaluate any thinning and notching of the rim tissue, which would indicate glaucomatous damage. The notch is defined as localized defect in the NRR on the cup side of the rim. The notch is usually a small defect and the circumferential extent of the notch occupies less than or equal to 60°, i.e. 2 contiguous clock hours (Figure 2a). If the area of damage is larger then it would be referred to as a thinning of the neuroretinal rim and as the thinning progresses it would be referred to as a focal rim loss (Figure 2b). A notch is usually associated with a nerve fiber layer defect. The cardinal feature of glaucomatous optic neuropathy is the loss of NRR from the inner edge of the rim. This loss can occur in all sections of the disc with regional preference depending on the stage of glaucoma[40]. The typical sequence of neuroretinal rim loss in glaucoma is loss of rim tissue at the infero-temporal and supero-temporal poles, followed by the temporal rim, and lastly the nasal rim[35].

The authors of the Chennai Glaucoma Study (CGS) stated a correlation between the rim area and the disc area. The study showed that the rim area had a strong positive correlation with the disc area. For every 1 mm^2 increase in disc area, the rim area increased by 0.5 mm^2 [39]. It has been observed that the larger is the optic nerve the larger is the NRR area and as the glaucoma progresses there is an increase in the cup area and thus correspondingly the NRR area decreases.

The changes which may be noted in the neuroretinal rim are:

Focal atrophy

a) This is due to focal loss of neural rim tissue in glaucoma that primarily occurs in the infero-temporal or supero-temporal region.
b) It begins as a small, discrete defect, referred as polar notching \ focal notching \ pit like change.
c) This defect enlarges and deepens, developing a sharp nasal margin referred to as sharpened polar nasal edge
d) As progression of glaucomatous atrophy continues, the local thinning reaches the neural rim of the disc margins, thus forming the sharpened

Figure 3: *Figure showing a deep inferior notch in the left eye of a patient. The "laminar dot" sign can be clearly seen in the picture (black arrow).*

Figure 4: *Figure showing the optic discs of the right and left eye of a subject. The right eye has an average sized disc with an average sized cup while the left eye shows a larger disc and hence a larger cup leading to a cup-disc ratio asymmetry between the two eyes.*

rim.

e) If the retinal vessels cross this sharpened rim, it bends sharply at the edge of the disc, termed as the bayoneting of the vessels at the disc edge.

Concentric Atrophy

This occurs less commonly, but when it occurs, it usually begins temporally and then progresses circumferentially towards the poles which is referred to as temporal unfolding.

Deepening of the cup

This is seen as glaucoma progresses and the following may be noted:

a) Over pass cupping – in which, vessels initially bridge the deepened cup and later collapse into it.

b) Laminar dot sign – which is owing to the exposure of underlying lamina cribrosa, by the deepened cup (Figure 3).

Pallor/ cup discrepancy

In early stages of glaucomatous optic atrophy, enlargement of the cup progresses ahead of the area of pallor. It may occur with diffuse/focal enlargement of the cup.

a) *Saucerisation:* It is the extension of diffuse shallow cupping towards the disc margin with retention of central pale cup and is an early sign of glaucoma.

b) *Focal saucerisation:* More localized shallow cup usually in the inferotemporal quadrant.

c) *Tinted hollow:* It is the retention of normal neural rim color in the area of focal saucerisation.

d) *Shadow sign:* Replacement of the tinted hollow by a greyish hue on progression of glaucomatous cup.

Advanced glaucomatous cupping

Occurs in the advanced stages of glaucoma leading to total loss of neural rim and bending of all vessels at the margin of the disc. It is sometimes also referred to as bean pot cupping.

Cup - Disc Ratio

Ganglion cells are scattered all over the retina, and their fibers converge on the optic nerve head. The layer of fibers gets quite thick just at the nerve head and then the fibers pile up and dive into the opening. The optic nerve head or the disc, is mostly filled with fibers. There is left over space in the middle of the nerve head called the cup, and the fibers are grouped around the cup in the rim. The size of the cup is determined by the size of the optic disc. There is a positive correlation between the size of the disc and the size of the cup. A large disc will have a large cup and a small disc will usually have a small cup or practically no cup at all.

The cup-disc ratio (CDR) is the value obtained by dividing the cup diameter by the disc diameter and is usually expressed in decimal values. Usually when the CDR is mentioned it is the vertical cup to disc ratio of that individual. The reason why the vertical CDR is important is that early neuroretinal rim loss occurs preferentially at the upper and lower poles of the disc. The direction or point of deviation of small blood vessels on the surface of the ONH is used to determine the size of the optic cup (contour method) but not the area of pallor in the center of the optic disc (colour contrast method[21].

A CDR asymmetry between two eyes with equal overall optic disc size may be suggestive of loss of neuroretinal rim tissue and should thus raise the suspicion of glaucoma (Figure 4). There is some inconsistency in the literature as to what cut offs to use for a small or large disc, but in general a disc can be considered small if ≤ 1.5 mm and large if ≥ 2.2 mm.[21] Mean area of the optic cup in Indian eyes as found in the Vellore Eye Study (VES) is 0.98 mm^2. The same study revealed that the area of the optic cup is independent of age, refractive error, and sex, axial length of the globe and depth of the anterior chamber[17]. The mean horizontal C:D diameter ratio is around 0.66 and the mean vertical C:D diameter ratio is 0.56. Thus the diagnosis of glaucoma should be considered if the vertical CDR is ≥0.7 (seen only in 10% of normal individuals) or the CDR asymmetry between the two eyes is more than 0.2 (seen only in 1% of normal individuals).

The evaluation of CDR in normal subjects, subjects with physiological cup, and glaucoma patients is difficult. The application of the evaluation rules of CDR is not appropriate for subjects with an optic nerve or disc anomaly (tilted, hypoplasic, dysplasic optic discs). It is to be kept in mind that the size of the optic cup always seems smaller in monoscopic examination than in stereoscopic examination[21].

Disc Haemorrhages

Jannik P. Bjerrum was the first to publish a report of optic disc hemorrhage (DH) in 1889. He observed that a number of glaucoma patients whose eyes had elevated intraocular pressure (IOP) also had bleeding within the optic nerve head. However it was Dr. Stephen Drance and Dr. Ian Begg who suggested that DH was an important marker of glaucomatous damage in 1970. Thus the disc haemorrhages are sometimes referred to Drance haemorrhages. DH has been reported to be a risk factor for the onset and progression of glaucomatous optic neuropathy[41,42,43].

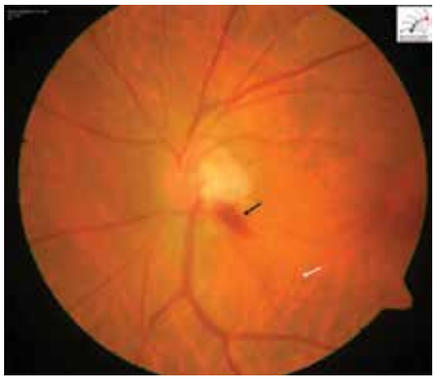

Figure 5a: *Figure showing a disc with a large disc haemorrhage in the infero - temporal aspect of the disc (black arrow). It is a typical flame shaped haemorrhage with feathered edges. An NFLD is also evident (white arrow).*

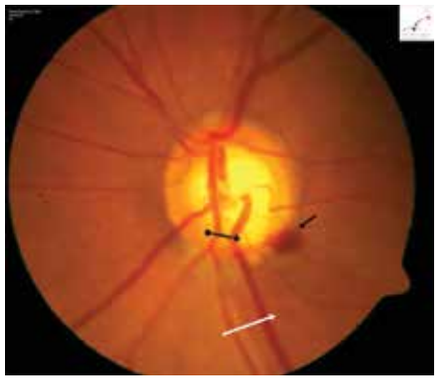

Figure 5b: *Figure showing a disc with a large disc haemorrhage in the infero - temporal aspect of the disc (black arrow) There is a deep inferior notch(black arrow with bulb) and a broad based nerve fiber layer defect(white arrow).*

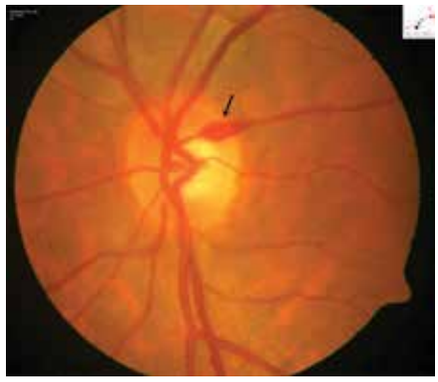

Figure 5c: *Figure showing why disc haemorrhages can be easily missed.Here the disc haemorrhage(black arrow) is present over the underlying vessel and can be easily overlooked.*

However there is some controversy as to whether disc haemorrhages are pathognomonic of glaucoma as it is still a poorly understood phenomenon and its exact etiology is still unknown. Most researchers would agree, however, that a DH in a glaucomatous eye is a negative prognostic factor and, in most cases, indicates advancing damage to the retinal nerve fiber layer (RNFL)[41-44].

A disc hemorrhage is a splinter or flame-shaped haemorrhage (and is sometimes referred to as such), with feathered edges, oriented radially and perpendicular to the disc margin (Figure 5a). The most common location of DH is at the temporal aspect of the disc. Disc hemorrhages tend to be small (but at times may be large) and extend from within the RNFL of the optic disc into the peripapillary region. is often associated with notching and structural change in the optic disc rim, focal defects of the RNFL, progressive defects of the visual field (VF), and beta zone peripapillary atrophy (β PPA) (Figure 5b). Sometimes the disc haemorrhages may be very small or subtle and may be mistaken for a blood vessel or just overlooked if the clinician is not specifically looking for it (Figure 5c). DHs are rarely found in normal eyes, but they are detected in approximately 4 to 7 percent of eyes with glaucoma[45]. It is located within one disc diameter from the optic disk border and one should rule out presence of optic disc edema, papillitis, diabetic retinopathy, central or branch retinal vein occlusion, or any other retinal disease associated with hemorrhage.

The prevalence of disc hemorrhage ranges from 0.6 to 1.4% in the normal population and from 1.9 to 16.9% in subjects with glaucoma[46]. The cumulative incidence of optic disc hemorrhages is reported as 0.5% per year in ocular hypertensives and 2.5% per year in eyes after the development of primary open angle glaucoma (POAG)[41]. In the Indian scenario the APEDS reported an incidence of 9.8% in the POAG group[38]. In the PACG group the reported incidence is around 5.4 % over a follow up of 9 years[47].

The ocular hypertension treatment study (OHTS) showed that optic disc hemorrhages are a predictive factor for the development of POAG in patients with OHT[48]. In the Collaborative Normal Tension Glaucoma Study (CNTGS) and the Early Manifest Glaucoma Trial (EMGT), glaucomatous eyes with disc hemorrhages experienced significantly more visual field progression during follow-up than eyes without hemorrhages[49,50]. Thus in glaucoma patients, the presence of a disc haemorrhage is indicative of disease progression and is also an indicator that more aggressive therapy should be instituted.

Retinal Nerve Fiber Layer

Discussion of the optic nerve in relation to glaucoma would be incomplete without mentioning the RNFL, which is composed of retinal ganglion cell axons which are covered by astrocytes and bundled by Muller cell processes[10]. The RNFL is seen as bright fine striations fanning off the optic disc. In normal eyes, the retinal nerve fiber layer (RNFL) is usually best visible in the inferior temporal part of the fundus, followed by the superior temporal region, the nasal superior region and the nasal inferior region[17]. The RNFL is least visible in the nasal sector. Histologically also it has been seen that the RNFL thickness is more superiorly and inferiorly compared to the nasal and temporal regions. This distribution correlates with the configuration of the neuroretinal rim, the diameter of the retinal arterioles, the location of the foveola, and the lamina cribrosa morphology. With increasing age, the RNFL visibility decreases diffusely without preferring special fundus regions and without the development of localized defects[9]. With all optic nerve diseases, the visibility of the RNFL is decreased in addition to the age-related loss, in a diffuse and/or a localized manner. Defects within the RNFL appear as darker zones in areas of expected brightness. This will cause retinal vessels to appear redder and darker, and will allow small vessels to become more visible.

To examine the RNFL it is always advisable to dilate the patient. A stereoscopic view of the fundus is achieved with a slitlamp and a non-contact lens. A lens which gives lesser magnification but a wider field of view is preferred. First the fundus is examined under normal conditions and any subtle changes in the RNFL are to be looked for (Figure 6a). Then red free illumination is used to visualize the fundus again (Figure 6b). The normal pattern of the fiber bundles can be detected as bright striations in the retinal reflex. If during fundus evaluation the RNFL is markedly better detectable in one sector then the examiner should carefully observe the other sectors to compare the visibility of the RNFL in those sectors. The retinal vessels are normally embedded in the retinal nerve fibers and thus do not look very bright and have a matt or dull look. When there is diffuse RNFL loss the vessels are covered only by the thin inner limiting membrane so are better visible and look brighter[9] (Figure 6c).

The RNFL defects which are initially

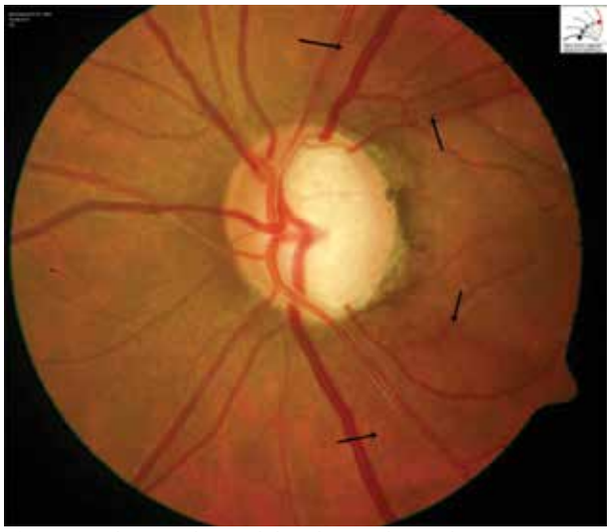

Figure 6a: *Shows a disc with bipolar notching. The corresponding large broad based NFL defects (black arrows) in the super-temporal and infero-temporal aspects can be seen.*

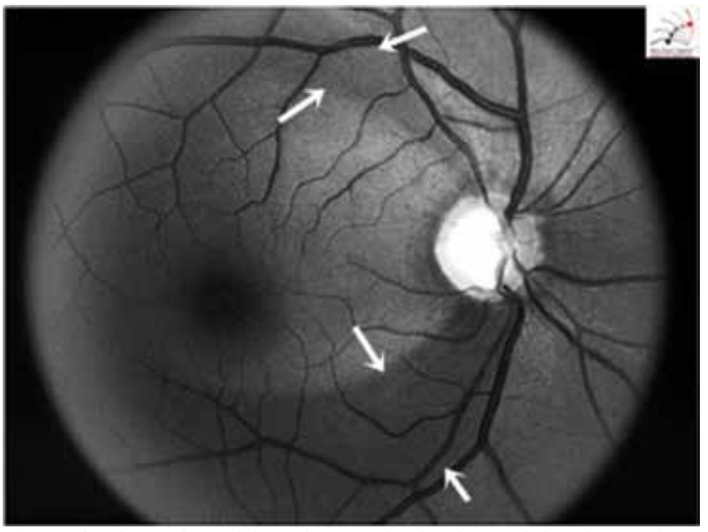

Figure 6b: *Shows the red free photograph of a disc with bipolar notching. The corresponding large broad based NFL defect can be seen in the infero-temporal aspect and a smaller typical RNFL defect can be visualized in the supero-temporal aspect (white arrows).*

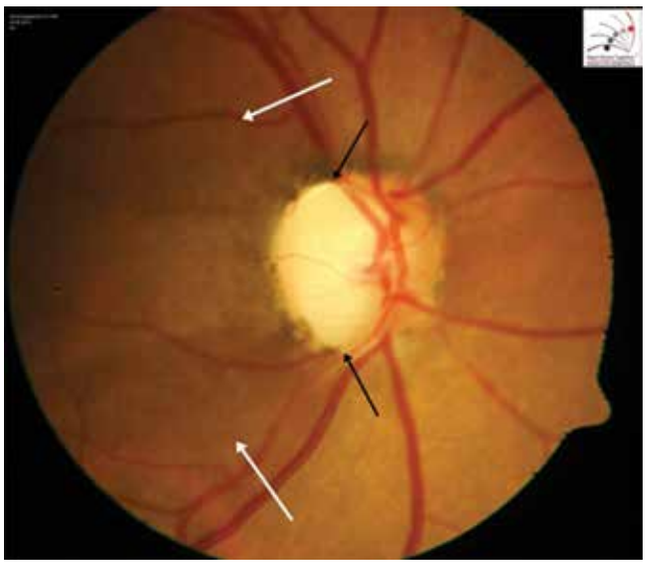

Figure 6c: *Shows a disc with bipolar rim loss (black arrows). The corresponding large broad based NFL defects in the super-temporal and infero-temporal aspects can be seen (white arrows). Note the better visibility of the retinal vessels which are sharper and clearly defined.*

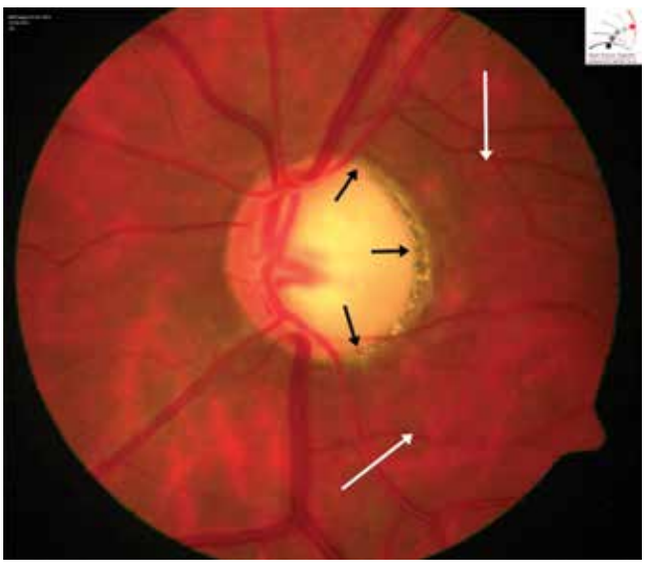

Figure 6d: *Shows a disc with bipolar rim loss (black arrows). The RNFL loss here is diffuse and is difficult to visualize (white arrows) but increased sharpness and prominence of peripapillary vessels, and clearer visualization of the underlying choroid can be appreciated.*

seen in early glaucoma are the localized defects. The localized defects are wedge-shaped and not spindle-like defects, running toward or touching the optic disc border. A localized defect is defined as a wedge-shaped defect running toward or touching the optic disc border occupying not more than 60° of the circumference of the disc[51]. This has to be differentiated from a pseudodefect which may be a spindle shaped area of RNFL defect away from the disc and not approaching or touching the disc. The number of localized defects are more in early and moderate glaucoma. As the glaucoma progresses the RNFL loss becomes more diffuse and it becomes more difficult to visualize it[51]. Diffuse RNFL defects are the most difficult to detect. The clinician should compare the striations between the superior and inferior bundles of the same eye, as well as the striations between the right and left eyes and look for any loss of brightness, increased sharpness and prominence of peripapillary vessels, and clearer visualization of the underlying choroid (Figure 6d).

While examining a patient of glaucoma along with the disc evaluation very careful assessment of the peripapillary region and the nerve fiber layer is extremely important. There may be subtle changes visible clinically in the RNFL during a fundus evaluation even before the disc changes like a notch or a thinning become evident. Quigley et al described these RNFL changes to be sensitive indicators of early optic nerve damage seen earlier than optic disc changes[52]. On the other hand if a notch or a thinning is evident, then close examination of the RNFL surrounding the disc may reveal the characteristic RNFL changes and that will help to establish the diagnosis of glaucoma. RNFL defects occur in about 20% of all glaucomatous eyes but they are not pathognomonic of glaucoma since they can also be found in other ocular diseases, such as optic disc drusen, toxoplasmotic retinochoroidal scars, longstanding papilloedema or

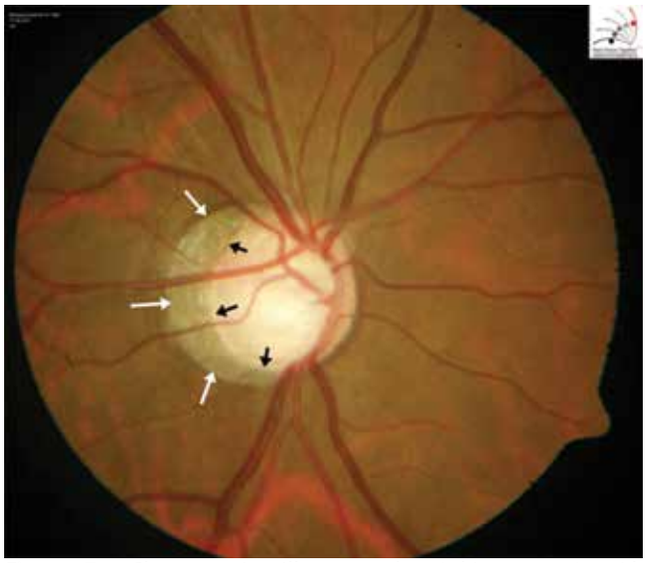

Figure 7a: *Shows peripapillary atrophy (white arrows) with corresponding thinning of the neuroretinal rim (black arrows).*

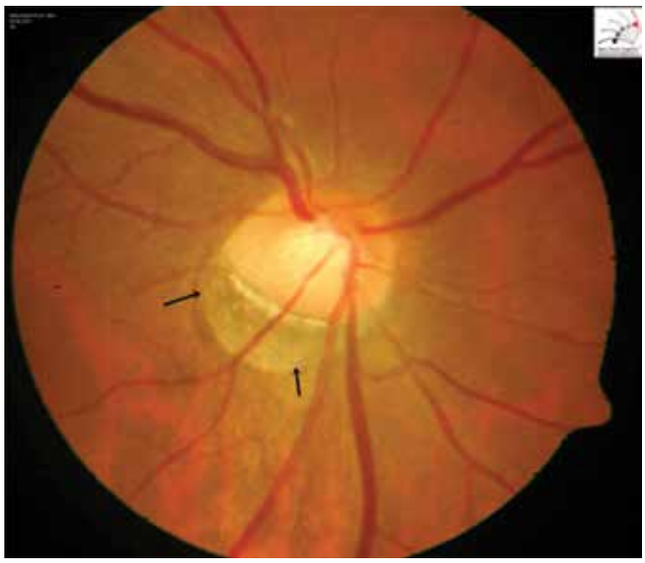

Figure 7c: *Shows peripapillary atrophy (black arrows) associated with a "tilted optic disc".*

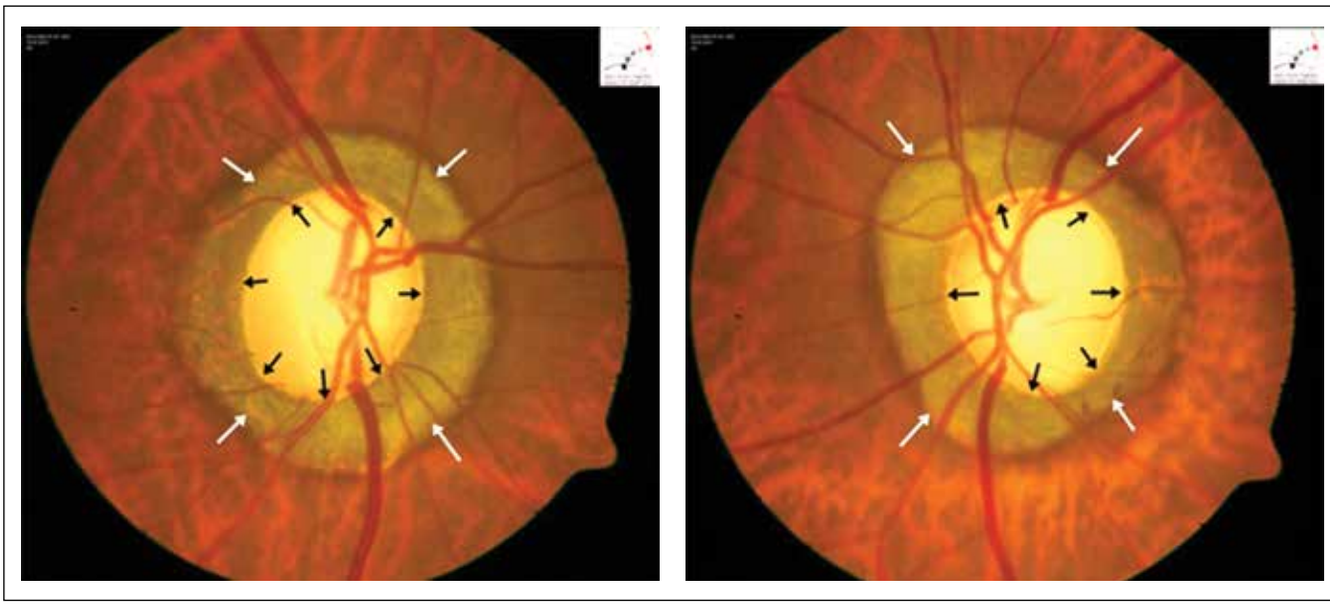

Figure 7b: *Shows peripapillary atrophy (white arrows) with corresponding advanced thinning of the neuroretinal rim in both eyes of the same individual (black arrows).*

optic neuritis[51]. Since they are not present in normal eyes, they almost always signify an abnormality but it may not specifically be glaucoma. RNFL evaluation is especially helpful for early glaucoma diagnosis and in glaucoma eyes with small optic discs. RNFL defects are found more commonly in normal tension glaucoma followed by primary open angle glaucoma and then secondary open angle glaucomas. In advanced optic nerve atrophy, other examination techniques, such as perimetry, may be more helpful for following optic nerve damage.

Considering its great importance in the assessment of optic nerve anomalies and diseases and taking into account the feasibility of its ophthalmoscopic evaluation using green light, the retinal nerve fiber layer should be examined during any routine ophthalmoscopy.

Peripapillary Changes

Irregular pigmentation around the optic nerve is a non-specific finding that can be seen in many healthy eyes. However the presence of peripapillary atrophy should raise a suspicion for glaucoma, specially if additional risk factors are identified in the patient. The atrophy in the peripapillary region differs from normal peripapillary variants in the respect that the atrophy is typically irregular and patchy, whereas crescents are typically very uniform in colour and shape. The clinical appearance of PPA is a moth-eaten pattern of the RPE temporal to the optic nerve head; if truly associated with glaucoma, there is typically neuro-retinal rim thinning adjacent to the area of atrophy[37,53,54,55].

Ophthalmoscopically and histopathologically, parapapillary atrophy may be divided into a peripheral alpha zone and a central beta zone. The alpha zone is characterized by an irregular hypopigmentation and hyperpigmentation of the retinal pigment epithelium and slight thinning of the chorioretinal tissue layer. Nasally it is always separated from the neuro-retinal rim by either zone beta if present, or by the scleral ring if zone beta is absent, and temporally it is bounded by normal retina. There is thinning of the chorioretinal layer above this region. Zone alpha is a non-specific finding that is present in both normal and glaucomatous eyes[10,11,54,55].

The beta zone is characterized by a complete loss of the retinal pigment epithelium, marked atrophy of the retinal photoreceptor layer and the

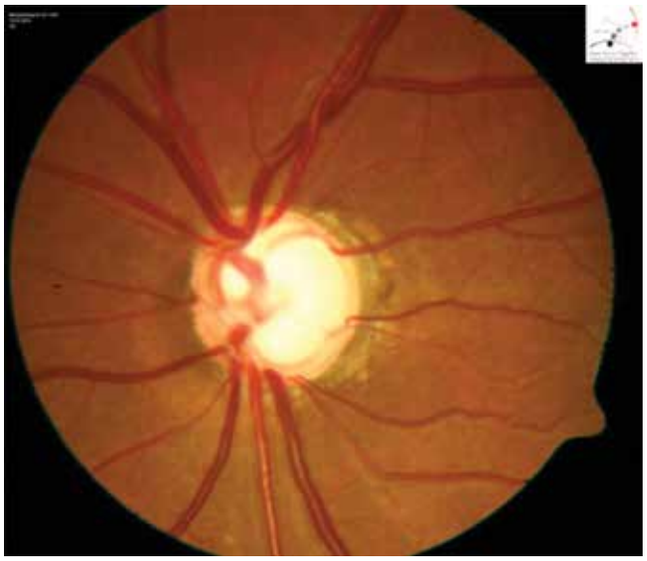

Figure 8: *Figure showing the bayoneting of the blood vessels in a case of advanced glaucomatous cupping.*

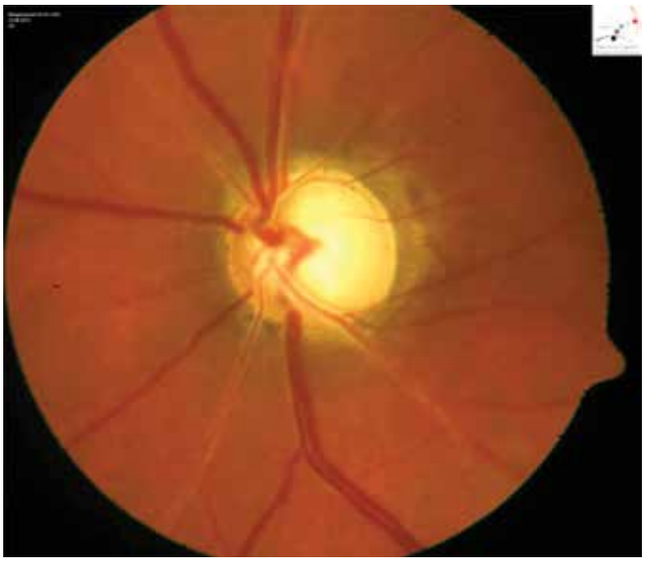

Figure 9: *Figure showing the nasalization of the blood vessels in a case of advanced glaucomatous cupping.*

choriocapillaris, clear visibility of the large choroidal vessels and sclera, and round boundaries to the adjacent alpha zone on its peripheral side and to the peripapillary scleral ring on its central side. It is thought to be caused by poor perfusion of the peripapillary area, and though it may also be present in normal eyes, it is much more common in glaucomatous eyes[11,54,55].

The importance of the alpha zone and the beta zone is to help the clinician differentiate between glaucomatous and non-glaucomatous optic nerves, particularly when additional anatomic changes suggest the presence of early glaucoma damage (Figure 7a). Additionally, because progression of beta zone is associated with progression of glaucoma, it may be a subtle yet important indication to alert the clinician that more aggressive glaucoma therapy may be necessary in a patient already diagnosed with the disease[11,54,55]. Some authors state that progressive changes in the beta zone are IOP independent. This is supported by the fact that pronounced alterations in the peripapillary region are seen in normal tension glaucoma[56] (Figure 7b).

Clinicians must differentiate the alpha and beta zones from the myopic scleral crescent in eyes with high myopia and from the inferior scleral crescent in eyes with "tilted optic discs"[57] (Figure 7c). In the region of the myopic crescent, only the inner limiting membrane and the underlying retinal nerve fiber layer or its remnants cover the sclera. In contrast, in the glaucomatous beta zone, Bruch's membrane and the choroid are interposed between the remnants of the retina and the sclera[58,59,60]. The alpha and beta zones may also be present in an eye with high myopia. Both zones are significantly larger in highly myopic eyes with glaucoma than in glaucomatous eyes that are not severely nearsighted[61].

Vascular Changes

Apart from optic disc haemorrhages which has been mentioned previously in this article several vascular changes can be observed in glaucomatous eyes. These include baring of circumlinear vessels, bayoneting, nasalization of vessels, optic nerve shunts, and retinal artery attenuation.

Baring of circumlinear vessels occurs in areas where neuroretinal rim tissue has been lost, thus the structural support for the vessels leaving the optic nerve is no longer present and is clinically seen as vessels "hanging" across the optic nerve cup without adjacent support of neuroretinal rim[20]. It is a subtle change to look for carefully in order to aid in the diagnosis of glaucoma.

Bayoneting of vessels is seen in areas of significant neuroretinal rim tissue loss, whereby visualization of the course of a particular blood vessel is temporarily lost as it makes its way along the excavated nerve borders and re-emerges at the edge of the rim from the deeply excavated cup[20] (Figure 8). It is typically seen in advanced cupping or in nerves with localized notching of the neuroretinal rim.

Nasalization of blood vessels occurs in very advanced glaucoma whereby the only structural support remains along the nasal rim due to severe loss of superior, inferior, and temporal rim tissue[20] (Figure 9). It is easily observable in advanced cupping and will not be present in early disease. Retinal artery attenuation can also occur in glaucomatous eyes, but is typically a subtler finding than the aforementioned vascular changes. It likely results due to decreased metabolic demand from an increasingly thinner rim tissue[10,11]. It is a very subtle but important change to look for in helping the clinician determine the level of suspicion for early glaucoma.

THE FIVE RULES OF ONH AND RNFL EVALUATION

Fingeret et al published an article in 2005 where they enumerated five rules to evaluate the optic disc and retinal nerve fiber layer for glaucoma[37]. This is a small but very helpful checklist to go through while examining a patient. The authors concluded that optic disc and RNFL assessment could be performed according to 5 rules that include the following:

a. Evaluation of optic disc size
b. Rim shape and area
c. Presence of RNFL loss
d. PPA, and
e. Retinal or optic disc hemorrhages.

The authors stated that by following these 5 rules, a thorough and systematic review of the optic disc and RNFL could be done and that would improve the ability to diagnose and manage glaucoma[37].

DIFFERENTIAL DIAGNOSIS OF GLAUCOMATOUS CUPPING

- OD Coloboma (Figure 10)
- Optic Disc pit
- Morning glory syndrome (Figure 11)

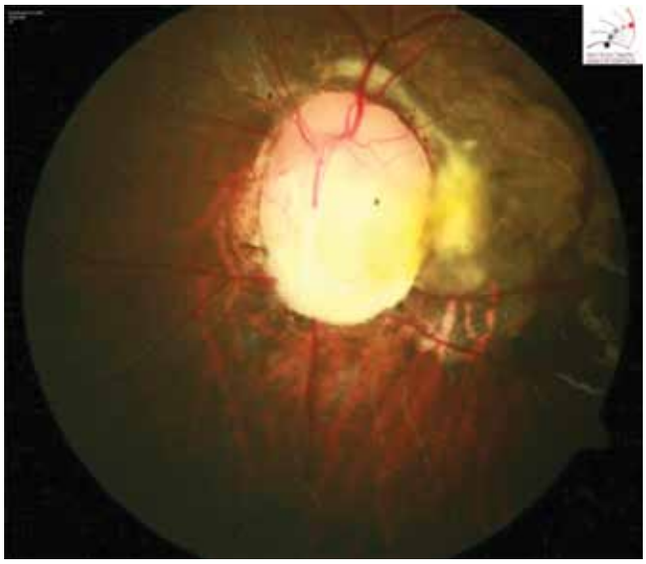

Figure 10: *Figure showing an optic disc coloboma.*

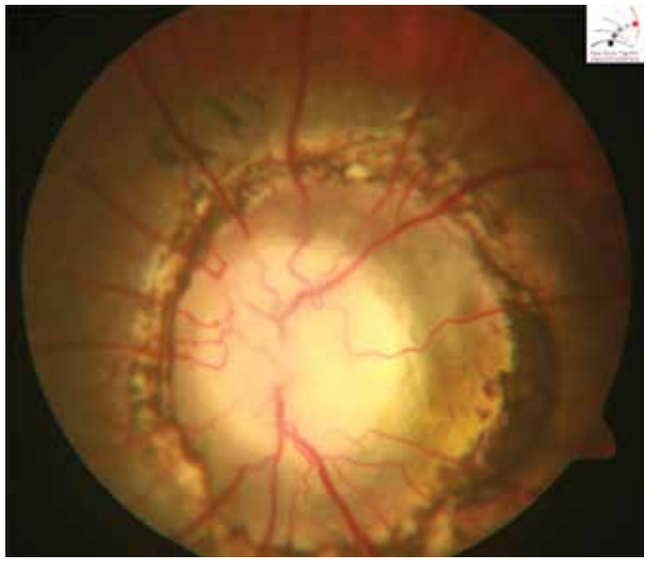

Figure 11: *Figure showing a Morning Glory disc.*

- AION (Anterior Ischaemic Optic Neuropathy)
- Sellar lesions
- Methyl alcohol poisoning
- Myopic disc
- Tilted disc

CHECKLIST FOR OPTIC NERVE EVALUATION

- *Disc Size:* Measure the vertical size of the OD at the slit lamp through dilated pupils.
- *CDR:* Determine the vertical CD ratio and consider it carefully in relation to the size of the disc.
- *NRR:* Evaluate the integrity of the NRR, and look specifically for early changes or alterations like thinning, notching or pallor.
- *Vascular changes:* Evaluate for the presence of any vascular changes: Disc hemorrhages, nasalization of vessels, baring of circumlinear vessels and optociliary shunt vessels.
- *RNFL:* Evaluate the integrity of the RNFL with a red-free filter.
- *PPA:* Evaluate for the presence and extent of peripapillary atrophy.

CONCLUSION

Evaluation of the optic nerve head is crucial for the early diagnosis and management of glaucoma. Clinicians must keep in mind that the cup-disc ratio is not the only factor to consider when evaluating the optic nerve, and due importance should be given to the neuroretinal rim and its surrounding peripapillary tissue and vasculature. Clinicians must also remember that glaucoma usually causes cupping without much pallor, therefore the presence of pallor of the neuroretinal rim must prompt the clinician to investigate for a different or additional optic neuropathy. Once the characteristic changes which suggest glaucoma - in terms of the NRR changes, the vascular changes, the peripapillary changes etc. have taken place it is fairly straightforward to make a diagnosis of glaucoma. The challenge lies in the early diagnosis of glaucoma. Very careful assessment of the optic disc, the vasculature and the peripapillary region to diagnose the subtle signs of glaucoma is pivotal for the early diagnosis prior to development of significant structural and functional damage. By following the steps outlined in this article one should be able to become proficient in this evaluation over time in order to prevent under-diagnosis, delayed diagnosis, as well as over-diagnosis of this disease.

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MONITORING GLAUCOMA PROGRESSION

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Glaucoma is a disease of the optic nerve, characterised by a specific pattern of progressive injury to retinal ganglion cells and their axons, which results in the alteration of optic disc topography, commonly known as "cupping", and associated with visual field loss. Glaucoma is, therefore, a disease that is defined, staged, longitudinally assessed, and treated on the basis of structural appearance of the optic nerve and its function[1].

Most glaucoma patients show slow progression of structure and function over many years. However, a subset of glaucoma patients will demonstrate fast progression and are at risk of significant visual disability or blindness. To reduce the probability of visual disability, clinicians after diagnosing glaucoma and initiating treatment, should focus primarily on whether the disease is stable or whether there are progressive changes that require an increase in therapy.

RISK FACTORS FOR PROGRESSION

There are several risk factors for glaucoma progression, including higher intraocular pressure, pseudoexfoliation, older age, lower ocular perfusion pressure, advanced disease at time of presentation and the presence of an optic disc haemorrhage. Cardiovascular disease is an important risk factor for rapid glaucoma disease progression irrespective of IOP control. Patients with significant risk factors for progression should be followed more closely to ensure that the treatment plan is sufficient.

TOOLS FOR DETECTING GLAUCOMA PROGRESSION

European and American guidelines explain progression as a deterioration of structural and/ or functional defects .More detailed definitions of progression however have not yet been established. According to the World Glaucoma Association, both functional and structural testings should be conducted throughout the course of the disease. Previously, it was generally accepted that optic disc changes precede VF damage. However, the Ocular Hypertension Treatment Study (OHTS)[2] and the European Glaucoma Prevention Study (EGPS)[3] have shown that structural and functional damage seldom coincide in patients converting from ocular hypertension (OHT) to glaucoma, and the nonlinear relationship between MD and RGC counts indicates that face value interpretations of rates of MD loss over time can be misleading. It remains unclear why some patients seem to first develop a structural change, while others first change in function. But this could be related to the accuracy of the methods used to evaluate structural and functional changes as well as individual morphology and factors governing susceptibility to damage.

While visual fields and optic disc photography have been considered the gold standard for detecting progression, no one particular test is perfect for detecting progression. Additionally, there is not always agreement among tests or those interpreting the tests.

For decades, clinicians have used standard automated perimetry (SAP) to detect functional progression in glaucoma patients. Despite the subjective nature of the testing and the importance of patient's attention and cognitive abilities, it remains a decisive component of glaucoma testing. Structural progression can be detected using a variety of tools, including optic disc and RNFL photography and OCT.

SAP TO DETECT FUNCTIONAL PROGRESSION IN GLAUCOMA

Criteria from The Collaborative Normal-Tension Glaucoma Study (CNTGS) and The Early Manifest Glaucoma Trial (EMGT)

THE CNTGS

The CNTGS' investigators determined progression using the threshold numbers in full-threshold Humphrey Visual Fields. If 2 or more points within or adjacent to an existing scotoma worsened by at least 10 dB or 3 times the average of the short-term fluctuations, whichever was larger, that field was thought to have progressed after confirmation on 2 subsequent fields. These numbers, however, may not apply to Swedish Interactive Threshold Algorithm (SITA) visual fields for 2 reasons. First, the short-term fluctuation is not measured in the SITA program. Second, a 10-dB change in full threshold may not be equivalent to a 10-dB change in a SITA field.

THE EMGT

The Glaucoma Progression Analysis software (Carl Zeiss Meditec Inc., Dublin, CA) incorporates the EMGT's statistical method for identifying glaucomatous progression. For the indication of likely progression, the Glaucoma Progression Analysis software requires that 3 consecutive visual field tests contain 3 or more identical points that have changed at a statistically significant level.

DETECTION OF PROGRESSION AND ESTIMATION OF RATES OF PROGRESSION

Detection of progression and estimation of rates of disease deterioration are essential in order to evaluate risk of functional impairment and establish treatment strategies.

RATE OF PROGRESSION

Rate of progression provides important information about

the risk of vision loss. SAP is the most commonly used method for assessing rates of visual function loss in glaucoma and estimating risk of impairment from the disease. Glaucoma progression rate varies widely, even among patients under careful management, and risk factors alone cannot accurately predict which patient will progress rapidly versus slowly. While some patients progress very slowly and need only minimal therapy, a minority of treated patients will progress at rate that could rapidly lead to disability, if left unchecked. Therefore, an understanding of each patient's rate of progression is helpful in individualizing treatment and in identifying patient at high risk for progressing to visual disability.

By tradition, rates of change have been measured by SAP using linear regression over time with parameters such as mean deviation (MD) and expressed in units of decibels/year (dB/y).

Progression may have different clinical consequences depending on the age and level of visual field (VF) loss. Progression in an 80-year-old patient with early damage has different implications compared to a 45-year-old with advanced damage. In individual patient, the rate of VF change allows the clinician to predict the possibility of lifetime visual disability by taking into account factors, such as age, life expectancy, and the amount of presenting VF loss. Numerous reports have estimated that the average rate of VF change, in glaucoma patients ranges from 0 to -1.1 dB/y[4]. More recently, Heijl et al. reported a median MD rate of - 0.62 dB/y in patients undergoing routine care[5].

In a recent study, Chauhan and colleagues have suggested that rates of MD change slower than -0.5 dB/y would be unlikely to lead to visual disability. While a patient with early visual field loss (MD=-4dB) and a rapid rate of progression (-2 dB/y), could be expected to develop total (-30 dB) in 13 years[6]. Such reasoning is fundamentally based on the assumption that rates of MD change over time are linear. However, there is very little evidence in the literature to support this notion.

A change of -0.5 dB in MD in early stages of the disease (with initial MD close to 0 dB) would correspond to a loss of approximately 100,000 RGCs. Such loss would actually be greater than the loss of approximately 35,000 cells that would be associated with a 2-dB change in MD for an eye with severe damage and MD of -15dB.

ESTABLISHING A RELIABLE BASELINE

Establishing a reliable baseline is essential for detection of glaucoma progression. Functional assessment requires repeated VF tests to overcome the patient's learning curve. The first documentation of a VF defect should be confirmed as soon as possible on at least 2 additional consecutive examinations. The VF in stable severe glaucoma shows more fluctuations compared to stable mild glaucoma[7]. It should be emphasized that obtaining a representative baseline is foundational to future management decision.

FREQUENCY OF TESTING

In the evaluation of functional defects, the EGS has made recommendations regarding the frequency of VF testing using specific analysis tools. The frequency of testing is to be adapted to the severity of glaucoma damage and the rate of progression.

As per EGS guideline[8] 3 fields per year—including baseline tests—in the first 2 years after initial diagnosis should be done. This amount of testing usually is enough to detect rapidly progressing eyes- those worsening by -2 dB/year or more. The World Glaucoma Association 2011 Consensus Statement on Glaucoma Progression made a similar suggestion. In summary, we need to perform field-testing more frequently in patients with manifest glaucoma and field loss in the first few years after diagnosis, and continue to test yearly for the next 5 years or so. Thereafter, in clearly stable patients and in elderly patients, with mild VF defect and slow rate of progression we may be able to further reduce the number of fields, in some cases perhaps to one field every second year.

MEASUREMENT OF VISUAL FIELD PROGRESSION IN GLAUCOMA

The most extensively available analysis aid for measuring visual field progression is the Humphrey Perimeter's Guided Progression Analysis or GPA. Two commonly used methods to identify change in VF defects over time are the event-based and the trend-based progression analyses. GPA helps doctors identify and quantify VF progression in glaucoma patients, using both event and trend analysis. Event and trend analysis are different but have complementary goals. The goal of event analysis is to assess whether there has been any statistically significant worsening in the VF. The goal of trend analysis is to quantify any observed rate of change, and to help the practitioner measure the risk of future disability associated with that rate. The recently introduced Guided Progression Analysis by the Humphrey VF Analyzer (Carl Zeiss Meditec, Inc. Dublin, CA, USA) provides both an event-based progression analysis and a trend-based analysis on the same printout.

In clinical practice, information from both these analyses is essential, because it is not only adequate to identify VF progression in glaucoma but also to decide the rate of progression (ROP), so that the treatment can be more aggressive in patient with fast rate of progression.

GPA EVENT ANALYSIS

Event-based analysis determines VF progression to be either present or absent depending on a predefined change in the VF parameters. The event-based progression analysis, called the glaucoma progression analysis (GPA), is based on the criteria designed to identify VF progression in the EMGT[9].

GPA offers a plain language event analysis called GPA Alert. GPA Alert will show the message 'Possible Progression' when 3 or more test points show statistically significant deterioration on 2 successive follow- up examinations, compared to a baseline of two field tests. A 'Likely Progression' message will be found when the same 3 or more significantly deteriorated test points appear in at least 3 consecutive follow -up tests.

SYMBOLS USED IN GCMPS

GCPMs use triangle symbols to highlight statistically significant deterioration from a baseline consisting of the average of two chosen tests. Each follow-ups field is compared to that baseline, and open triangles indicate test point locations with deterioration that is statistically significant at the 5% level. Half black triangles indicate test point locations that have shown statistically significant deterioration in 2 consecutive follow-up examinations, and filled-in black triangles designate locations where such deteriorations has been observed in 3 or more consecutive tests[10].

While evaluating GCPMs one can

expect that each test point will have a 5% risk of being falsely flagged simply from random test variability. GCPMs are not calculated for fields having an MD value worse than -20dB.

GPA TREND ANALYSIS

Trend-based analysis provides the actual rate of change of VF parameters and is based on the ROP of the visual function of the eye through a linear regression model using a new global index, VF index (VFI).The goal of trend analysis is to quantify how quickly each patient is changing and thereby to help doctors identify patients who are progressing at rates that threaten to cause considerable visual disability within the patient's expected life time.

This regression analysis is automatically displayed in the GPA summary and the Full GPA reports whenever a sufficient number of visual field tests are available. VFI is a single number that summarizes each patient's VF status as a percentage of the normal age-corrected sensitivity. Therefore, a completely normal VF would have a VFI of 100%, and a perimetrically blind VF would have a VFI of 0%.

LIMITATIONS OF EVENT AND TREND ANALYSIS

Both of these are known to have some limitations. One of the major limitations of the trend-based analysis is the length of the follow-up required to detect progression, which itself is influenced by a number of factors, including examination frequency, media opacities like cataract, underlying rate and type of progression[11]. The ability of the event-based analysis to detect progression is dependent upon the degree of change exceeding test–retest variability of stable glaucoma patients, which is known to be already high for damaged locations[12]. Therefore, the event-based approach is also likely to be less sensitive to smaller changes in the VF parameters. In addition, event-based analyses have also been shown to be vulnerable to threshold variability.

INTERPRETING VFI PROGRESSION RATE

Interpretation of rates of progression can be quite intuitive if one considers the patient's current level of visual function and life-expectancy. Ideally it would be better to prevent all progression, but a minimum goal could be trying to retain at least a VFI of 50% in the better eye. The US Social Security Administration has defined an MD of -22dB as a threshold for visual disability. An MD of -22dB corresponds to a VFI of approximately 30%[13].

ALTERNATIVE ANALYSES

Overview

The overview report puts all of a patient's VF tests into a single report. The Overview also is the preferred standard format in follow-up of diseases other than glaucoma, such as neurological field loss. While this report does not quantify change, it provides a broad qualitative overview of a patient's VF history.

CHANGE ANALYSIS

The Change Analysis report was first offered in the original HFA over 25 years ago and has largely been replaced by the newer GPA report. It contains a linear regression analysis of MD that may be useful in certain situations.

Challenges

One should not assume that all VF progression is due to glaucoma. Patients with glaucoma are generally elderly and either have or can develop other diseases. The practitioner should rule out other causes of a worsening VF such as vascular occlusive disease, age-related macular degeneration, non glaucomatous optic neuropathies, and even central nervous system lesions or strokes. Before changing a patient's management, one should obtain at least 2, preferably 3, confirmatory visual fields-a potentially challenging clinical practice. Without these confirmatory visual fields, physicians may diagnose progression when there is not any. The researchers from the CNTGS and EMGT agree that confirming progression with more than one follow-up field is significant.

OPTIC DISC TO DETECT STRUCTURAL PROGRESSION IN GLAUCOMA

Progressive neuroretinal rim thinning, increased excavation, and diffuse and localized loss of the RNFL are all recognizable features of structural damage in the disease. However, their precise relationship with functional deterioration in patients with glaucoma remains largely unclear.

Stereoscopic photography (ideally simultaneous, with a fixed angle) is the preferred method of qualitative imaging. Images obtained with digital scanning devices are dependent on software for interpretation. Often, 3 images are necessary during the first 18 months to distinguish progression from fluctuation. If colour photography is not available, manual drawings are still useful to provide a record of the optic disc appearance.

Challenges

Regulatory agencies throughout the world generally have not approved structural assessment of the optic nerve as a primary end point in clinical trials of glaucoma drugs and devices. Both the Ocular Hypertension Treatment Study[14] and the European Glaucoma Prevention Study demonstrated that a substantial proportion of patients with ocular hypertension who developed glaucoma showed a change first in optic disc photographs. However, despite being included as end points for glaucoma conversion in these studies, progressive optic disc damage has not yet been demonstrated to translate into worse clinically relevant outcomes for these patients.

Previous investigations have shown that baseline structural measurements predict future development of VF loss in suspected glaucoma suggesting a potential role for these measurements in early detection of the disease. Such evidence comes from studies using cross-sectional grading of optic disc photographs and imaging methods for structural evaluation in glaucoma, including confocal scanning laser ophthalmoscopy, optical coherence tomography, and scanning laser polarimeter. However, measures of predictive ability reported in these studies have generally indicated a low accuracy of cross-sectional structural measures for predicting individual functional outcomes. This is likely due to the wide variation in the appearance of the optic nerve, which makes it difficult to identify early signs of disease at one time.

OCT TO DETECT PROGRESSION IN GLAUCOMA (TD- OCT AND SD-OCT)

OCT is an imaging technique originally developed to provide objective and quantitative estimates of the thickness of the RNFL. OCT RNFL measurements are reproducible and have been shown in cross-sectional studies to be able to discriminate glaucomatous from healthy eyes. Today's spectral

domain (SD-OCT) instruments provide high resolution and highly repeatable images that can be used in the diagnosis of glaucoma and detection of structural progression. More recently, macular imaging with OCT has emerged as an important parameter in the diagnosis of glaucoma. There are several advantages to using macular scans compared to optic nerve and RNFL parameters. At a fundamental level, glaucoma is a disease of retinal ganglion cells. Since the macula contains more than 50% of the ganglion cells of the entire retina, a macular scan will sample the majority of retinal ganglion cells. In addition, while the optic disc and peripapillary region have highly variable structural characteristics among normal and glaucoma patients, there is much less variability in the macular region[15]. Detecting and following glaucoma progression using macular thickness is the newest area of interest, and the research is still emerging.

MEASURING GLAUCOMA PROGRESSION BY OCT

The statistical approaches used in assessing glaucoma progression can be divided into event based and trend based. In event analysis, progression is recognised when a follow-up measurement exceeds a predetermined threshold for change from baseline. It is assumed that any change lower than this threshold is due to natural age-related loss and/or measurement variability, whereas changes exceeding the threshold represent actual progression. The threshold for a change can be determined from an individual subject's variability or from variability in a normal reference group. Event analysis is intended to identify a gradual change over time that eventually crosses a threshold or to detect an acute event that exceeds a threshold. However, a confirmatory test is always recommended, particularly in the latter case, to prevent a measurement produced by an artefact and being labelled as a real event.

A trend analysis identifies progression by monitoring the behaviour of a parameter over time. A regression analysis or mixed effect analysis of a dependent variable (ie, RNFL thickness) is performed on follow-up measurements, providing a rate of progression over time. This method is less sensitive to sudden change and the variability among consecutive tests because it is neutralized by the overall rate of change.

The rates of localized thickness change are shown to have higher discriminating ability between progressing and non-progressing group than the global RNFL thinning rate. Thus, focal RNFL loss may not always result in a detectable change in global RNFL thickness. The inferotemporal (7 o'clock) sector is the most frequent location that showed progression, suggesting that this location is not only important in discriminating glaucomatous from healthy eyes but it should also play an important role in detecting glaucomatous progression.

For the global RNFL thickness, mean rate of change is −0.72 µm/year for progressors and 0.14 µm/year for non-progressors. The rates of change are widely variable among the eyes.

Challenges

The detection of glaucoma progression with OCT remains a challenge because when measuring structural changes over time, it is hard to distinguish between glaucomatous structural damage and measurement variability or age-related structural loss. Studies analysing healthy subjects demonstrated a considerable negative correlation between age and average RNFL thickness of −0.33 µm/year while other studies reported a −0.52µm/year rate of age-related loss of RNFL.

Although the test itself is objective, interpretation is subjective and influenced by clinician's experience. In addition, there are limitations to OCT interpretation, such as: other ocular diseases, signal-to-noise ratio, instrument/image artefacts and the stage of the disease.

The impact of concomitant macular disease renders macular OCT scans ineffective in glaucoma. Other conditions may impact the optic nerve (epiretinal membranes are a common source of artefacts in RNFL scans) and RNFL measurements, as well. The development of posterior vitreous detachment (PVD) also influence RNFL scans, as focal traction at the vitreoretinal interface may cause the RNFL to look thicker. As the PVD advances and the traction are released, the RNFL measurement becomes thinner. Without careful evaluation, this thinning may be misinterpreted as progression. Uveitis can also influence RNFL scan.

OCT IN DIFFERENT DISEASE STAGES

Stage of glaucoma disease has a significant impact on OCT relevance. The RNFL layer contains blood vessels, glial tissue and ganglion cell axons; even in eyes with no light perception due to glaucoma, the RNFL does not fall below 30µm; the floor effect on most commercial instruments is considered to be around 45µm to 50µm. As the RNFL approaches this floor in advanced glaucoma, the thickness is more heavily influenced by other structural components, such as blood vessels, and less by actual RNFL thickness, making progression detection more difficult[16]. Patients with mild to moderate glaucoma may show significant rates of change in both RNFL and macular/ganglion cell layer thickness. In a study of advanced glaucoma patients, however, there may be a significant difference in the rate of change of macular thickness, but not in RNFL thickness, between progressive and non-progressive patients[17].

SUMMARY OF MONITORING PROGRESSION WITH TD-OCT AND SD-OCT[18]

TD-OCT is a sensitive measure of glaucoma progression. Studying both overall average and sectoral RNFL thicknesses is important in detection of progression. SD-OCT with its increased resolution, image registration capabilities, higher reproducibility, and three-dimensional rendering capabilities offers potential advantages over TD-OCT. SD-OCT is a valuable clinical tool for glaucoma diagnosis and detection of progression. RNFL parameters have been demonstrated to provide accurate information for disease diagnosis and sensitive method for disease progression. Initial studies evaluating macular and ONH parameters show encouraging results. The limited agreement between functional and structural tests emphasizes the importance of assessing both structure and function when making clinical decisions regarding glaucoma progression.

FREQUENCY OF TESTING

No fixed guidelines have been developed regarding the frequency of OCT testing. The principle is to obtain scans at roughly the same rate as VF. After 2 years, if the patient appears to be stable, the frequency of testing can be decreased. If progression is assumed, the frequency of examinations can be increased.

When progression is suspected based on OCT, clinicians should take a

systematic approach to make appropriate clinical decisions.

1. Repeat the test. To understand that the suspected change is definite rather than due to artefact.
2. Next, make a decision whether or not the change is typical of glaucomatous change versus a factor of age or due to other disease.
3. If the change appears to be glaucomatous, determine the rate at which the progression has occurred.
4. Calculate the rate of changes and compare it to the patient's life expectancy and stage of the disease. It is important in deciding, on the basis of the rate, how aggressively to treat, or even whether, to modify therapy.
5. Finally, if therapy is increased, revise the baseline for all testing (VF, OCT and photography) so future changes are compared to an appropriate baseline.

CONCLUSION

It is crucial to monitor both the structural and functional change in order to identify glaucoma progression. Creating a reliable baseline is essential to detect progression. Repeated visual field testing with same threshold algorithm is needed to set up a functional baseline. Documentation of the optic disc for structural baseline can be done clinically or with imaging device. The presence of progressive optic disc damage on stereophotographs is a highly predictive factor for future development of functional loss in glaucoma. It is important to realize that these 2 methods are complementary and cannot substitute each other. RNFL thickness is a dominant parameter in the detection of glaucoma progression. However, macular parameters might provide a useful alternative for glaucoma progression assessment. Researchers suggest that the analysis and interpretation of rates of SAP and OCT change over time in glaucoma should depend on the stage of the disease. There is a strong need for approaches combining structural and functional data for detection of progression and estimation of rates of change in the disease.

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MANAGING COEXISTING CATARACT AND GLAUCOMA

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Glaucoma is the most important cause of irreversible blindness worldwide. At least 70 million people are suffering from glaucoma of which 10% are bilaterally blind[1]. Elevated intraocular pressure (IOP) is the most important risk factor in the development of the disease. Lowering the IOP is most important for management of glaucoma.

According to the WHO, cataract is the main cause of reversible blindness worldwide. Within the aging population, it is increasingly frequent for cataract and glaucoma to coexist in the same patient. The treatment of coexistent cataract and glaucoma is a prevalently clinical challenge. The treatment of either condition can influence the course of the other.

In recent years, changes in surgical technique have greatly impacted the surgical method to patients with coexisting cataract and glaucoma. Especially, there has been an extensive tendency toward the application of combined phacoemulsification with intraocular lens (IOL) implantation and trabeculectomy (phacotrabeculectomy) as one choice of the surgical management for this situation[2].

This article will evaluate the different aspects that affect the choice and result of surgical treatment in patients with coexisting glaucoma and cataract.

PHACOEMULSIFICATION VS TRABECULECTOMY VS PHACOTRABECULECTOMY

Therapeutic options for coexisting cataract and glaucoma:

- Cataract surgery alone
- Sequential surgery – Trabeculectomy followed by cataract surgery
- Combined glaucoma and cataract surgery

In this article, we will be referring to phacotrabeculectomy for combined glaucoma and cataract surgery as it is the most preferred surgical technique for coexisting glaucoma and cataract.

Cataract Surgery Alone

Indications-

- Mild to moderate POAG/PACG well controlled on medical therapy with visually significant cataract
- Ocular Hypertensives with cataract
- Phacomorphic glaucoma with short history

Advantages-

- Lowers IOP in normal and glaucomatous eyes[2-4 mmHg]
- Reduction in the number of anti-glaucoma medications [41% reduction]

Mechanism Of Iop Reduction-

- Post-operative anatomic alterations or aqueous humor dynamic changes that could relate to an enhanced aqueous out flow through either the trabecular meshwork or the uveoscleral pathway

Disadvantages-

- Post-operative pressure spikes after cataract surgery [Elevation of IOP to 30mmHg in 55% of normal and 77% of glaucomatous eyes]

Intra/Post Operative-

- Clear corneal temporal incision is preferred
- Remove all the viscoelastic material at the end
- Monitor for post op IOP spikes
- Cautious use of steroids

PHACO VS PHACOTRAB: Combined cataract and glaucoma surgery may provide a small benefit in terms of controlling IOP than cataract surgery (phacoemulsification) alone[4] [Systematic Review 2015].

Sequential Surgery – Trabeculectomy followed by Cataract Surgery

Indications-

- Advanced glaucomatous damage requiring IOP in low teens
- Uncontrolled IOP with maximum tolerable medical therapy
- Moderate glaucomatous damage with visually insignificant cataract
- Presence of risk factors for filtration failure-conjunctival scarring/healed uveitis/neovascular glaucoma, etc.

Advantages-

- The success of bleb formation and IOP control is better with trabeculectomy alone as compared to combined surgery[5]

Disadvantages-

- Two separate surgical procedures
- Increased chances of cataract development
- High likelihood of loss of IOP control or bleb failure after lens extraction
- Eyes with previous successful trabs had higher IOPs and required more medications after subsequent cataract surgeries[6].

Intraoperative-

- A conventional superior filtration surgery with or without anti-metabolites may be performed initially and cataract extraction carried out later, preferably after 6 months
- Interval of fewer than 6 months- significant risk factor for loss of IOP control[7].

Combined Glaucoma and Cataract Surgery [Phacotrabeculectomy]

Figure 1(a): *Fornix based peritomy*

Figure 1(b): *Subconjunctival application of MMC soaked sponge*

Figure 1(c): *Rectangular superior scleral flap*

Figure 1(d): *Dissection of scleral flap 1-2 mm into the cornea*

Figure 1(e): *Entry into AC using keratome beneath flap*

Figure 1(f): *Phacoemulsification carried through main port under the flap*

Figure 1(g): *PCIOL insertion through the main port*

Figure 1(h): *Excision of deep scleral block and iridectomy*

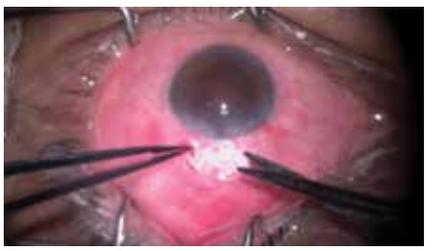

Figure 1(i): *Suturing of scleral flap using 10-0 nylon*

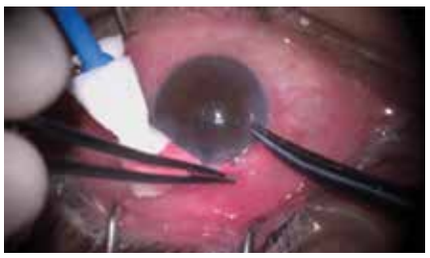

Figure 1(j): *Conjunctival suturing using 8-0 vicryl*

Indications-

- Mild /moderate or severe glaucoma with borderline/ uncontrolled IOP on maximum tolerable medical therapy with visually significant cataract
- Advanced glaucomatous optic atrophy at risk of damage due to post-operative IOP spikes
- Moderate to severe glaucoma, with controlled IOP, where there is an urgent need for visual recovery
- The need to eliminate medication because of non-compliance, allergies, side-effects, or unsustainable economic expenses

Advantages-

- Eliminates the risk of two invasive procedures
- Early visual rehabilitation as compared to trabeculectomy followed by cataract extraction
- Favorable outcome in elderly patients
- Better patient satisfaction, compliance and economy

Disadvantages-

- Increased intra operative manipulations, time, complications like vitreous loss, corneal endothelial damage and post-operative inflammation &hyphaema
- The risk of endophthalmitis is higher
- Compared to trabeculectomy, relatively lesser long term reduction in IOP and lower long term bleb success[8].

TRAB VS PHACOTRAB: Compared with trabeculectomy plus phacoemulsification, trabeculectomy alone is more effective in lowering IOP and the number of glaucoma medications, while the two surgeries cannot demonstrate statistical differences in the complete success rate, qualified success rate, or incidence of adverse incidents [Meta-analysis 2018].

SURGICAL TECHNIQUE OF ONE SITE PHACOTRABECULECTOMY [SCLERAL FLAP METHOD]

- A bridle suture or a corneal traction suture.
- Limbus based (8-9 mm behind limbus) or fornix based (incision at limbus extended 5-6 mm) conjunctival flap is made first (Figure 1a).
- Sponges soaked inMMC 0.2mg/ml are kept under the conjunctival flap for 2min and then washed throughly with BSS. (Figure 1b).
- A triangular (3mmx2mm) or rectangular (3mmx 4mm) superficial scleral flap is made and extended upto 1-2 mm on the cornea. (Figure 1c,d).
- Entry into AC is made either from side port or from main port and a CCC is made (Figure 1e).
- The main port entry is then used to complete steps of phacoemulsification and PCIOL implantation (Figure 1f,g).
- After completion of phaco, under intracameral pilocarpine to constrict the pupil, excision of deep scleral block is done with a Kelly's punch (or a vannas scissors) followed by a

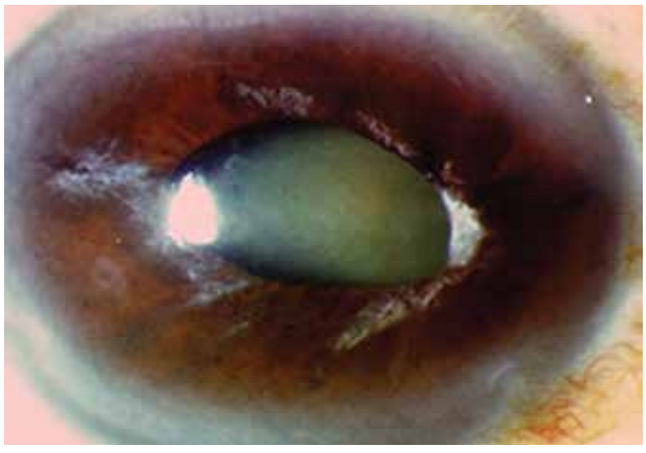

Figure 2(a): *Case of PACG with uncontrolled glaucoma on maximal medication and brown cataract.*

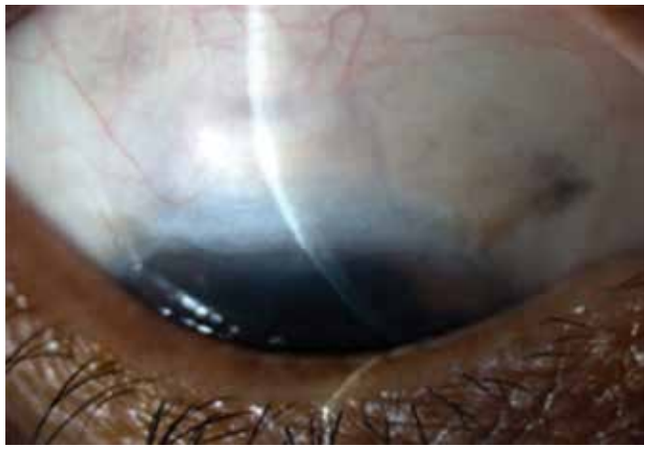

Figure 2(b): *Same eye post single site phacotrabeculectomy showing diffuse moderately elevated and vascularized bleb.*

peripheral iridectomy (Figure 1h).

- Suturing of scleral flap with 10-0 nylon (a releasable suture is preferable) under viscoelastic in AC to prevent a shallow AC. (Figure 1i).
- The releasable sutures may be of two types: Wilson's or Cohen's technique.
- Viscoelastic material is removed through irrigation/aspiration.
- Suturing conjunctival flap with 8-0 or 10-0 vicryl with an additional corneal attachment to ensure zero leakage is the next step (Figure 1j).
- (Figure 2a,b) illustrates a case of Primary Angle closure Glaucoma uncontrolled on maximal medical therapy with brown cataract successfully treated with one site phacotrabeculectomy.

VARIATIONS IN SURGICAL TECHNIQUE OF PHACOTRABECULECTOMY: ONE SITE VS TWO SITE

ONE SITE technique-

Advantages:

- Saves Time
- One wound is made
- No need for the surgeon to change his/her position and the microscope

Disadvantages:

- More post-operative inflammation
- Excessive conjunctival manipulation
- Longer visual recovery
- Care needed to avoid spillage of antimetabolites into the anterior chamber, if used after creation of a scleral flap.

TWO SITE technique-

Advantages:

- Improved exposure for cataract extraction through temporal clear corneal approach especially helpful in deep set eyes, narrow palpebral fissure
- Less inflammation and less manipulation of the conjunctiva superiorly enhances bleb survival and facilitates rapid visual recovery.

Disadvantages:

- May take longer
- Surgeon needs to change position

> **ONE SITE VS TWO SITE:** Both techniques yielded similar results concerning final BCVA and IOP reduction. However, the two-site group had less induced astigmatism and a better postoperative IOP control with less required postoperative anti-glaucoma medications compared to the one-site group .

NEWER MODALITIES OF COMBINED SURGERY:

Although phacotrabeculectomy is still the most widely performed surgery for coexisting cataract and glaucoma, there have been various other newer techniques coming up with promising results:

1. Microincision cataract surgery [MICS] and trabeculectomy: MICS permits phacoemulsification through clear corneal wounds <1.5 mm using a sleeveless phaco tip and irrigating chopper. It can be combined with trabeculectomy in which the IOL is implanted through the trabeculectomy site thus, avoiding the need for larger corneal wound. Moreover, the trabeculectomy fistula is not traumatized by phaco energy.

> **MICS +TRAB VS PHACOTRAB:** MICS + trabeculectomy provided 1 year IOP control comparable to that with two-site phacotrabeculectomy with similar amount of complications and similar final BCVA

2. Others- there are few other modalities of combined surgery which are not routinely performed in Indian scenario and require further long term studies to establish their effect. To enumerate a few:

1. Phaco- viscocanalostomy
2. Phaco- deep sclerectomy
3. Phaco- trabectome
4. Phaco- ExPRESSminishunt
5. Phaco- iStent
6. Phaco-canaloplasty
7. Phaco-endoscopic cyclophoto-coagulation

CONCLUSION

To conclude, phacotrabeculectomy with MMC is considered to be a safe and effective treatment for glaucoma patients with cataracts. It eliminates the risk of two invasive procedures and simultaneously provides a satisfactory IOP reduction and good visual outcome as compared to trabeculectomy alone. However, careful patient selection is essential in order to avail maximal benefit of this surgery.

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DELHI OPHTHALMOLOGICAL SOCIETY

NOTICE & ANNOUNCEMENTS

DOS ELECTION-2019

Nominations are invited from the valid Delhi Members of the Delhi Ophthalmological Society for the following posts:

1.	Vice President	(1 Post)
2.	Secretary	(1 Post)
3.	Joint Secretary	(1 Post)
4.	Treasurer	(1 Post)
5.	Editor	(1 Post)
6.	Library Officer	(1 Post)
7.	Executive Members	(8 Posts)
8.	DOS Representatives to AIOS	(2 Posts)

Nomination form can be collected from the DOS Secretariat during working hours. The valid Delhi Members have to fill this form, duly proposed and seconded by a Delhi DOS Member **(not in arrears)**.

The hard copy of duly filled nomination form should reach the Secretary's Office on or before March 15th, 2019 at 2.00 pm.

Dates to Remember:-

Nominations filing Opens	March 1, 2019, 10:00 am
Nominations filing Closes	March 15, 2019, 2:00 pm
Last Date of withdrawal of Nomination	March 22, 2019, 5:00 pm
Date of Scrutiny of Nomination	March 23, 2019
Date of Election	April 14, 2019 (Time 10.00 am - 3.00 pm) at Venue of the Annual Conference 2019

Note:

1. All the contestants have to follow the guidelines issued by Chief Election Commissioner. Any violation of guidelines issued by Chief Election Commissioner may result in disqualification of candidature of the candidates.
2. One member is allowed to contest the election for one POST Only.
3. Secretariat reserves its right to verify the address of the contestants.
4. For all other posts except editor DJO the members cannot contest 2 consecutive terms.
5. The registrar of the Society has been requested to provide the original constitution of the DOS and amendment if any approved by the registrar vide my letter dated 1st January 2019. The notice may be modified or changed after receiving the clarification.
6. Voter list will be made av available once it is verified by the Treasure.

Eligibility of various posts on page no. 56.

Prof. Subhash C. Dadeya
Secretary,

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It's Safe to Stop Antiglaucoma Drugs

Dr. Sourabh Sharma, Dr. Bhupesh Singh, Dr. S. Bharti

Bharti Eye Hospital and Foundation, New Delhi, India

Glaucoma is the leading cause of irreversible blindness worldwide. Globally, over 64.3 million people were estimated to be affected by glaucoma in 2013 and these numbers are expected to increase over time to 76.0 million by 2020 and 111.8 million by 2040[1]. In India, the estimated number of cases of glaucoma is 12 million and nearly 1.2 million people are blind from the disease[2].

Many studies have reported that a large percentage of glaucoma patients remain undiagnosed and are therefore at risk of progressive visual loss. The early detection of glaucoma is important in order to enable appropriate monitoring and treatment, and to minimize the risk of irreversible optic nerve damage[3].

Although measures to improve early glaucoma diagnosis are unquestionably the primary objective, the inclusive management of glaucoma may also be examined from a different perspective. Elevated intraocular pressure (IOP) is the main risk factor for glaucoma and the most widely-used treatment for glaucoma is daily eye-drops to lower IOP. Drugs for glaucoma need to be taken life-long and consistent follow-up with an ophthalmologist is needed to continuously modify the therapy for maximum effect. Once a diagnosis of glaucoma has been made and eye drops are started, it may be challenging for subsequent examining doctors to question its rationality and take responsibility for discontinuing medications. Thereby, a vicious circle is developed with periodic re-examination and continued medications and it becomes difficult to break its continuity.

BUT higher-than-normal eye pressure doesn't always mean that one has glaucoma. In fact, some people with normal pressure can have glaucoma, while others with higher levels may not. It is observed that nearly half of the glaucoma patients using ocular hypotensive medication do not need the medications or are over-diagnosed and treated[4]. Some practitioners may rely too heavily on newer technology, such as Optical Coherence Tomography (OCT)[5] and diagnosis is sometimes based on suspicious appearance of the optic disc, increased cup-disc ratio as in physiological cupping (Figure 1) reduced OCT parameters due to peri-papillary nerve thickness measurements (Figure 2)[6]. Disorders of the optic nerve can also produce visual field findings, nerve fiber layer loss and disc appearance that can mimic glaucoma. The false negative changes in visual field due to eyelid defects, rim artifacts, unreliability can also lead to glaucoma misdiagnosis. Over-reliance on glaucoma diagnostics in isolation without taking into consideration the complete clinical picture compounds the problem. One has to be careful before starting glaucoma medications and proper optic disc examination with repeat tests is necessary before diagnosis of glaucoma is made.

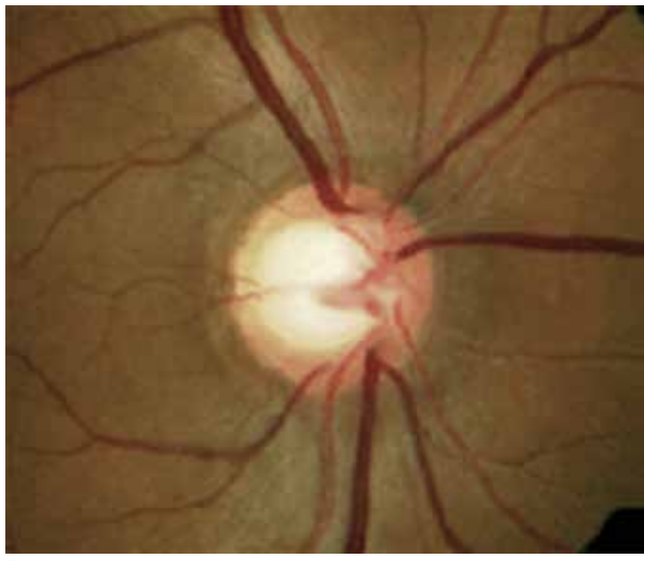

Figure 1

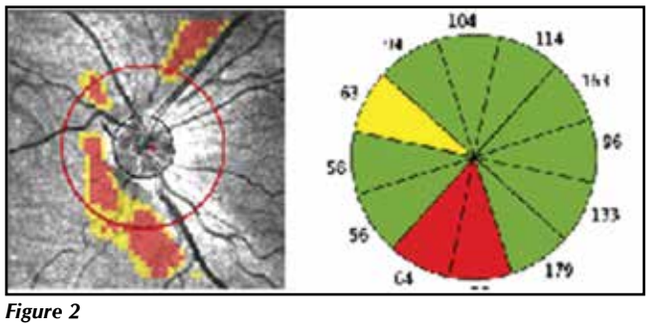

Figure 2

When taking the IOP reading, it is also advisable to consider central corneal thickness (CCT). It is a common practice to start medications just on the basis of high IOP measurements while the optic disc and visual field shows no changes. It is not wrong to treat such ocular hypertensive patients, but presence of other risk factors like family history, myopia, migraine have to be taken into account before starting lifelong treatment. Similarly, primary angle closure and primary angle closure suspects can also be observed if IOP is constantly maintained after laser iridotomy.

Starting glaucoma medication is very easy but stopping isn't. There will always a doubt in clinicians mind regarding stopping glaucoma medications, particularly if the patient is using it for a very long time. Liberal use of anti-glaucomatous medications also add a substantial economic burden to patients and health care systems. This can also cause significant ocular surface morbidity and can compromise the success of any medical or surgical anti-glaucomatous treatment that may

Standard drug	Class of medication	Washout period
Brimonidine[7]	Alpha-2 agonists	5 weeks
Latanoprost	Prostaglandin analogues	4-6 weeks
Pilocarpine[8]	Cholinergics/Miotics	3 days
Dorzolamide[9]	Carbonic anhydrase inhibitors	1-2 weeks
Timolol[10,11]	Beta blockers	4 weeks

actually be required in the future.

So, it is sometimes wise to stop glaucoma medications and keep a close watch on IOP.

Knowledge of the washout periods for topical medications is crucial for the evaluation of the effects of their withdrawal and subsequent discontinuation of medical therapy. This information is important to determine the optimal timing of follow-up visits for the patient. Though only few studies involving standard drugs have been done and it is assumed that other drugs belonging to the same class of medication behave similarly. The following table gives us a rough idea about the washout period of some standard glaucoma drugs

One should exercise patience and prudence in making a glaucoma diagnosis or amplifying therapy. Regular comprehensive eye exams are the best form of prevention against glaucoma and other eye diseases, but we believe that the treating physicians should be more aware of the perils of glaucoma over-diagnosis and long term medication use, as well as the risk of missing undiagnosed glaucoma cases and subsequent progression.

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Trans-Scleral Diode Cyclophotocoagulation

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Various cyclodestructive procedures like surgical excision of ciliary body, cyclodiathermy, cycloirradiation, cycloelectrolysis, cyclocryotherapy, ultrasound, microwave cyclodestruction, and cyclophotocoagulation have traditionally been the last resort of eye surgeons for refractory glaucomas. Of these, laser cyclophotocoagulation, both transcleral diode cyclophotocoagulation, DLCP, and endoscopic cyclophotocoagulation, ECP, cause a targeted destruction of the melanin in the ciliary epithelium and consequently, less pain and inflammation (Figure 1), and are therefore preferred. Modern cycloablation can broadly be classified into the following[1,2]:

1. Contact (transcleral) cycloablation
   Cyclocryotherapy
   - Diode
   - Nd:YAG
2. Noncontact cycloablation
   - Nd:YAG
   - Diode
3. Transpupillary argon green cyclophotocoagulation
4. Endolaser ablation
   - Diode
   - (Reproduced from ISGS Textbook of Glaucoma Surgery, first edition, 2014, Jaypee Brothers Medical Publishers)
   - This article will concentrate on transcleral DLCP, the most commonly used method of cycloablation.

MECHANISM OF ACTION

The mechanisms of the IOP lowering action of DLCP[1-5] include:

1. DLCP targets and destroys the melanin-containing pigmented ciliary epithelium resulting in decreased aqueous production (Figure 1).
2. Destruction of ciliary blood vessels results in ischemia, and results in coagulative necrosis.
3. The induced inflammation also contributes to the decrease in IOP in the immediate postoperative period.
4. There may also be an increase in uveoscleral outflow and the creation of a trans-scleral flow as in a cyclodialysis, which may contribute to further IOP lowering.

INDICATIONS[1-34]

1. Primary glaucomas refractory to conventional glaucoma therapy, including surgeries.
2. Pain relief in a glaucomatous blind eye/ eye with poor visual potential.
3. Uncontrolled high IOPs in eyes with poor visual potential.
4. Neovascular glaucoma.

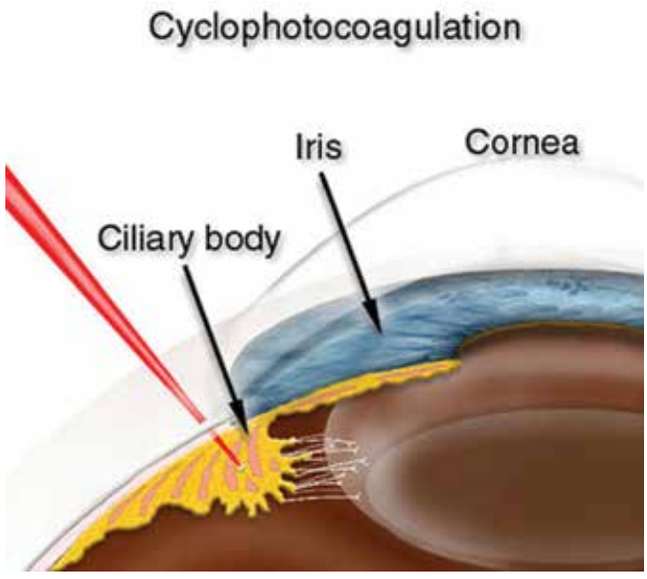

Figure 1: *Mechanism of action of DLCP, destruction of ciliary epithelium.*

5. Secondary glaucomas including post traumatic glaucoma, Post penetrating keratoplasty glaucoma, Post VR surgery glaucomaand uveiticglaucoma.
6. Failed trabeculectomy.
7. Failed drainage implants.
8. Congenital glaucoma with multiple failed surgeries.
9. In patients not fit for incisional surgery.
10. Patients refusing conventional glaucoma surgery.

CONTRA-INDICATIONS

The following conditions require extra careand careful titration of the energy settings, and are not really contraindications:

- Post keratoplasty glaucomas.
- Post glaucoma drainage devices.
- Excessively thinned sclera/ patients with collagen vascular disease.
- Pigmented conjunctiva, nevus.

SURGICAL STEPS

Step 1: Preoperative work up

A written, comprehensive, informed consent, detailing the risks, benefits and alternatives of the procedure is essential before the patient is taken up for DLCP. Also, the patients complete preoperative work-up, including details of vision, eye pressure, visual field and optic nerve head status must be recorded before planning surgery.

The patient must be explained the possibility of postoperative pain and decrease of vision. In addition, the patient must understand that more than one transscleral CPC treatment session may be required to achieve adequate IOP control, despite continued glaucoma medications.

Step 2: Anesthesia

The procedure is performed under peribulbar anaesthesia, under full aseptic precautions.

Step 3: Performing DLCP

A. Probe placement

- The semi-conductor solid state diode laser system (OculightSLx, Iridex Corporation, Mountain View, CA) which has a wavelength of 810 nm is used to perform transscleralcyclophotocoagulation (Figure 2).
- The hand piece (Iridex, Mountain View, CA) is placed 2 mm posterior to the limbus in the region of the ciliary body. The G probe is preferred for delivery of the laser. If using the G probe, the probe is placed with its edge at the limbus (Figure 3). The laser delivery is thus automatically centred 1.2 mm posterior to the limbus (Figure 4).
- The fiber optic transmission system protrudes 0.7 mm from the footplateand indents the conjunctiva and sclera (Figure 5). The pressure effect of the indentation helps to empty out the para limbal conjunctival vessels, therefore optimizing the laser transmission to the ciliary body.
- Contiguous spots are applied using the G probe.Care should be taken that thetrailing edge of the footplate bisects the temporary indentation on the conjunctiva at the site of the previous application. This ensures that the laser application is contiguous. If not using the G-probe is not used, make sure that each subsequent application is equidistant, and at a space of one-half the width of the footplate.

B. Settings

- To begin with, the power setting is kept at 1500 mW for 2 seconds. Most surgeons prefer to put 17-21 spots over 270 degree (sparing 3 and 9 o'clock) 7 spots per quadrant.
- Some surgeons advocate leaving the superonasal quadrant for future surgeries, and also may prevent possible anterior segment necrosis.
- The power used is then individualized and titrated on a case to case basis, depending on the tissue response. In case a "pop" sound is heard, it signifies a tissue explosion within the ciliary body or the iris root.The power is thendecreased in 100mW increments till the classic popsound is not heard. In case no pop is heard, power is increased in 100mW increments till the pop is heard, and then decreased to 100mW below that power setting. The maximum power that may be used is 2250 mW.
- The variability in the clinical response to DLCP may be due to variability in the pressure exerted over the sclera, differences in scleral thickness and variation in probe inclination.

TIPS AND TRICKS

- For pigmented eyes, use lower power settings for a longer treatment duration.For example, for a dark iris, start with settings of 1.25 W, for a 4.0second duration, titrating the energy depending on the popsound. On the other hand, for lightly pigmented eyes, a power setting of 1.5 W, with a 2.0second duration is recommended. Either case requires the titration of energy to just below the pop sound, as explained earlier.1-5, 18,20
- Avoid the 3:00 and 9:00 o'clock positions, in order to decrease pain. These are the positions of the ciliary nerves.
- Avoid areas of increased conjunctival pigmentation to avoid surface burns15.
- Try and keep the cumulative energy used to a minimum, in order to minimise postoperative inflammation.
- In case you are reusing the probe, make sure it is cleaned meticulously. Clean the debris that accumulates at the tip of the probe before reuse, since the charring of this debris is the most common cause for scleral and conjunctival burns.

POSTOPERATIVE MANAGEMENT

- At the end of the procedure, the eye is bandaged for 6-8 hours, preferably overnight.
- Make sure you prescribe adequate oral analgesic and anti-inflammatory medication.
- Continue the previous anti-glaucoma medications, these may be withdrawn gradually as the effect of the cyclophotocoagulation sets in.
- Prescribe additional oral anti-glaucoma medication in the immediate postoperative period to deal with postoperative IOP spikes.
- Prescribe topical steroids (Prednisolone Acetate eyedrops 1%) at least four times a day, for at least a week, and then taper over two weeks.
- The use of topical cycloplegics (Atropine 1% eyedrops, three times

Figure 2: *Semiconductor solid state diode laser system (Oculight SLx, Iridex Corporation, Mountain View, CA).*

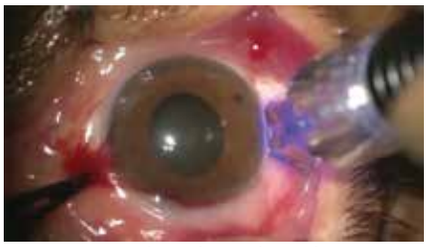

Figure 3: *Foot plate of G-probe with its anterior curved edge at the limbus.*

Figure 4: *Foot plate of IRIS G-probe showing laser delivery point, situated 1.2mm posterior to the anterior edge.*

Figure 5: *Side view of IRIS G-probe showing protruding fibre optic (0.7mm) from foot plate.*

Table 1: Treatment parameters for Noncontact versus Contact TS-DLCP

(Reproduced from Manual of Glaucoma, first edition, 2016, Jaypee Brothers Medical Publishers)

Parameter	Non Contact TS-DLCP	Contact TS-DLCP
Energy	1.2 mWwatts (To be titrated as per "pop")	1.25-1.5 mW (To be titrated as per "pop")
Duration	990 milliseconds	2.0-4.0 seconds
Spots	40	24-30
Circumference treated (in degrees)	360	270-360

a day) help in managing the post-operative pain, and is an individual choice.

COMPLICATIONS

The therapeutic window of all cycloablative procedures is narrow, and it is important to keep a look out for these complications after DLCP. This list of complications is by no means exhaustive, but these possible complicatons must be discussed with the patient while taking the informed consent.

- Surface burns, ranging from superficial conjunctival burns (common) to scleral perforations with uveal prolapse (rare)[15]
- Postoperative inflammation ranging from mild inflammation to severe uveitis and associated pain and photphobia
- Atonic pupil
- Decrease or loss of vision
- Hyphema and vitreous haemorrhage, especially in eyes with NVG.
- Hypotony, ranging from mild hypotony to phthisis bulbi, especially in eyes following GDD
- Cataract
- Scleral thinning and staphyloma
- Corneal decompensation
- Malignant glaucoma[33]
- Sympathetic Ophthalmia[34]

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GONIOTOMY

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Literal meaning of goniotomy is giving incision at the site of angle of anterior chamber (gonio- angle of anterior chamber, tomy: incision)[1]. It was first described in 1893 by De Vincentiis. Barkan first reported the successful outcomes with goniotomy in 1942 with IOP control in 16 out of 17 eyes[2]. The mechanism of action is to restore aqueous outflow through the schlemm's canal which is exposed after giving incision at the site of trabecular meshwork or in front of iris root in cases of very high iris insertion. Goniotomy can be performed under direct visualization of angle using direct gonio lens in cases of clearer cornea.

In cases of primary congenital glaucoma, two types of angle morphology have been described by Sampaolesi et al which are important to prognosticate the outcome[3].

Type 1 angle: Angle is covered by obstructing tissue, considered as better prognostic factor with good outcomes after goniotomy

Type 2 angle: There is very high iris insertion and angle structures are not visible; considered as severe goniodysgenesis with poor surgical outcome after goniotomy (Figure 1). In such cases, incision is given just in front of the iris root and angle opening is suggested by falling back of the iris and formation of cleft.

Indications of goniotomy: Goniotomy has been successfully used for the cases with goniodysgenesis including primary congenital glaucoma (PCG), Juvenile open-angle glaucoma (JOAG), glaucoma associated with aniridia and also for glaucoma secondary to chronic childhood uveitis[4-6].

Direct gonio lenses for goniotomy: Barkan, Koeppe, Swan-Jacob

PROCEDURE

First procedure is done from the temporal side to treat the nasal angle, the extent of which can vary from 5-9 clock hours. Extent of angle treatment is increased by rotating the globe clockwise or anticlockwise using tooth forceps or locking forceps applied at the site of muscle insertions. It's difficult to treat temporal angle because of the obstruction by the nose and it's usually done in case 2nd goniotomy is required. Steps of the procedure are as follows:

1. Operating microscope is tilted forward for about 30° and patient's head is tilted away from the surgeon side. Viscoelastic is placed over the cornea and angle is first visualized before beginning the surgery.
2. After proper positioning of the microscope and the patient, anterior chamber entry is made with clear corneal incision using microvitreoretinal (MVR) knife.
3. Injection pilocarpine is injected into anterior chamber (AC) to constrict the pupil.
4. Dispersive viscoelastic is injected to deepen the AC and angle recess. Cohesive viscoelastic may be injected at the site of angle which is to be treated.
5. Small amount of cohesive viscoelastic is placed over the cornea and under direct visualization using direct gonio lens, incision is given for 5-6 clock hours at the site of trabecular meshwork (TM) or just in front of iris root in cases with high iris insertion and non-visibility of TM. Incision can be given using MVR knife (advantage of smooth sharp cut) or 23-gauge needle mounted on a viscoelastic syringe (advantage of injection of viscoelastic to prevent collapse of AC and to improve the visibility in case of bleeding) (Figure 2).
6. Side port incision is closed using 10,0-vicryl or nylon suture.

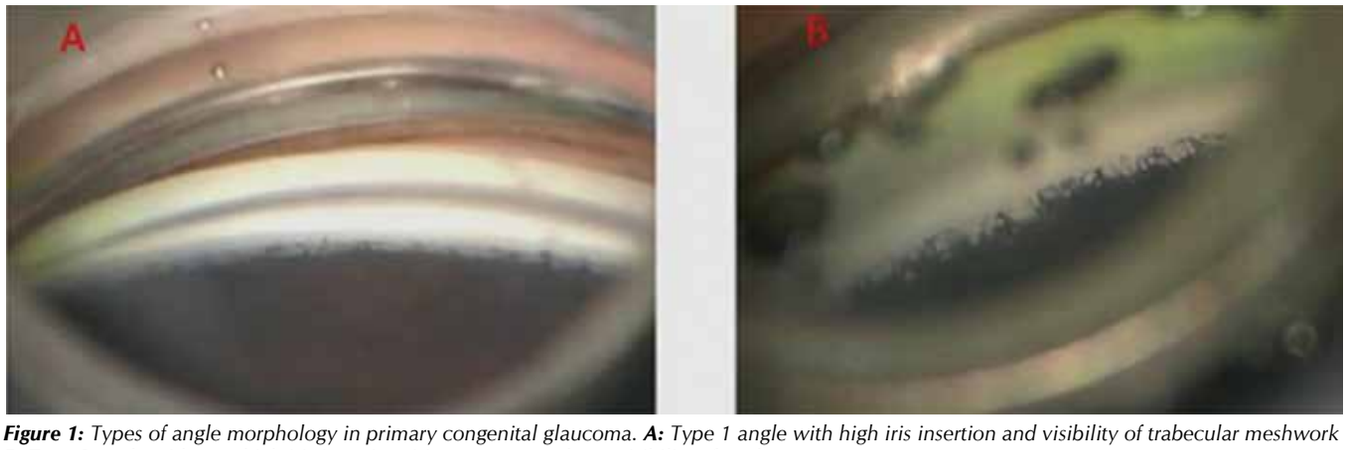

Figure 1: *Types of angle morphology in primary congenital glaucoma.* ***A:*** *Type 1 angle with high iris insertion and visibility of trabecular meshwork* ***B:*** *Type 2 angle with very high iris insertion, iris processes and non-visibility of angle structures*

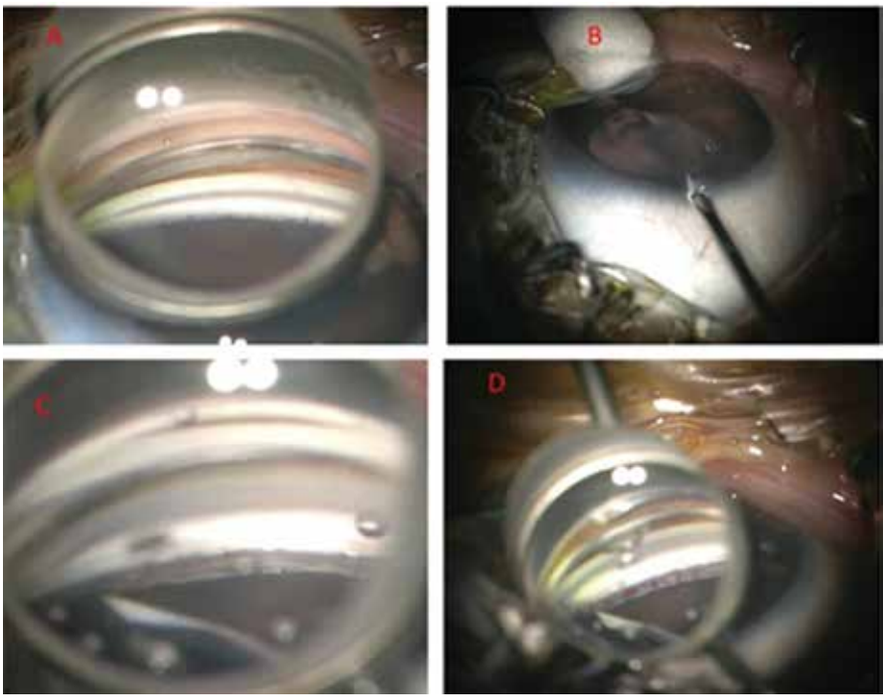

Figure 2: *Major surgical events.* ***A:*** *Visualization of angle using direct gonio lens.* ***B:*** *Entry into anterior chamber using clear corneal incision by MVR knife.* ***C:*** *Incision at the site of trabecular meshwork using MVR knife with opening up of the angle suggested by falling back of the iris and formation of the cleft.* ***D:*** *Reflux of blood through schlemm's canal which leads to hyphaema*

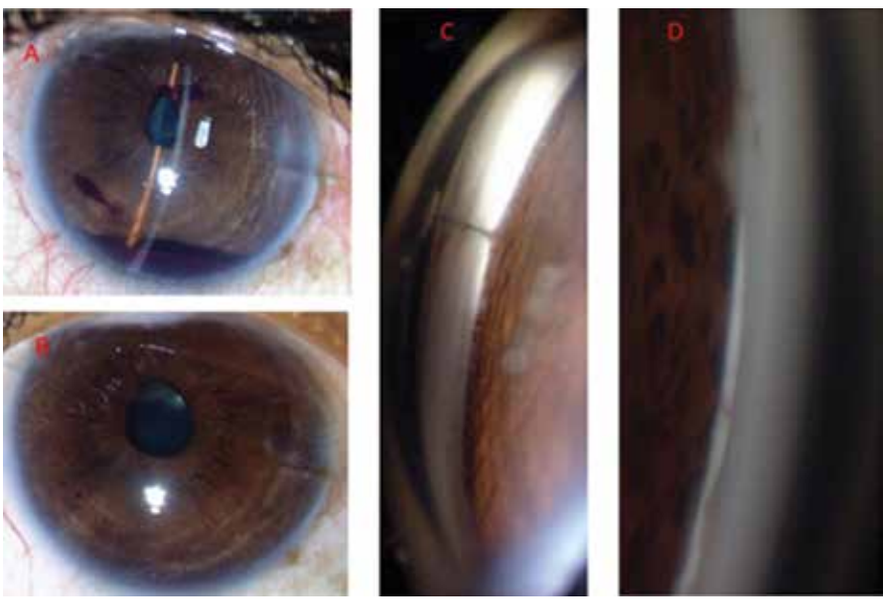

Figure 3: *Postoperative pictures of goniotomy in a case of JOAG.* ***A:*** *Postoperative day 1 photograph with grade 1 hyphaema in anterior chamber.* ***B:*** *Resolution of hyphaema after 10 days.* ***C:*** *Untreated temporal angle showing high iris insertion and no clear TM visible. Note the nylon suture in place where the entry was made temporally.* ***D:*** *Treated nasal angle (magnified view) showing the cleft in the TM that occurred during the procedure. Note the difference in the treated and untreated angles.*

POST-PROCEDURE TREATMENT

Immediate postoperative treatment consists of lateral posture away from the site of treated angle (Right lateral in case of right eye, left lateral for left eye after treating nasal angle) and oral antiglaucoma medicines (acetazolamide) for short-term. Lateral posture is advised for 7-10 days until the resolution of hyphaema.

Antibiotic drops qid for 2 weeks, steroids in tapering doses and miotics (pilocarpine 2% tds) for 6 weeks.

Success rate: Success rates are variable depending on the diagnosis.

- ***For primary congenital glaucoma:*** A larger study with long-term outcomes of goniotomy (3-28 years; mean 11 years) has reported successful IOP control in 72% eyes with one goniotomy. 18% eyes required 2nd goniotomy and 10% eyes required 3rd goniotomy[7]. Other studies have reported outcomes in the range of 58-89%[8-10]. One of these studies has reported 60% complete success and 94% qualified success after goniotomy at 1year follow-up. Success rates of trabeculotomy at 1,2 and 3 years have been reported to be 92%, 82% and 74%[11]. With procedure combined trabeculotomy with trabeculectomy (CTT), success rates of 90% at 1 year and 78% at 3 years have been reported[12,13].
- ***For juvenile open angle glaucoma:*** A study has reported complete success in 53%, qualified success in 23.5% and failure in 23.5% at a mean follow-up of 7.8±6.2 years (0.1-16.3 years).
- ***Childhood uveitic glaucoma:*** A study by Freedman et al has described success rate of 60% after single goniotomy for glaucoma secondary to uveitis with mean cumulative probability of successful outcome of 79% at 1 year and 55% at 3 years for single goniotomy and 70% after 1 or 2 surgeries at 3 years[14]. The mean time to failure in this study was 8.8 ±3.8 months and no failure occurred after 15 months of IOP control. Presence of peripheral anterior synechiae (PAS) at the site of goniotomy cleft have not been found to affect the outcome of surgery. Another study by Ho et al[15] on 40 eyes of 31 patients with uveitic glaucoma has described success rate of 72.5% after mean follow up of 98.9 months. This study reported 100% failure rate in cases with preoperative PAS extending for >6 clock hours.

ADVANTAGES

Though success rate in term of IOP control is slightly lower with goniotomy compared to trabeculotomy/ CTT,[16] it has the advantages in terms of being minimally invasive, sparing the conjunctiva for future glaucoma surgery and it avoids the complications of mitomycin-C including hypotony maculopathy, cystic bleb, bleb leak, endophthalmitis. It should be considered as the first line surgical treatment for congenital glaucoma in cases with clearer cornea.

COMPLICATIONS

Most common complication is hyphaema which can occur in about 75-90% of the cases and usually resolves spontaneously within 1 week. (Figure 3) Rarely, there can be iridodialysis, lens capsule puncture with cataract formation.

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Gonioscopy: An Essential Skill to Combat Glaucoma Blindness

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Gonioscopy is the name given to the technique of viewing angle of anterior chamber and structures therein, utilizing specialized lenses. The technique owes its existence to a serendipity by Alexios Trantas who viewed angle structures in a case of keratoglobus in 1907, by indenting the limbus with his finger and a direct ophthalmoscope. He coined the term 'gonioscopy' with Gonia meaning "angle" and skopein "observe" in Greek[1]. Goniolens was first invented by Maximilian Salzmann in 1914, using a contact lens to neutralize corneal optics. This lens was further refined by Koeppe in 1919, by steepening its curvature. Gonioscope was developed by Toroncoso and given its final form by Hans Goldman in 1938. For nearly a century gonioscopy has remained an essential tool in management of glaucoma cases, but the technique has been extremely underutilized, due to lack of training in this essential skill.

RELEVANCE IN INDIAN CONTEXT

Glaucoma is the second leading cause of blindness in adult population of India, of which primary angle closure glaucoma (PACG) is the more blinding entity. Population based studies like APEDS (Andhra Pradesh Eye Disease Study), Aravind comprehensive eye survey (ACES), Chennai glaucoma study (CGS) have reported PACG accounting for twice as much blindness as POAG. A startling aspect highlighted by both CGS and APEDS was, that of the patients previously diagnosed with glaucoma, almost two-third were being treated as POAG due to lack of gonioscopy being performed at the treating centre[2]. Keeping in mind the natural history of primary angle closure disease, almost 1/4th patients with primary angle closure glaucoma suspect (PACS) progress to primary angle closure (PAC), and 1/4th PAC cases further progress to blinding Primary angle closure glaucoma (PACG) over a period of 5 years[3,4]. This relentless progression to blindness could be halted by a peripheral iridectomy in time, which is only possible if gonioscopy is done in all cases of glaucoma. Keeping these facts in perspective, it is imperative that gonioscopy is performed in all glaucoma suspects or those presenting with high intraocular pressure. Clinical examination of anterior chamber depth by flashlight test, van Herick test or anterior segment ocular coherence tomography (ASOCT) do not predict occludable angles reliably enough to be considered as alternative to gonioscopy[5].

OPTICAL PRINCIPLE

When light rays pass from medium with greater index (read aqueous, cornea) to lesser index (read air), the angle of refraction (r) exceeds angle of incidence (i). When this refractive angle equals 90 degrees, the i is said to have reached the critical angle. The critical angle for air cornea interface is 46^0 and since light rays exiting from anterior chamber exceed it, they get reflected back (internal reflection), precluding angle visibility. Elimination of corneal optics by replacing the air interface with a contact lens, having similar refractive index to cornea, neutralizes this internal reflection. Gonioscopy uses such a contact lens and by refracting or reflecting rays from the angle makes the structures therein, visible. In direct gonioscopy the rays refracted through the steep goniolens do not achieve the critical angle, and thus exit out of eye. In indirect gonioscopy light from angle is reflected by a mirror, to exit 90 degrees to contact lens-air interface (Figure 1).

The differences between Direct gonioscopy (using goniolens) and Indirect gonioscopy (using gonioprism) are tabulated in (Table 1).

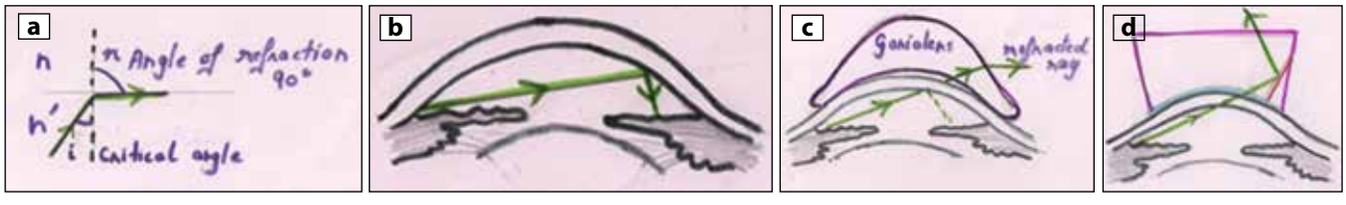

Figure 1: *Optical principles of gonioscopy;* ***a:*** *Ray diagram of light ray passing from denser to lighter refractive index;* ***b:*** *Light rays originating from angle of anterior chamber undergo* ***total internal reflection*** *by corneal surface;* ***c:*** *Rays of light emerging through Koeppe lens;* ***d:*** *Rays of light emerging through Goldmann single mirror gonioscope*

Table 1: Comparision of Direct and Indirect Gonioscopy		
	Direct gonioscopy	**Indirect gonioscopy**
Instrument	Goniolens (Figure 2) a. Prototype: Koeppe 14-16mm (50D) b. Surgical lenses: Hoskin, Barkan, Thorpe, Swan Jacob c. Smaller lens (for infants & preterms): Richardson Shaffer, Layden	Gonioprism a. Goldman single / double / three mirror b. 4 mirror -With handle Posner - Fixed handle Zeiss - Detachable Unger holding forceps - Sussman - hand held
View	Direct- angle seen as it is	Indirect - opposite angle seen
Angle view	Panoramic - 360 degrees simultaneously	One / two / four quadrant seen
Ease of viewing	Good, as examiner looks down over the convex iris	Needs manipulation due to iris convexity obscuring angle- "over the hill phenomenon"
Patient position	Supine	Sitting
Coupling fluid	Saline /none	Methylcellulose/ saline for 1, 2, 3 mirror lenses, Normal tears alone suffice for 4 mirror
Additional instrument	Hand held slit lamp or an operating microscope	Slit lamp optics
Ease	Cumbersome & rarely used	Easy & commonly used
Indications	Children - angle examination under GA or during goniotomy procedure	Diagnostic: Angle closure disease , angle anomalies Therapeutic: Break acute angle closure attack, laser /surgical procedures of angle

INDIRECT GONIOSCOPY (GONIOPRISM)

Goldman family

The prototype is Goldman lens with the single mirror / double mirror or three mirror. The latter is infrequently used for gonioscopy due to its weight and size. The smallest mirror is the gonioscopy mirror.

Four mirror family

This includes Zeiss (with removable Unger fork, Posner (fixed handle) and Sussman (no handle) Difference between two types is given in (Table 2).

TYPES OF GONIOSCOPY

a. Direct and Indirect gonioscopy with goniolens or gonioprism respectively
b. Static gonioscopy and Dynamic (manipulative) gonioscopy with Goldmann lenses
c. Forbes Indentation gonioscopy with 4 mirror lenses only[7].

Static gonioscopy: In this method gonioscopy is done in a dimly lit room, using a narrow slit beam with patient looking straight ahead. It needs to be remembered that diagnosis of occludable angle is made by static gonioscopy.

Manipulative gonioscopy: In this gonioscopy the narrow angle recess is brought into view by making patient look in direction of mirror, which enables examiner to look down into angle recess over the convex iris - "over the hill view". This maneuver is done to look for additional features or abnormalities in the angle, after its occludability has been assessed by static gonioscopy. Tilting or pushing gonioscope tangentially on sclera, towards the angle which needs to be viewed, pushes aqueous into opposite part of angle, making it slightly wider than it really is and thereby enhancing visibility. Thus manipulative gonioscopy can be done by two manoeuvres - first make patient look in direction of mirror or examiner pushes gonioscope towards angle which needs to be viewed.

Indentation gonioscopy: This can be performed with 4 mirror gonioscope only. The small diameter and flatter radius of curvature of the 4 mirror lens, ensures smaller, central area of contact, thereby permitting indentation (central corneal compression) to be easily done. This gonioscopy is done for diagnostic purpose to differentiate appositional (iridotrabecular contact ITC) from synechial closure (peripheral anterior

Table 2: Differences between Goldmann and 4 mirror gonioscopes		
	Goldmann lenses	**4 mirror lenses**
Diameter	12 mm (larger, touches limbus)	9 mm (smaller, remains inside limbus)
Mirror	-Single mirror with 62^0 angulation -Double or three mirror with 59^0 angulation	-Four mirror -Angulation of each mirror is 64^0
Radius of curvature	7.38 mm (steeper)	7.85 mm (flatter), closer to corneal curvature
Coupling fluid	Required - methylcellulose, lubricating jelly or saline	Not required - natural tears suffice for coupling
Angles viewed	Opposite quadrant, so rotation of gonioscope required to view entire angle	Opposite, but presence of 4 mirrors ensure all 4 quadrants become visible with slight tilting of the gonioscope only
Learning curve	Easier initially (can be done in uncooperative patient aided by viscous coupling fluid holding lens on the eye)	Difficult initially (tear fluid being the bridge, these lenses do not stabilize the globe and patient squeezing can distort viewing)
Speed	Slower	Rapid, once initial learning curve mastered
Type of gonioscopy	Static and Manipulative	Static and Indentation

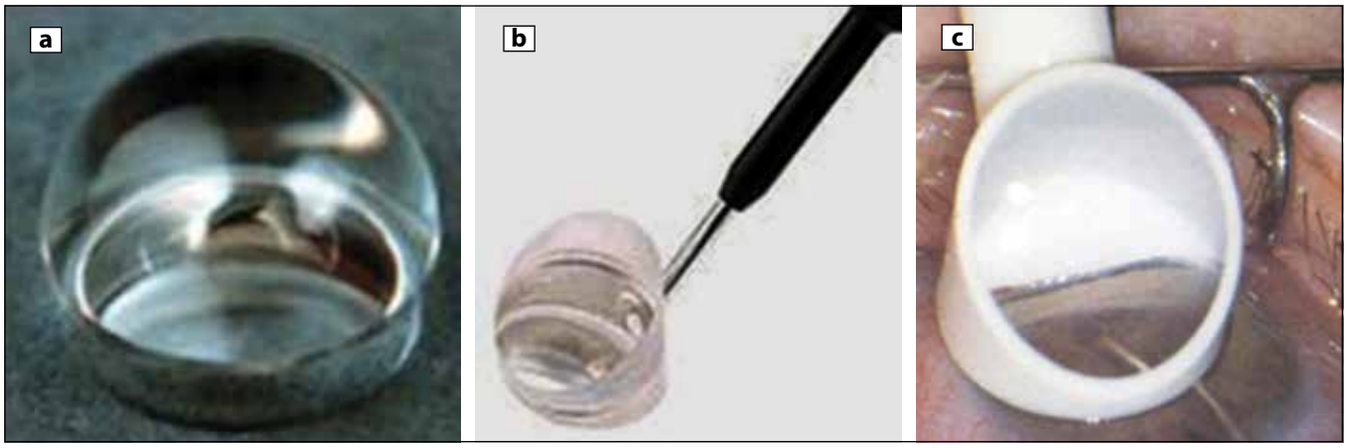

Figure 2: *Direct gonioscopy lenses;* ***a:*** *Koeppe lens;* ***b:*** *Swan Jacob surgical goniolens;* ***c:*** *Swan lens in situ (Courtesy Dr G Spaeth, Wills Eye Hospital, Philadelphia, USA).*

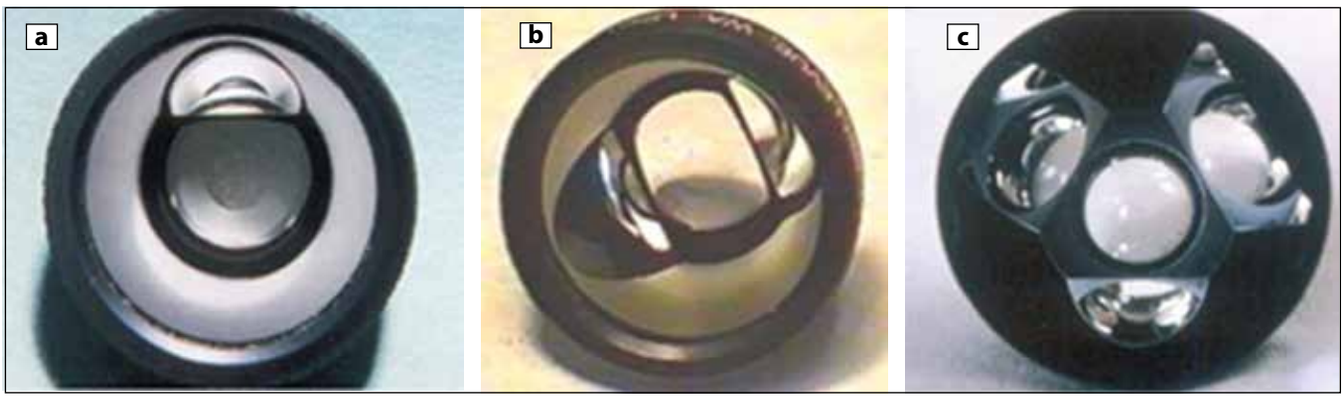

Figure 3: ***a:*** *Goldmann single mirror lens;* ***b:*** *Goldmann two mirror lens;* ***c:*** *a. Goldmann three mirror lens (infrequently used for gonioscopy, shortest mirror is the gonioscopy mirror).*

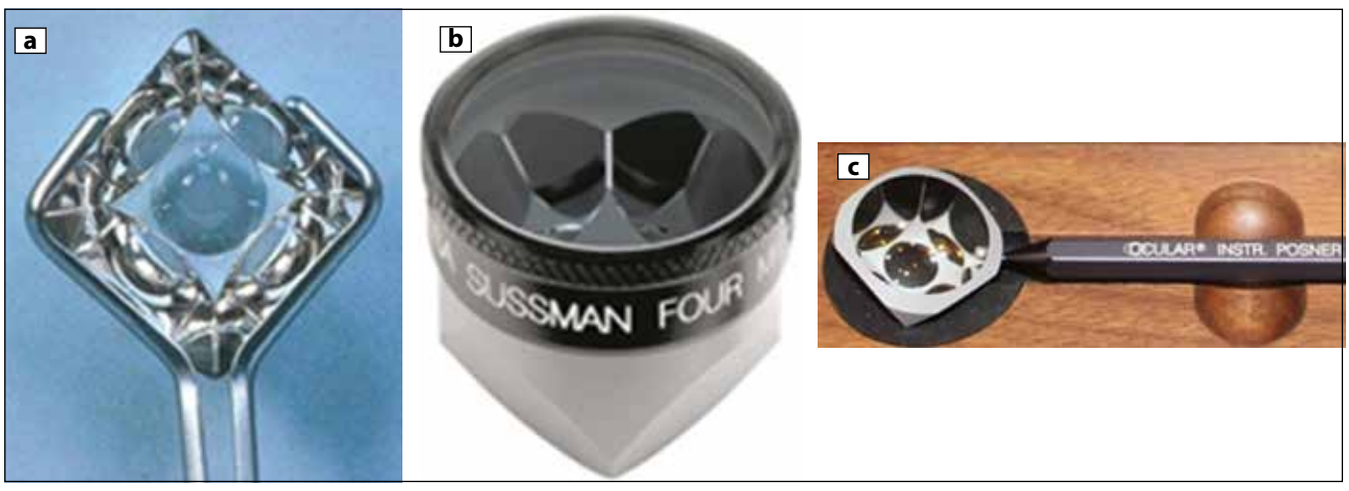

Figure 4: ***a:*** *Zeiss four mirror lens with Unger fork;* ***b:*** *Sussman hand held gonioscope;* ***c:*** *Posner 4 mirror with handle*

synechiae), the former will break and latter will not (Figure 5). It is also used as a therapeutic measure to break acute attack of angle closure glaucoma by displacing aqueous humor against the iris tissue.

Before going further it is worthwhile to recapitulate the currently accepted staging of primary angle closure disease (PACD) as given by International Society of Geographical and Epidemiological Ophthalmology (ISGEO) classification. Gonioscopy is essential in order to categorize the angle closure disease patient into these 3 stages, which then determine further management and prognosis.

- *Primary angle closure suspect (PACS):* At risk cases. Iridoctrabecular contact (ITC) between peripheral iris and posterior trabecular meshwork, with greater than or equal to 270 degrees of post pigmented trabecular meshwork not visible on Static gonioscopy[8]. The European Glaucoma Society

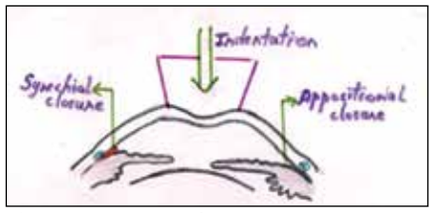

Figure 5: *Indentation gonioscopy differentiating appositional from synechial closure.*

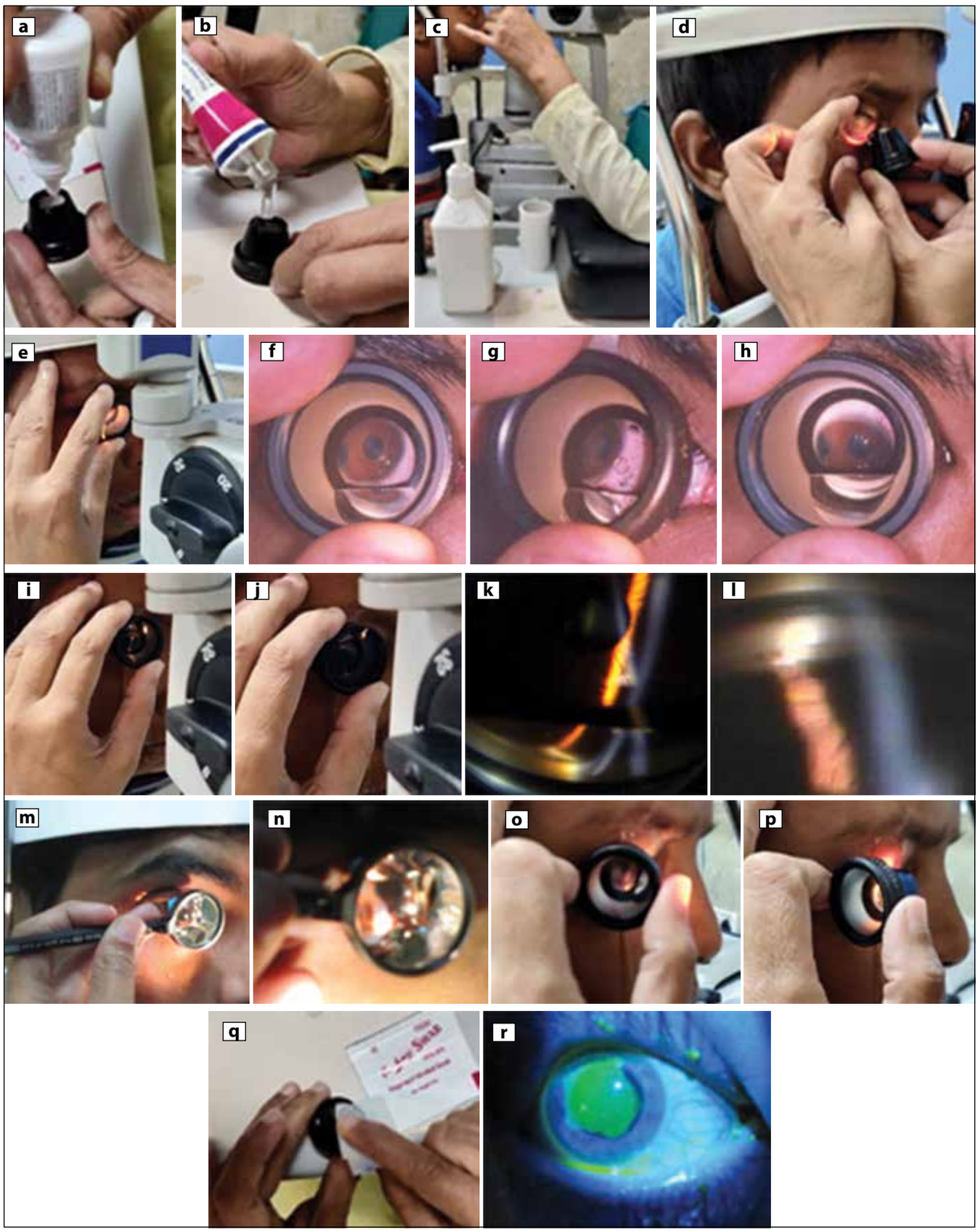

Figure 6 a- r: *Procedure of gonioscopy (see text).*

guidelines however give the figure of 180 degrees ITC[9]. The intraocular pressure (IOP) is normal and optic nerve head shows no damage. Such an angle is an occludable angle and warrants prophylactic treatment[10].

- *Primary angle closure (PAC):* Occludable angle with features of prior trabecular obstruction on Indentation gonioscopy eg Peripheral anterior synechiae/ pigmentation (in absence of prior surgery/comorbidity). The other features range from increased IOP, iris whorling or atrophy, sphincter atrophy, glaukomflecken.
- *Primary angle closure glaucoma (PACG):* Features of PAC and optic nerve damage with or without visual field defects. The IOP may or may not be high at time of examination.

PROCEDURE OF GONIOSCOPY (Figure 6)

- After explaining procedure to patient, the eyes are anaesthetized with 1-2 drops of 2% topical xylocaine applied into the lower cul-de-sac.
- The gonioprism is removed from case, washed with saline, wiped with soft tissue (Figure 6a).
- The concave part is filled with lubricating gel or saline, avoiding air bubbles (Figure 6b).
- Patient is seated on slit lamp and lights in the room are dimmed. Gonioprism is held between index finger & thumb while supporting the elbow on arm rest (Figure 6c).
- Patient is asked to open both eyes and look upwards. Lower lid is pulled downwards creating a pouch (Figure 6d).
- Lower rim of gonioscope is gently inserted into the lower cul-de sac, it is then smoothly slid forward onto the cornea. Gonioscope is then held with three fingers of one hand, leaving other hand free to operate slit lamp.
- Slit beam is then brought from at an angle to illuminate the gonioprism keeping the slit beam parallelopiped co-axial (Figure 6e).
- The gonioscope placement needs to be checked. The edge of mirror should be at limbus for the angle structures to be viewed (Figure 6f,g). depict wrong positioning and (Figure 6h) is the correct position.
- The slit beam needs to be kept long initially to get an overview of the angle, (Figure 6i) then reduced to least illumination & magnification to confirm occludability (Figure 6j) Around 2-3 mm beam length suffices.
- Patient is asked to look straight ahead. The gonioscopy algorithm is followed and starts from checking the pupillary margin, iris surface for any pseudoexfoliation material, sphincteric atrophy, iris atrophy / nodules.
- Then beam width is then shortened to view the angle, ensuring that the slit beam does not cross pupil to prevent "on off phenomenon". Fig 6 k depicts long beam crossing the pupil and would result in artificial widening of angle subsequent to light induced pupil constriction.
- It needs to be kept in mind that the angle viewed in the mirror is 180° away but not crossed.
- The inferior angle is viewed first as it is usually wider and more pigmented due to gravitational settling and aqueous circulation. This makes identification of structures easier in the inferior angle (viewed by mirror placed superiorly) (Figure 6l).
- Lens is then rotated to examine all quadrants. Clockwise examination is preferred for ease of remembering pathological changes according to the clock hours. Initial procedure is done with low magnification for a wider view, increased magnification is resorted to for detail.
- The anterior chamber angle width and structures are then identified by static gonioscopy. In case the entire angle structures are not visible, manipulative gonioscopy (if using Goldmann gonioscopes) or indentation gonioscopy (if using 4 mirror gonioscopes) is resorted to, in order to see the entire angle (Figure 6m,n).
- The examination is terminated by gently rolling the lens off the eye by a clockwise motion aided by asking patient to squeeze lids (Figure 6o,p). It should anti clockance never be pulled off the eye in the z axis.
- Lens is then washed with saline or running tap water. It is then sterilized by wiping it with 70% isopropyl alcohol (Figure 6q).
- Alternatively it can be soaked in 1:10 bleach solution for 5-10 minutes or 2% Glutaraldehyde for 5 minutes, followed by thorough rinsing.
- It must be ensured that the alcohol, disinfecting solution is dried and rinsed off with saline prior to being used in next patient. (Figure 6a) Placing the gonioscope with traces of alcohol on the anaesthetized eye can cause epithelial abrasion while removing it. As the eye is anaesthetized, patient will not complain of pain immediately. Such a complication is noted when patient presents with epithelial defect a few hours after the examination (Figure 6r).

The algorithm of evaluating gonioscopy findings in sequence is

I. Angle width and last structures visible
II. Peripheral iris configuration/ insertion
III. Trabecular meshwork pigmentation
IV. Abnormal structures visible like synechiae, blood vessels, pseudo exfoliation material

I. Angle width and last angle structure visible

- The first structure which needs to be identified is the Schwalbe's Line. This thin, glistening white, sometimes pigmented line represents termination of Descemet's membrane. It is localized by creating a narrow slit and tracing the two linear reflections of external and internal corneal reflexes, the corneal wedge. The intersection of the two reflections or termination of corneal wedge is the Schwalbe's line (Figure 7). Difficult to see in younger patients, it often acquires a smattering of pigment with age.
- The next structure to be identified is the Trabecular meshwork. This translucent, light grey structure acquires varying degrees of pigmentation with age, pathology, surgery, post laser or surgery. It is divided into two parts - the anterior 1/3 non pigmented trabecular meshwork (ATM) and post 2/3 pigmented trabecular meshwork (PTM), the latter being the filtering part. Schlemm's Canal (SC) is covered by the pigmented, filtering portion of TM and is only clearly visible if filled with blood (Figure 8).
- This is succeeded by the Scleral spur. Scleral spur is a thin, whitish prominent band. It is the anterior most projection of sclera where the longitudinal muscle of ciliary body is attached.
- Next structure visible is the Ciliary body band. This greyish brown structure, is broader in inferior and temporal angle. It's width depends on iris insertion and is wider in myopic eyes.
- Last structure to be identified is the Fuch's last roll of iris (Figure 9).

GRADING OF ANGLE

Many methods exist for angle grading namely - Shaffer, Schie, Spaeth, Kanski Shaffer. To prevent confusion it is preferable to individually label the last structure visible on both static and manipulative gonioscopy. As depicted in the figure below (Figure 10).

The different gradings in use are - Shaffer (most popular) (Figure 11), Spaeth (most detailed), Schei (reverse of Shaffer, with occludable angle being Grade IV). Table 3 details the different

Figure 7: *Corneal wedge denoting Schwalbe's line*

Figure 8: *Schlemm's canal filled with blood in Sturge Weber glaucoma case*

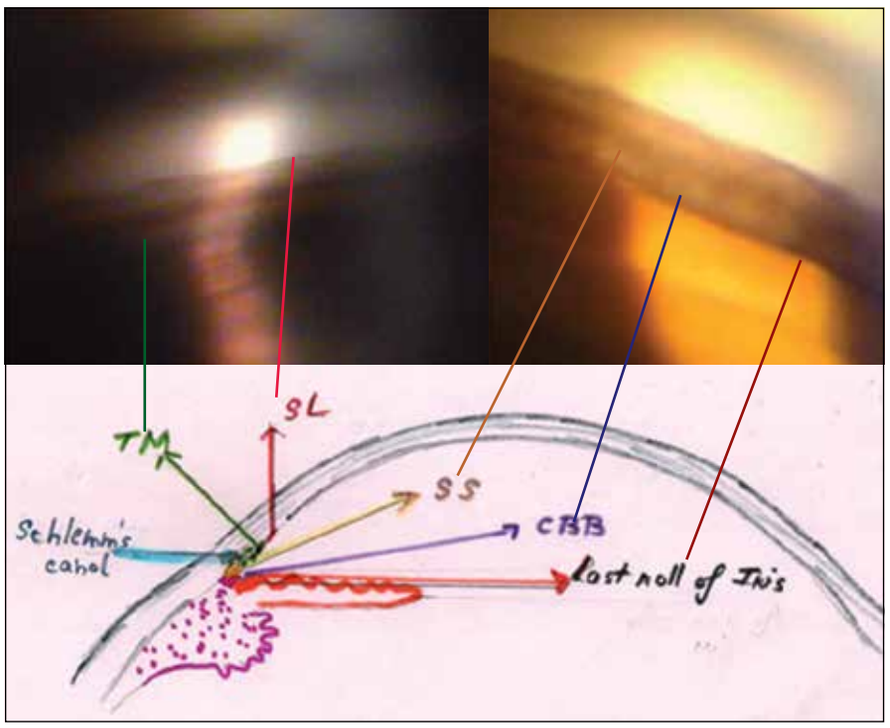

Figure 9: *Labelled diagram of angle structures in a widely open angle*

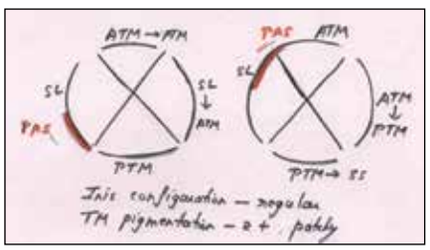

Figure 10: *Gonioscopy diagram (The Goniogram). The symbol → implies structure visible after doing manipulation. In the Fig above SL→ ATM, means Schwalbe's line was visible on static gonioscopy and anterior trabecular meshwork became visible only post manipulation indentation.*

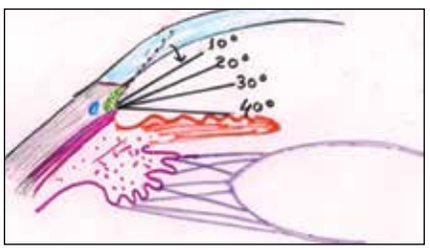

Figure 11: *Angle width (approximate geometry) in 4 grades of Shaffer classification*

classifications.

The following gonio pictures detail the different grades of Shaffer classification on angle. For sake of image clarity, while taking the gonioscopic photographs, the authors have taken the liberty to make the slit beam little longer, in actual practice it needs to be short and not traverse the pupil (Figures 12 ,13,14,15).

Spaeth grading system further details the angle based on iris insertion, iris configuration and trabecular pigmentation (Table 4)

II Iris peripheral configuration and insertion

This is the next aspect to be looked for. Peripheral iris insertion has been described by G. Spaeth as b, p, f, c (Figure 16,17).

B is *anteriorly bowed* (convex configuration) iris and is seen in pupil block glaucoma and hypermetropes. It is graded 1-4 with 4 being severe iris bombé.

F is *flat iris*, previously called as *regular iris*

C is *concave iris* with posterior bowing, previously called *queer iris*. It is seen in pigment dispersion syndrome, myopia, aphakia, subluxated lens.

P is *plateau iris* configuration - planar in centre with iris root angulating forward in periphery due to anteriorly situated ciliary process. The look is of a sudden curve in the iris and this can be clearly demonstrated by Ultrasound biomicroscopy (UBM) (Figure 18). The anteriorly situated ciliary processes cause bunching of peripheral iris presenting as classical "double hump/ sine wave" sign on gonioscopy (Figure 17d).

The other aspect of iris to be checked is iris insertion. It is denoted as A, B, C, D, and E as explained in (Figure 19).

Classically high iris insertion is seen in patients with juvenile open angle glaucoma.

III Trabecular meshwork pigmentation:

While assessing trabecular meshwork pigmentation, two aspects are important - the intensity or grade of pigmentation and pattern of pigmentation Figure 20 gives the pictures of different grades of pigmentation.

While assessing pigmentation it must be confirmed that the trabecular meshwork (TM) is affected, as sometimes Schwalbe's line can be more pigmented. Called as Sampaolesi line, this pigmented Schwalbe's line is seen in pigment dispersion syndrome or pseudoexfoliation syndrome (Figure 21c). It is important to understand this, otherwise mistaking the pigmented Schwalbe's line for Trabecular meshwork, would erroneously label a closed angle as open. Location of corneal wedge should be resorted to, in such situations. Excess pigmentation of trabecular meshwork should initiate search for other signs of pigment dispersion or pseudoexfoliation glaucoma like Krukenberg spindle or/ and iris transillumination defects.

This undescores the other aspect of pigmentation in angle - pattern of pigmentation. Figure 21 clearly depicts this.

IV. Other structures - abnormal/ normal

The last thing to be looked at is presence of abnormal structures like synechiae, new blood vessels, pseudo exfoliation material or broad ciliary body band.

Table 3: Different classification systems of angle structure grading

Angle recess in degrees & structures visible *Shaffer Kanski classification* [11]	**Risk of closure**	**Shaffer classification**	**Spaeth classification**	**Schei classification**
0^0: Irido-corneal contact or Dipping of beam Do indentation gonioscopy to differentiate appositional vs synechial closure	Closed angle	Grade 0	Grade A	Grade IV
0-10^0: Schwalbe line or anterior trabecular meshwork (non-functional part) visible	Closure possible	Grade 1	Grade B	Grade III
10-20^0: Posterior trabecular meshwork (functional part) visible (Extent : 90^0/180^0 PTM visible= PACS)*	Narrow, closure possible	Grade 2	Grade C	Grade II
25-35^0: Scleral spur visible	Closure impossible	Grade 3	Grade D	Grade I
35-45^0: Ciliary body visible	Closure impossible	Grade 4	Grade E	Grade 0
**PACS of ISGEO classification*				

Table 4: Spaeth grading system

Angular approach	**Iris insertion ABCDE**	**Peripheral iris configuration F B P C** **Old**	**New**	**Trabecular meshwork pigmentation**
Range 0 - 45^0	A. Anterior to Schwalbe's line	R regular	F flat	0 no pigment
	B. Between Schwalbe's line			1+ minimal
	C. Scleral Spur visible	S steep	B bowed anteriorly	2+ mild
			P plateau iris	
	D. Deep with ciliary body visible	Q queer	C concave	3+ moderate
	D. Extremely Deep with > 1 mm ciliary body visible			4+ intense
In Spaeth's scheme the angle is written as D 40^0, c, 2+ TMP (D = deep insertion, 40^0 = angle recess, c = concave iris configuration, 2+ TMP = grade of TM pigmentation)				

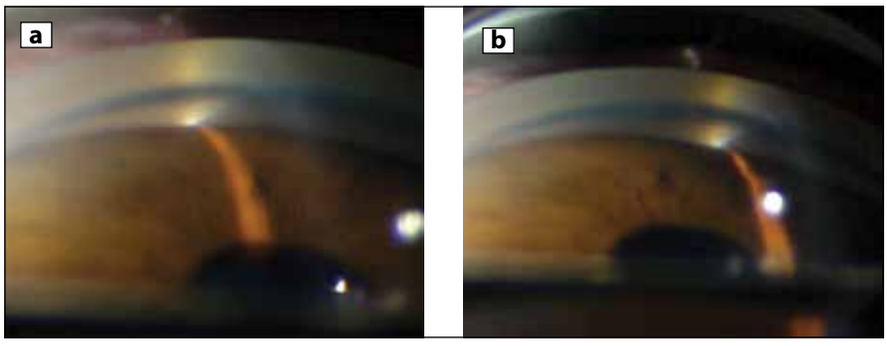

Figure 12a,b: *Shaffers Grade 0: Dipping of beam. This is an occludable angle and requires manipulative & indentation gonioscopy to see the structures.*

SYNECHIAE

Synechiae in the angle are of two types - peripheral anterior synechia (PAS) or goniosynechiae. Peripheral anterior synechia are coarse adhesions between iris and peripheral cornea. The characteristics of PAS are: broad pigmented structures that tent the iris and adhere anywhere, sometimes reach the Schwalbe's line, obscure scleral spur or trabecular meshwork, inhibit movement of the iris and flow of aqueous. Their presence implies pupil block or persistent shallow anterior chamber in the past (Figure 22).

Goniosynechiae on the other hand are fine pigmented bands which bridge the angle recess. They also can adhere to any level including Schwalbe's line and imply prior attacks of angle closure (Figure 23a).

Iris processes are delicate, lacy, thread like structures which wrap around the iris base. They are seen in young patients and of two types - V and W. The V type are common and reach the scleral spur or trabecular meshwork. The uncommon W type reach till Schwalbe's line and are seen in secondary developmental glaucoma like Axenfield Reiger syndrome (Figure 23b). Iris processes are often physiological and occur in almost 35 % of normal patients and wither with age. They never reach the Schwalbe's line and do not inhibit flow of aqueous (Figure 23c).

NEOVASCULARIZATION

Presence of new blood vessels in the angle need to be differentiated from normal vessels. Abnormal blood vessels are fine, superficial, extend beyond the scleral spur to arborize on trabecular meshwork. They run diagonally or follow erratic patterns on the iris surface. Normal vessels on the other hand, follow a circumferential or radial pattern and never arborize. Normal vessels become visible in cases of iris atrophy and they do not cross the scleral spur. Neovascularization of angle (NVA) often, but not always, coexists with neovascularization of iris (NVI), thus presence of NVA necessitates a re-look to rule out iris rubeosis (Figure 24).

CILIARY BAND WIDENING

Gonioscopy aids in diagnosis of various manifestations of ocular trauma like angle recession, cyclodialysis and iridodialysis (Figure 25).

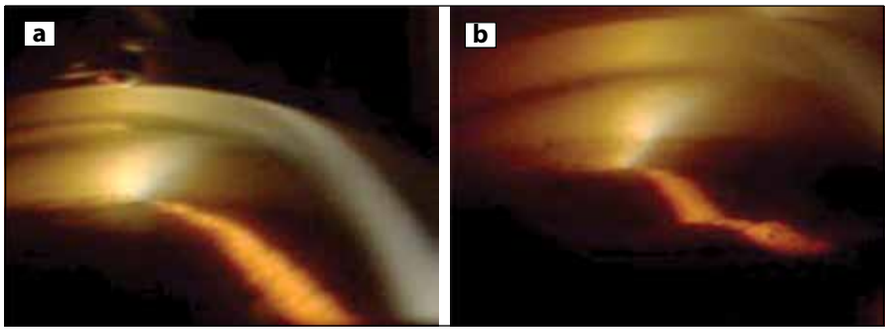

Figure 13: *Shaffers - Grade 1 (10^0)* ***a:*** *Anterior trabecular meshwork visible, in places post trabecular meshwork also visible;* ***b:*** *Post manipulation angle structures till scleral spur becomes visible. This is an occludable angle.*

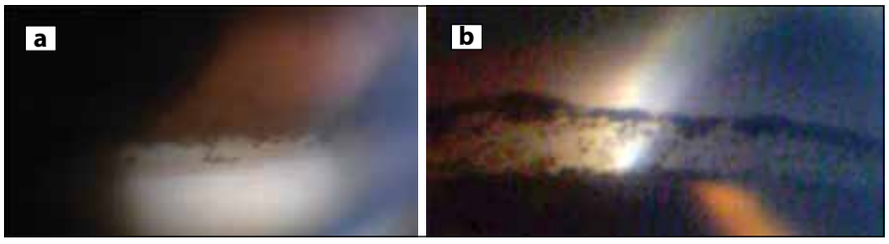

Figure 14: *Shaffers Grade 3. a. Scleral spur is visible in places Presence of* ***a:*** *goniosynechiae and* ***b:*** *dense patchy pigmentation of Schwalbe's Both cases require peripheral iridectomy, despite being non-occludable.*

Figure 15: *Shaffers grade 4 (45^0) Wide open angle. Ciliary body visualized with ease.*

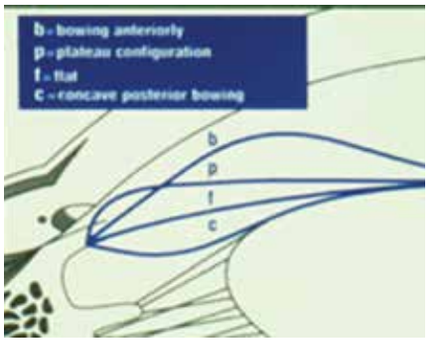

Figure 16: *Peripheral iris curvature (courtesy Prof G Spaeth).*

POSTERIOR EMBRYOTOXON

Prominent anteriorly displaced Schwalbe's line, often pigmented, occurs in Axenfeld Rieger syndrome (Figure 26). The condition has other stigmata like iris atrophy, corectopia, iridocorneal adhesions, dental abnormalities, maxillary hypoplasia etc.

GONIOSCOPY POST TRABECULECTOMY

Gonioscopy retains its usefulness as a diagnostic modality in cases of bleb failure post trabeculectomy. The most common cause of bleb failure is subconjunctival fibrosis (external cause of failure), rarely the inner sclerostomy gets blocked by iris tissue, blood clot or vitreous (internal cause of failure). Gonioscopy comes to the rescue in this scenario by ruling out the latter cause, namely internal ostium blockade. Therefore whenever the peripheral iridectomy is not clearly visible in scenarios of flat bleb, diagnostic gonioscopy needs to be done. (Figure 27). In case of internal ostium block, the iris tissue needs to be physically removed from ostium combined with needling of bleb for reviving the failed trabeculectomy. The reader must try and do gonioscopy after trabeculectomy to familiarize with the open sclerostomy look. In situations of Glaucoma drainage device surgery (GDD) gonioscopy helps in locating the tube, more so when it has retracted (Figure 28).

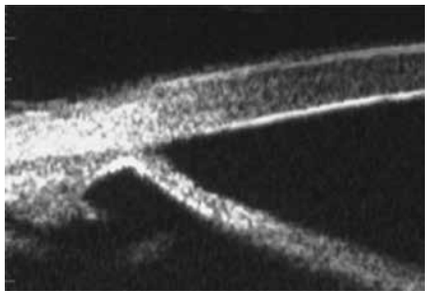

Figure 18: *Ultrasound biomicroscopy of plateau iris. Note peripheral bowing of iris of p configuration, due to anteriorly placed ciliary process. (Courtesy Prof G Spaeth).*

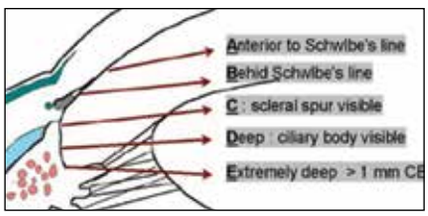

Figure 19: *Iris insertion patterns (courtesy Prof G Spaeth).*

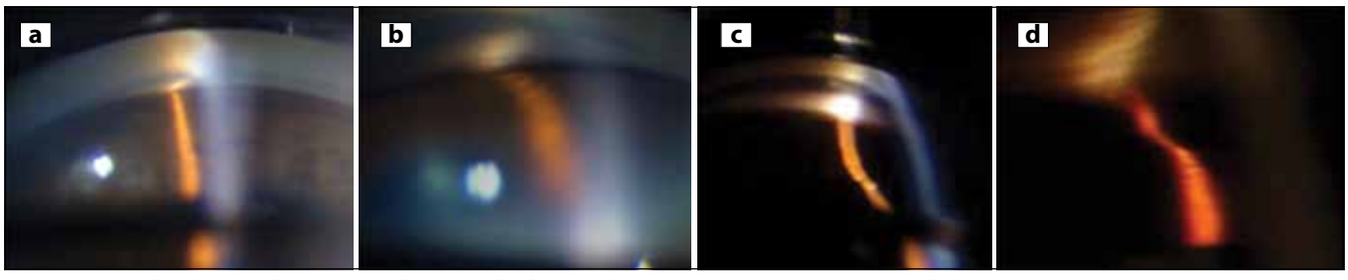

Figure 17: *Peripheral iris configuration;* ***a:*** *Flat or regular;* ***b:*** *Bowed or Convex;* ***c:*** *Concave or Queer* ***d:*** *Plateau (Sine wave sign)*

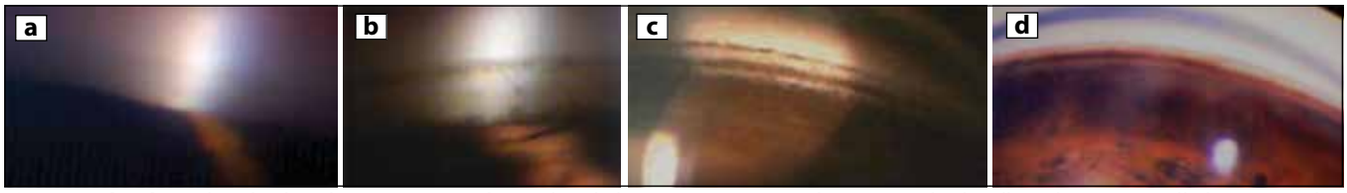

Figure 20a,b,c,d: *Grades of trabecular pigmentation from nil to dark pigmenation. Densely pigmented Schwalbe' s line in c is called as Sampoelesi line. Diffuse trabecular meshwork pigmenation as in c is sometimes called as Mascara line.*

Figure 21 a: *Highly pigmented Schwalbe's line with Patchy pigmentation and a paler trabecular meshwork;* ***b:*** *Moderately pigmented Schwalbe's line with Patchy pigmentation In both a, b angle closure glaucoma is a strong possibilty and other eidence of prior attacks - like glaucomflecken, iris atrophy would need to looked for* ***c:*** *Schwalbe line is diffusely pigmented, and this pigmentation is more than that seen in Trabecular meshwork . The Schwalbe line is the picture b is Sampoelsei line.*

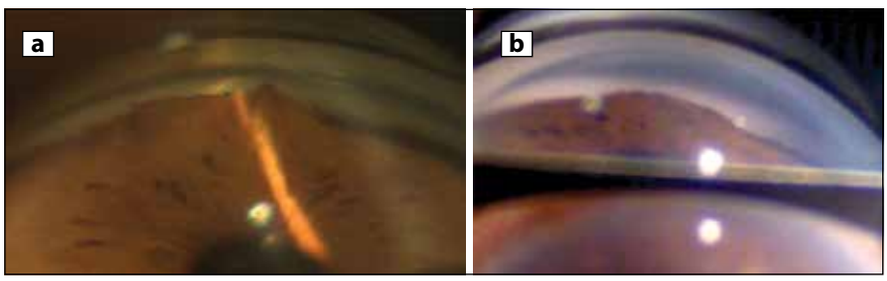

Figure 22a,b: *Peripheral anterior synechiae.*

Figure 23a: *Goniosynechia;* ***b:*** *Iris processes V type;* ***c:*** *Iris processes W type.*

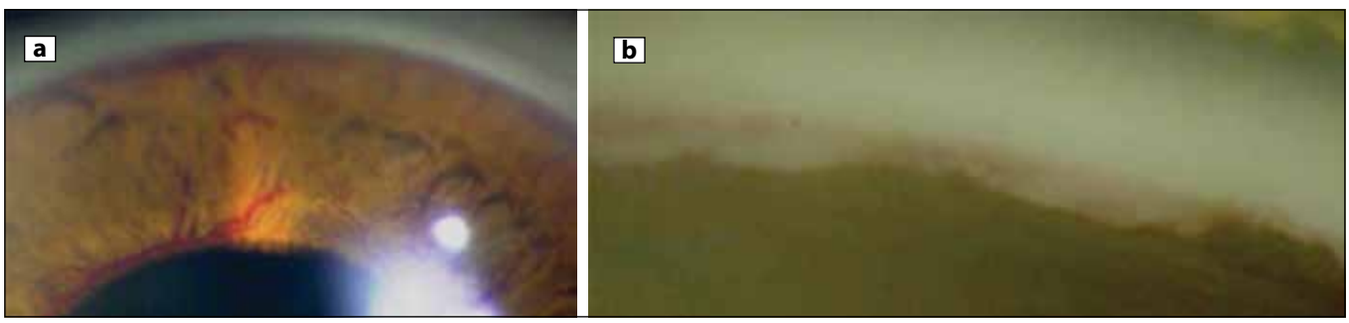

Figure 24a: *Rubeosis iridis & neovascularization angle;* ***b:*** *Neovasculrization of angle on Gonioscopy*

CONTRAINDICATIONS TO PERFORMING GONIOSCOPY

a. Perforated globe
b. Active infection -corneal ulcer, conjunctivitis
c. Corneal surface disease not permitting adequate placement of gonioscope

CLINICAL PEARLS AND CAVEATS

- During work up of a glaucoma case, gonioscopy is done after tonometry, since manipulations during gonioscopy may reduce the IOP by phenomenon of pseudofacility.
- Gonioscopy needs to be repeated at 2-3 yearly intervals, since crystalline lens growth makes angle anatomy dynamic[13].
- Perform gonioscopy in a relatively dark room, as photopic pupil response will constrict pupil and arte-factually open angle.
- Hyperopic patients are more likely to have narrow anterior chamber angles.
- Structures are seen of opposite angle

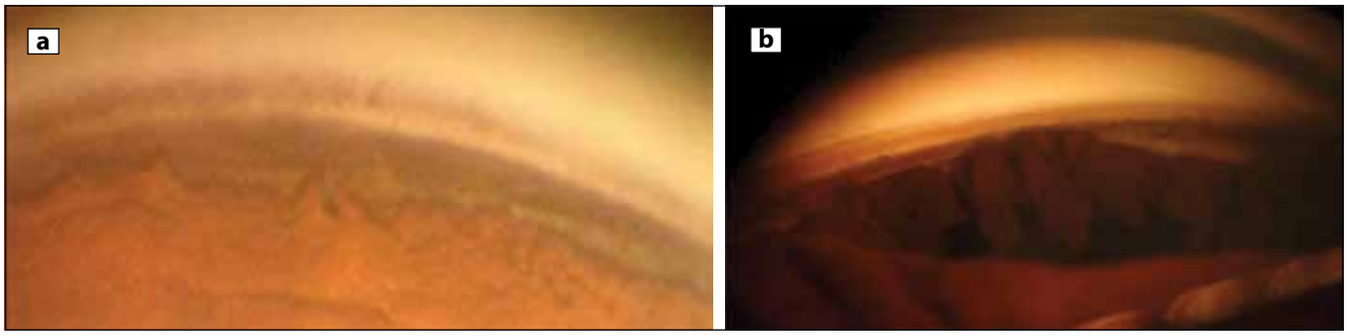

Figure 25a: *Angle recession with presence of wide Ciliary body band;* ***b:*** *Iridodialysis with cyclodialysis*

Figure 26: *Posterior embryotoxon - Anteriorly displaced Schwalbe line Axenfeld Reiger. Note obscuration of scleral spur due to high insertion of iris Behind Schwalbe's line (B).*

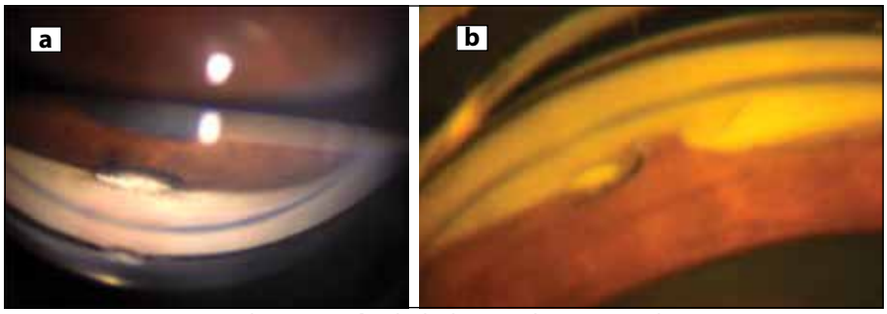

Figure 27a: *Patent inner sclersostomy;* ***b:*** *Blocked inner sclerostomy with iris tissue.*

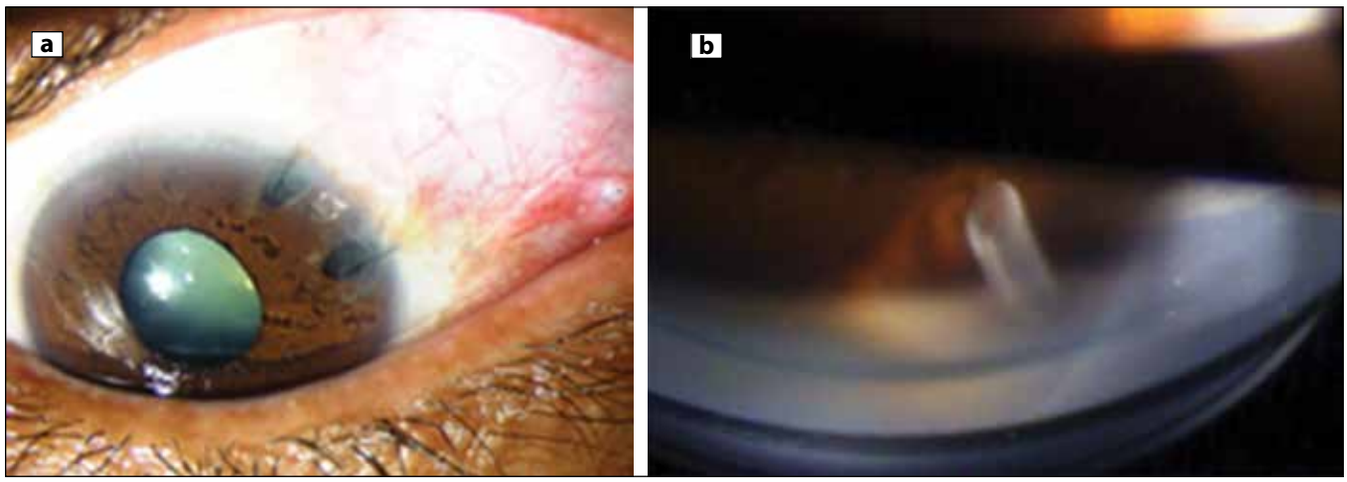

Figure 28a,b: *Tube shunt position and patency confirmed on Gonioscopy.*

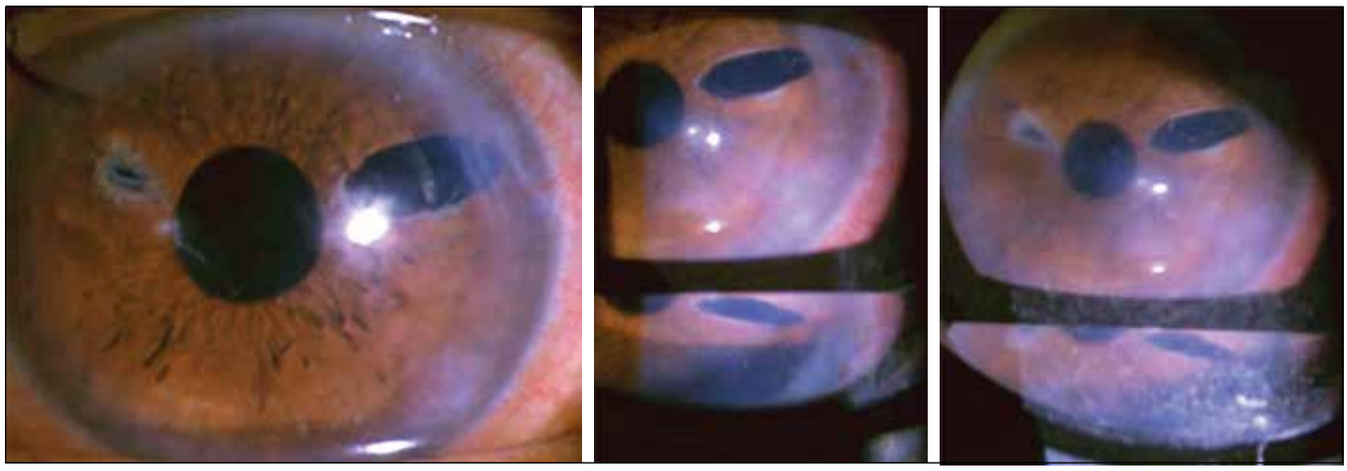

Figure 29: *Note a large surgical PI in temporal aspect of this eye. Through the gonioscope mirror the PI is visible in same direction, not crossed.*

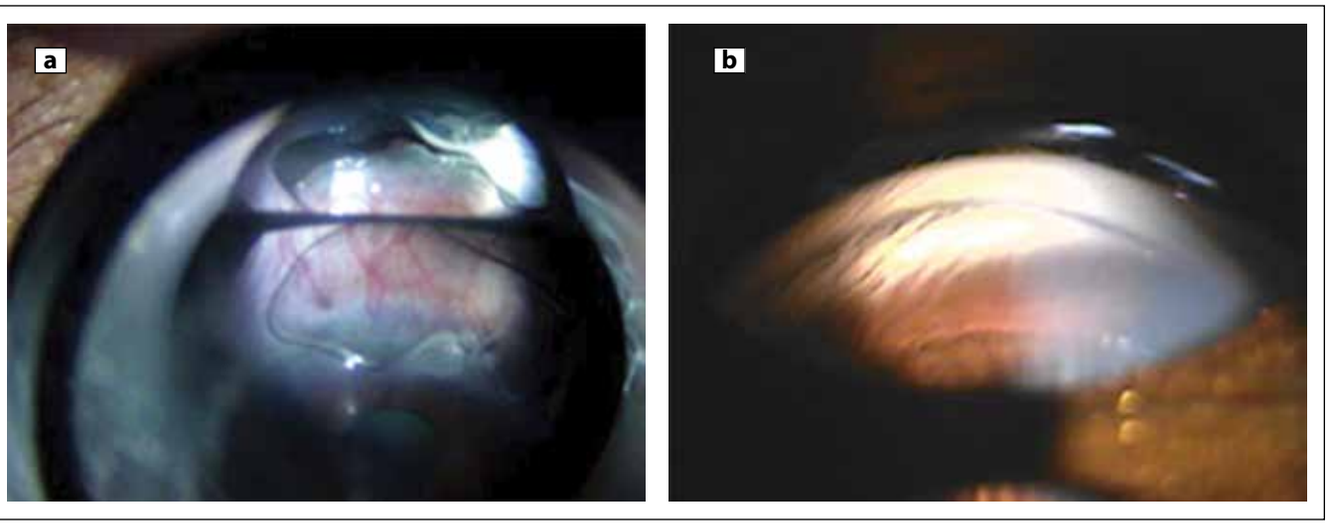

Figure 30a: *Air bubbles entrapped between gonioscope and ocular surface* ***b:*** *Excess pressure generates Descemet's folds.*

but are not crossed (Figure 29).

- Air bubbles often enter in the space between eye and gonioscopy lens. Tilting and rocking of lens can get rid of the small bubbles. If this fails lens removal and reinsertion is required (Figure 30a).
- Excess pressure on the gonioprism will generate folds on Descemet's, making visualization difficult and also falsely deepen the angle (Figure 30b).

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Optical Coherence Tomography Angiography in Glaucoma

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PATHOGENESIS OF GLAUCOMA

Glaucoma is a chronic optic neuropathy characterised by progressive loss of retinal ganglion cells (RGCs)[1]. Although the exact pathogenesis of glaucoma is not fully understood, two main theories have been proposed to explain the death of RGCs in glaucoma[2]. The "mechanical theory" postulates RGC death to be a consequence of raised intraocular pressure (IOP). It proposes that increased IOP causes an obstruction to the axoplasmic flow within the RGCs at the lamina cribrosa leading to RGC death[3]. Multiple studies have reported IOP to be a major causal factor for glaucoma, with the risk of incident glaucoma and its progression increasing with higher IOP[4-10]. However, it is well accepted that the mechanical theory alone, fails to explain the entire pathogenic mechanism of glaucoma. This is because glaucoma occurs and progresses even at normal IOP levels in a significant number of eyes, and not all eyes with ocular hypertension develop glaucoma. The "vascular theory", the alternate theory to explain glaucoma pathogenesis, proposes reduced blood supply to the RGCs, as the primary cause of glaucoma[11-13].

OCULAR BLOOD SUPPLY: ANATOMY AND PHYSIOLOGY

Ocular blood supply occurs predominantly through the retinal and the choroidal circulations which are both derived from the ophthalmic artery. The inner one-third of the retina is supplied by the central retinal artery (retinal circulation) while the outer two-thirds of the retina is supplied by branches of the choroidal vessels (choroidal circulation). Similarly, the superficial layer of the optic nerve head (ONH) which comprises of the RGC axons receives its blood supply via small branches of the central retinal artery. The deeper tissues of the ONH, such as the prelaminar region, are supplied by branches from recurrent choroid arterioles and the short posterior ciliary arteries[14,15]. The venous drainage of the entire ONH is via the central retinal vein.

The physiology of ocular blood flow has been enumerated in previous studies[16,17]. Retinal circulation is a low flow, high oxygen extraction system with no autonomic innervation. The presence of endothelial tight junctions results in a blood–retinal barrier, similar to the blood–brain barrier. Retinal circulation has autoregulation so that the blood flow is held fairly constant in spite of mild to moderate changes in the perfusion pressure and IOP. In contrast, choroidal circulation is a high flow, low oxygen extraction system. Choroid has a rich autonomic innervation and the endothelium of the choroidal vessels are fenestrated. The choroidal circulation has poor autoregulation, which renders the choroidal blood flow more dependent on perfusion pressure.

MEASURING OCULAR BLOOD FLOW IN HUMANS

Retinal and ONH blood flow in glaucomatous eyes has been investigated earlier using various techniques. Fluorescein angiography (FA), a common technique used to evaluate retinal vasculopathies, has been used to study ocular blood flow in glaucoma. The studies using FA have reported prolonged arteriovenous passage times[18,19] fluorescein filling defects in the disc[20,21] focal sector hypoperfusion of the optic disc and diffuse disc hypo-perfusion[22] in patients with glaucoma. However, FA is an invasive technique requiring the intravenous injection of a dye, and the transient presence of the dye in the eye makes quantification difficult.

Laser Doppler flowmetry (LDF) and laser speckle flowgraphy (LSFG) are two other non-invasive techniques that have been used to measure ONH perfusion. Multiple studies with these two techniques have reported significantly reduced neuroretinal rim (NRR) blood flow and peripapillary retinal blood flow in patients with glaucoma compared to controls[23-27]. However, measurements provided by LDF and LSFG are too variable for diagnostic application. Coefficient of variation (CV) for intra-visit repeatability with LDF has been reported to range from 6.6% to 21.2% and for inter-visit reproducibility from 25.2% to 30.1%[28-32]. With LSFG, CVs for intra-visit repeatability have been reported to range from 1.9% to 11.9%, and inter-visit reproducibility was 12.8%[33-35].

The search for a simple, non-invasive, reproducible method of evaluating the ocular blood flow lead to the development of optical coherence tomography (OCT) angiography.

OCT ANGIOGRAPHY

A number of techniques using OCT have been developed for imaging the ocular blood flow. Doppler OCT was one of the earliest techniques developed for vascular imaging. It assessed blood flow by comparing phase differences between adjacent A-scans[36]. Although Doppler OCT was appropriate for large vessels around the disc, it was not sensitive enough to measure accurately the low velocities in small vessels that make up the ONH and retinal microcirculation.

The current OCT angiography (OCTA) technology is capable of imaging large vessels as well as microvasculature of the retina and ONH by performing multiple OCT scans of the same region. The variation in OCT signal at each location is then studied since moving particles, such as red blood cells, result in

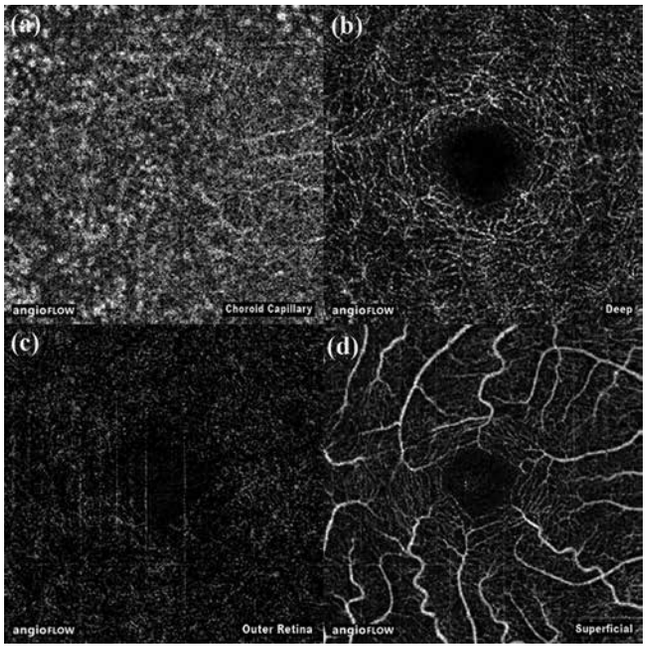

Figure 1: *Angiography slabs of the macular scan obtained using spectral domain optical coherence tomography showing the choriocapillaris (a), deep retinal (b), outer retinal (c) and superficial retinal (d) slabs.*

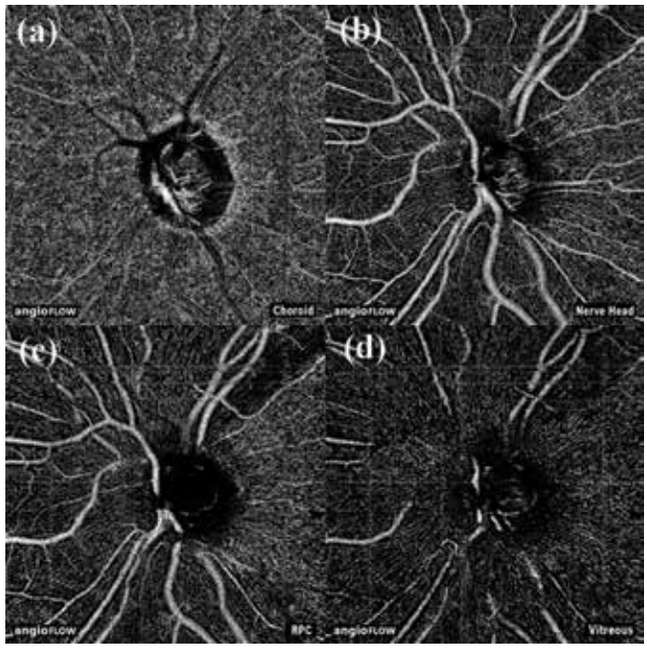

Figure 2: *Angiography slabs of the optic nerve head scan obtained using spectral domain optical coherence tomography showing the choroid (a), nerve head (b), radial peripapillary capillary, RPC (c) and vitreous (d) slabs.*

a high variance of the OCT signal between scans and this is used to identify blood vessels. There are several algorithms which have been developed to interpret the OCT signals to delineate the blood vessels. The split spectrum amplitude decorrelation angiography (SSADA) uses the variation in the intensity of the OCT signal to identify blood vessels. The fluctuating value of OCT intensities is considered as the decorrelation (D). Thus, pixels in the B-scan frame where blood is flowing have fluctuating intensities and yield high D values (approaching 1). Pixels in the B-scan frames that contain static tissue yield small D values (approaching 0)[37]. The principles of SSADA have been explained in detail by Jia et al.[38] The optical microangiography (OMAG), another algorithm that performs OCTA (Angioplex, Cirrus HD-OCT, Carl Zeiss Meditec Inc., Dublin, CA), uses the variation in intensity as well as the phase difference of the OCT signals for vessel delineation. In addition to tracing the blood vessels, these algorithms also strive to reduce motion artefacts and pulsatile bulk motion noise.

Two other developments that improved OCTA technology were the en face presentation and motion correction. En face presentation helps to reduce the data complexity by presenting angiography information in 2 dimensions. Retina is segmented into different slabs, such as choriocapillaris, outer and deep retina and superficial retina, and vessels in each of these slabs is presented in 2-dimensional format (Figure 1). ONH is similarly segmented into choroid, nerve head, radial peripapillary capillary and vitreous slabs (Figure 2). As the time required to obtain the scan with OCTA is close to 3 seconds, involuntary saccades and changes in fixation during data acquisition can lead to motion artifacts that may confound the interpretation of the final OCT angiogram. "Motion Correction Technology" (MCT) is an orthogonal registration algorithm which minimizes these motion artifacts[39].

SSADA has been optimized for the spectral-domain OCT (SDOCT) platform[40]. This algorithm is currently available on a commercial OCT device (RTVue-XR SD-OCT, Optovue Inc., Fremont, CA) making the OCTA technology available to clinicians. This review focusses only on OCTA performed using the SSADA algorithm.

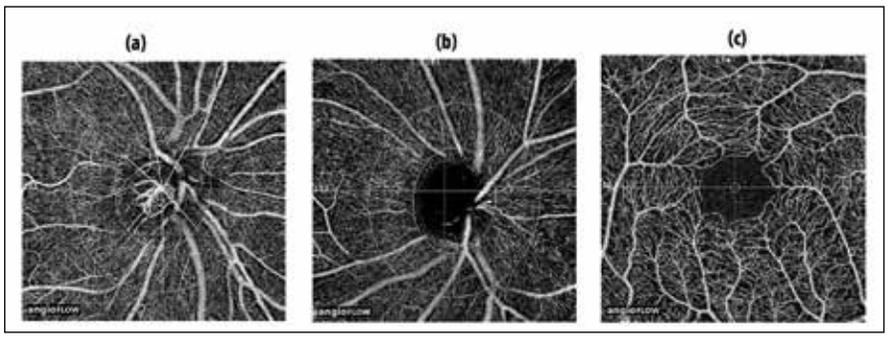

Figure 3: *Figure showing the optic nerve head (a), peripapillary (b), and macular (c) optical coherence tomography angiography images and the sectors where vessel densities are calculated. The optic disc vessel density is calculated within the optic nerve head from the nerve head segment of the en face angiogram, peripapillary vessel density over a 0.75 mm-wide elliptical annulus extending from the optic disc boundary from the radial peripapillary capillary segment, and superficial macular vessel density over a 1.5 mm-wide circular annulus centered on the macula.*

INTERPRETING THE OCTA PRINT-OUT OF A NORMAL EYE

The current generation of OCTA can scan the optic disc region and the macula. The optic disc OCTA scan is performed using volumetric scans covering an area of 4.5 × 4.5 mm and the software automatically fits an ellipse to the optic disc margin. The region within this margin is referred to as the "inside disc' region (Figure 3a). The peripapillary region is defined as a 0.75 mm-wide elliptical annulus extending from the optic disc boundary (Figure 3b). This region may be divided in 6 sectors based on the Garway-Heath map or into 8 peripapillary sectors similar to that of the

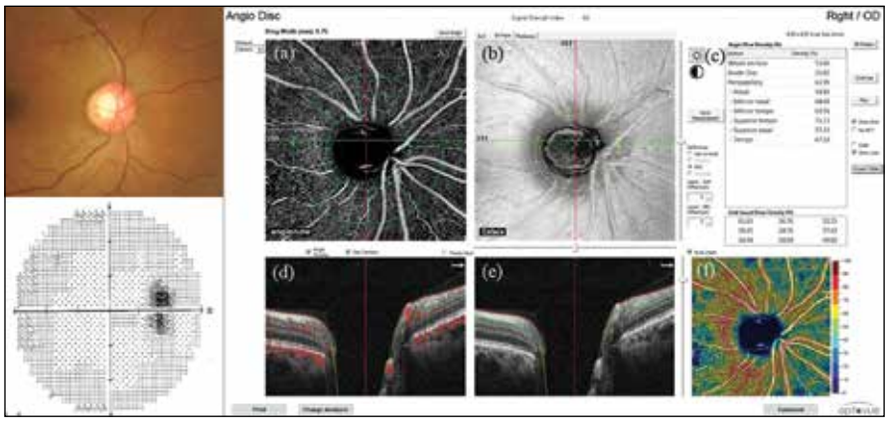

Figure 4: *Peripapillary OCTA report of an eye showing normal optic disc (upper left) and normal visual fields (lower left). The OCTA report shows dense radial peripapillary capillaries on the angiography image (a) and heat map (f) with vessel densities in different sectors quantified in the table (c).*

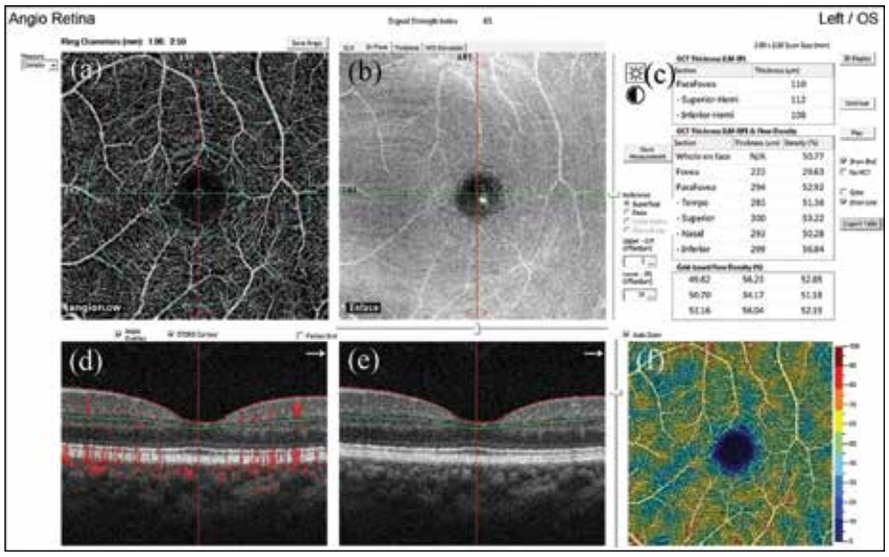

Figure 5: *Macular OCTA report showing the superficial retinal vessels of a normal eye. The OCTA report shows dense capillaries on the angiography image (a) and heat map (f) with vessel densities in different sectors quantified in the table (c).*

RNFL maps (temporal-upper TU, supero-temporal ST, supero-nasal SN, nasal-upper NU, nasal-lower NL, infero-nasal IN, infero-temporal IT and temporal-lower TL). The optic disc scan can be divided into several slabs for further analysis. The most superficial "vitreous" slab is usually used for assessing neovascularization of the disc and is not used in glaucoma. The "nerve head" layer extends from the internal limiting membrane (ILM) to 150 microns posterior and is used for assessing the vasculature within the optic disc. The "radial peripapillary capillary (RPC)" layer extends from the ILM to the posterior boundary of the RNFL and is used for assessing the vascular supply of the RNFL layer of the peripapillary region. And the "choroidal slab" is used to assess the deep retinal and choroidal vasculature.

The macular OCTA scan is performed using a volumetric scan covering a 3 x 3 mm area (Figure 3c). More recently 6 x 6 mm scans of the macula are also available. The macular region is divided in the small central foveal area and a 1.5 mm wide parafoveal, circular annulus. This parafoveal region is divided in 2 hemispheres of 180 degrees each (superior and inferior). Additionally, it may also be divided into 4 sectors of 90 degrees each (nasal, inferior, superior, and temporal sectors). The macular region is also divided into slabs for further analysis. The superficial retinal slab extends from 3 µm below the ILM to 15 µm below the inner plexiform layer (IPL). Deep retinal slab extends from 15 µm below IPL to 70 µm below the IPL. Outer retinal slab extends from 70 µm below the IPL to 30 µm below the retinal pigment epithelium (RPE) and choroid capillary slab extends from 30 µm below the RPE to 60 µm below the RPE.

OCTA quantifies the ocular circulation using two parameters: flow index and vessel density. Flow index is defined as the average decorrelation values in the measured area, and vessel density, which is the most widely used OCTA parameter, is defined as the percentage area occupied by vessels in the measured area. The threshold decorrelation value used to separate blood vessel and static tissue is set at 0.125, which is two standard deviations above the mean decorrelation value in the foveal avascular zone, a region devoid of vessels. Quantification of vessel density can be performed in the nerve head and the RPC slab of the optic disc scan, but not the choroidal slab. Similarly, vessel densities can also be determined for the superficial vascular plexus of the macula scan. The current OCTA machines do not contain a normative database for comparison of the patient's vessel densities. Currently these comparisons are made in research studies using control eyes.

Figure 4 shows the peripapillary OCTA report of a normal eye (showing normal optic disc and visual field). The OCTA report shows

(Figure 4a) angiography image showing large vessels and a dense network of capillaries in the RPC segment

(Figure 4b) En face image

(Figure 4d and e) B scan showing the segmentation lines (for the RPC segment) along with the blood vessels detected by the SSADA algorithm

(Figure 4f) Heat map showing dense network of vessels in the peripapillary region; represented by warm colors such as red and yellow

(Figure 4c) Table showing the vessel density in the entire scan region and various sectors

Figure 5 shows a macular OCTA report of a normal eye showing the superficial retinal vessels. Macular scan is performed using a 3 mm x 3 mm scan. The interpretation of the report is similar to that of the peripapillary report described earlier.

Interpreting the OCTA print-out of a glaucomatous eye: A qualitative analysis

Figure 6 shows a glaucomatous eye (mild severity of disease) with a superior neuroretinal rim notch and superotemporal RNFL defect (indicated by arrows on the disc photograph) with a correlating inferior hemifield defect on the visual fields. OCTA shows reduced vessel density in the superotemporal region on the angiography and the heat

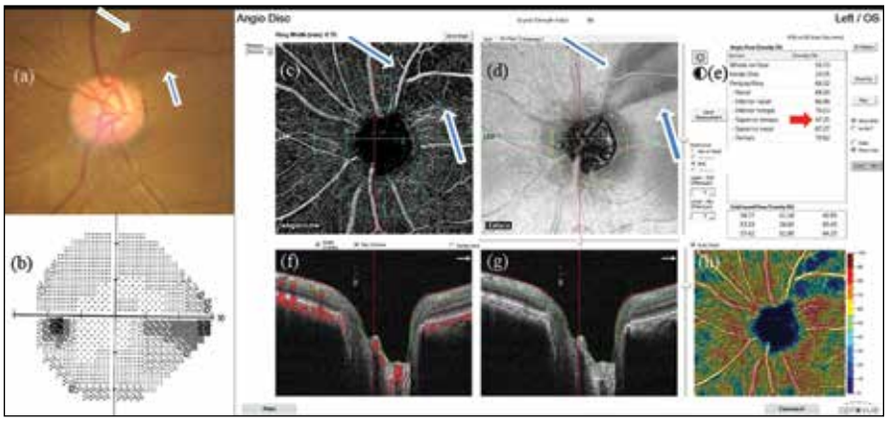

Figure 6: *Peripapillary OCTA report of a glaucomatous eyes with mild disease. Optic disc photograph (a) shows superior neuroretinal rim notch and superotemporal RNFL defect (indicated by arrows on the disc photograph) with a correlating inferior hemifield defect on the visual fields (b). OCTA report shows reduced vessel density in the superotemporal region as indicated by the arrows on the angiography (c) and heat map (h), along with a decrease in the vessel density in the corresponding region on the table (e, red arrow).*

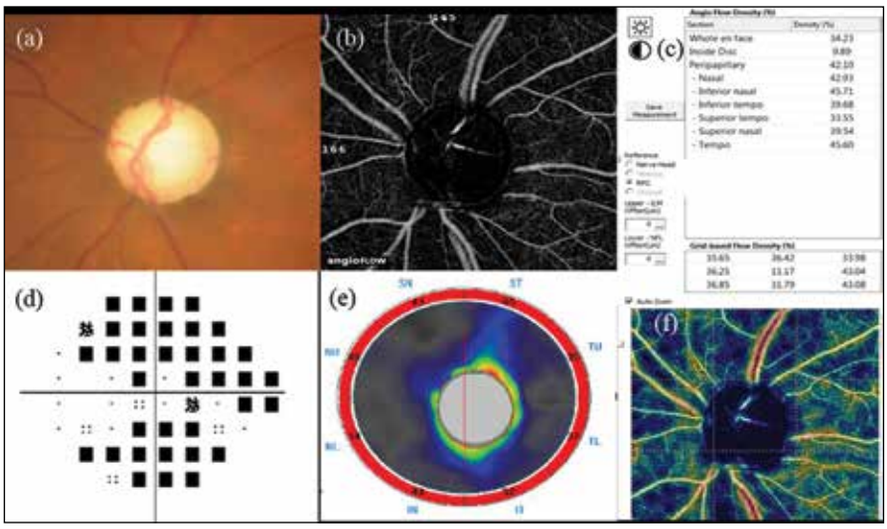

Figure 7: *Peripapillary OCTA report of a glaucomatous eyes with advanced disease. It shows advanced disc damage (a), bi-arcuate visual field loss (b) and diffuse RNFL thinning (e). OCTA report shows gross loss of capillaries on the angiography (b) and heat map (f), along with a decrease in the vessel densities in all peripapillary OCTA sectors in the table (c).*

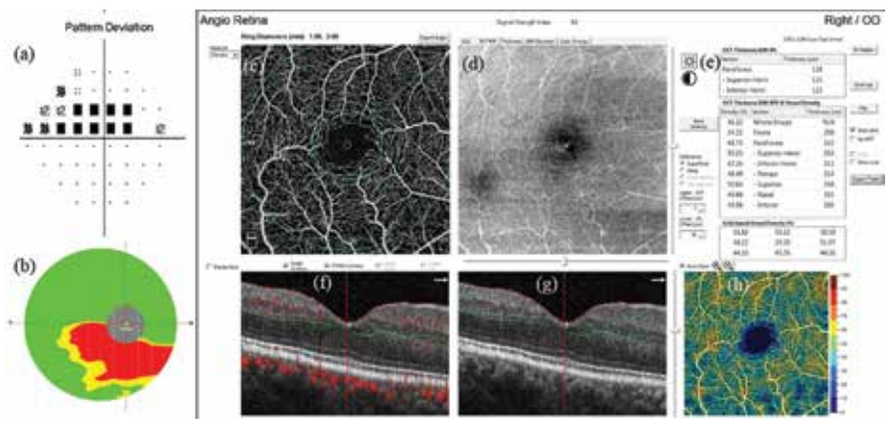

Figure 8: *Macular OCTA report of a glaucomatous eye which shows a superior hemifield defect (a) and a corresponding inferior ganglion cell complex thinning (b). OCTA shows reduced superficial macular vessel density in the inferior region better noted on the heat map (h) and quantified in the table (e).*

map, along with a decrease in the vessel density in the corresponding sector.

Figure 7 shows an eye with advanced glaucoma. OCTA shows gross loss of capillaries on the angiography and heat map, along with a decrease in the vessel densities in all peripapillary sectors in the Table.

Figure 8 shows a glaucomatous eye with superior hemifield defect and a corresponding inferior ganglion cell complex (GCC) thinning. OCTA shows reduced superficial retinal vessel density in the inferior macular region noted on the heat map. Figure 9 shows the heat map of macular OCTA scan of the same eye performed with 6 mm x 6 mm scan. Compared to the 3 mm x 3 mm scan, the vessel dropouts are more obvious on the 6 mm x 6 mm scan.

A quantitative analysis of OCTA changes in different subtypes of glaucoma

(i) POAG: All the initial studies with OCTA were performed in eyes with primary open angle glaucoma (POAG) and showed reduced flow index and vessel density inside the ONH and in the peripapillary region of eyes with POAG compared to controls[41-43]. Multiple studies subsequently showed that the OCTA vessel densities measured in the macular regions were also reduced in eyes with glaucoma compared to control eyes[44,45]. Peripapillary vessel density reduction was found to be significantly greater than that inside the ONH and the macular region in glaucomatous eyes.

(ii) Normal tension glaucoma: Vascular theory of glaucoma is considered to be more applicable in eyes developing glaucomatous damage at low IOP. A few studies compared the OCTA measurements in low pressure glaucoma (NTG) and high pressure glaucoma (POAG). However, no difference in OCTA measurements were seen between NTG and severity-matched POAG eyes[46].

(iii) Angle closure glaucoma: OCTA measurements in primary angle closure glaucoma (PACG) were found to be similar to that in POAG when the severity of disease was matched for[47] Like POAG (described below), OCT neuronal (NRR, RNFL and GCC) measurements had a better diagnostic ability compared to OCTA vessel density measurements (inside ONH, in peripapillary and macular regions) in PACG[48].

(iv) Pseudoexfoliation glaucoma: A few studies have evaluated the superficial retinal vasculature in the peripapillary region of PXG eyes and have reported that the reduction of vessel densities was greater in PXG compared to POAG eyes of similar disease severity[49, 50].

OCTA CHANGES IN PERIMETRICALLY INTACT REGIONS OF GLAUCOMATOUS EYES

It is important to determine the

temporal relationship of vessel density reduction on OCTA with respect to RNFL thinning and visual field defects. This would help us develop strategies to detect the disease in the earliest stages. A longitudinal study is required to address this question. However, OCTA is a relatively new technology and there are, currently, no longitudinal studies addressing this question. As an alternate approach, studies have been performed in eyes with established perimetric glaucoma, whose visual field defects are limited to one hemifield; and the vascular changes in regions corresponding to the intact hemifield have been examined. These studies have found reduced peripapillary vessel density and RNFL thickness in the hemiretina corresponding to the perimetrically intact hemifield compared to that of healthy eyes[51-53]. One of these studies also found that the temporal sector of the perimetrically intact hemifield (corresponding to the region of papillomacular bundles) showed reduced vessel density in the presence of normal RNFL thickness. This suggested that there may be regional variations in the alterations of RNFL thickness and vessel density measurements, and OCTA changes may precede RNFL changes in some sectors.

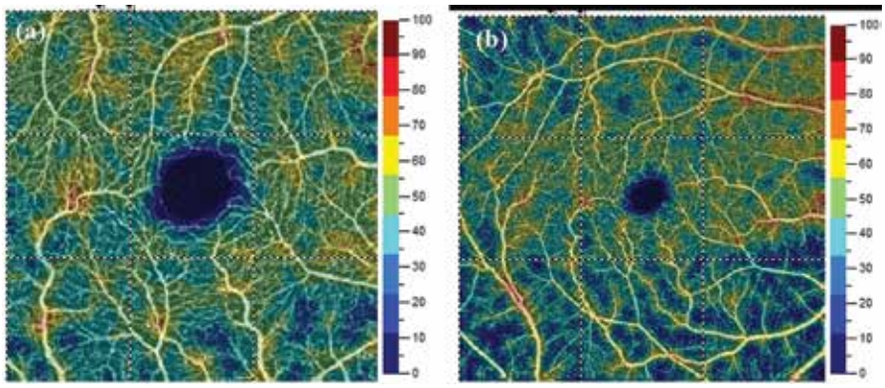

Figure 9: *Macular OCTA report of the eye shown in Figure 8 imaged using a 3 mm x 3 mm (a) and a 6 mm x 6 mm scan (b). Compared to the 3 mm x 3 mm scan, the vessel dropouts are more obvious on the 6 mm x 6 mm scan.*

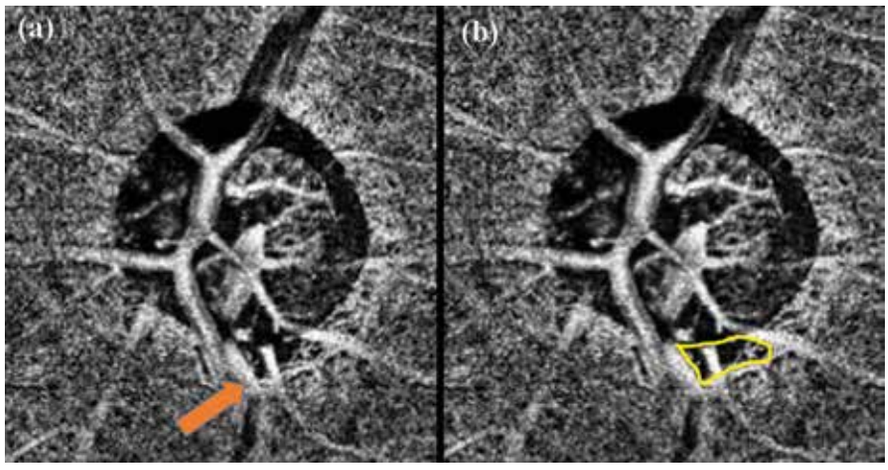

Figure 10: *Choroidal OCTA slab of a glaucomatous eye showing the presence of choroidal microvasculature dropout (CMvD) in the inferior region (a). Arrow points to the CMvD. Yellow line marks out the boundary of the CMvD (b).*

COMPARING OCTA WITH OCT MEASUREMENTS IN DIAGNOSING GLAUCOMA

A number of studies have compared the diagnostic abilities of OCTA measurements (vessel densities of the inside disc, peripapillary and macular regions) with corresponding OCT measurements (ONH neuroretinal rim area, RNFL and macular thickness) in glaucoma.

A few studies comparing the diagnostic abilities (area under the receiver operating characteristic curves [AUC] and sensitivities at high specificities) of peripapillary vessel densities and RNFL thickness in POAG have found them to similar. Depending on the severity of glaucoma patients included in these studies, the AUCs of both peripapillary vessel density and RNFL thickness have ranged between 0.85 to 0.95. A few other studies have reported a better diagnostic ability of RNFL thickness compared to peripapillary vessel density in POAG[54]. In spite of the AUCs being similar, one study showed that the sensitivity to detect glaucoma in early stages of severity was better with RNFL thickness compared to peripapillary vessel density measurements. Diagnostic abilities of vessel density measurements inside ONH were found to be significantly lesser than that of the OCT measured NRR area. Similar to the peripapillary measurements, diagnostic ability of superficial retinal vessel density at macula was found to be similar to that of macular GCC thickness by one study[55] while the same was found to be inferior to GCC thickness by another study. However, macular vessel densities in all these studies were evaluated on 3 mm x 3 mm scans, and a subsequent study showed that evaluating the macular vessel densities on 6 mm x 6 mm scans would be able to better detect glaucomatous changes[56]. It is still not clear if OCTA measured vessel density changes occur before or after OCT measured neuronal (NRR, RNFL and GCC) changes in glaucoma. Longitudinal studies in the future should be able to clarify this.

OCTA OF THE PERIPAPILLARY CHOROID

Peripapillary choroidal circulation is of particular interest in glaucoma as it may be a surrogate marker for the perfusion of the deep ONH structures. Recently, choroidal microvasculature dropout (CMvD, Figure 10), defined as the complete loss of choriocapillaris in localized regions of parapapillary atrophy (PPA), has been observed using OCTA in POAG eyes[57,58]. CMvD has been shown to be a true perfusion defect using indocyanine green angiography[59]. Studies have also reported a topographic association between the location of CMvD and structural defects (RNFL thinning and lamina cribrosa defects) as well as functional defects (visual field loss) in POAG eyes[60,61]. CMvD is a relatively novel finding in glaucoma and the clinical implications of it are not fully known. It has been argued that CMvD is likely to precede glaucomatous ONH damage[62]. A recent study reported an association between CMvD and progressive RNFL thinning in POAG eyes with DH[63]. Longitudinal studies are required to determine the clinical implication of CMvD in glaucoma.

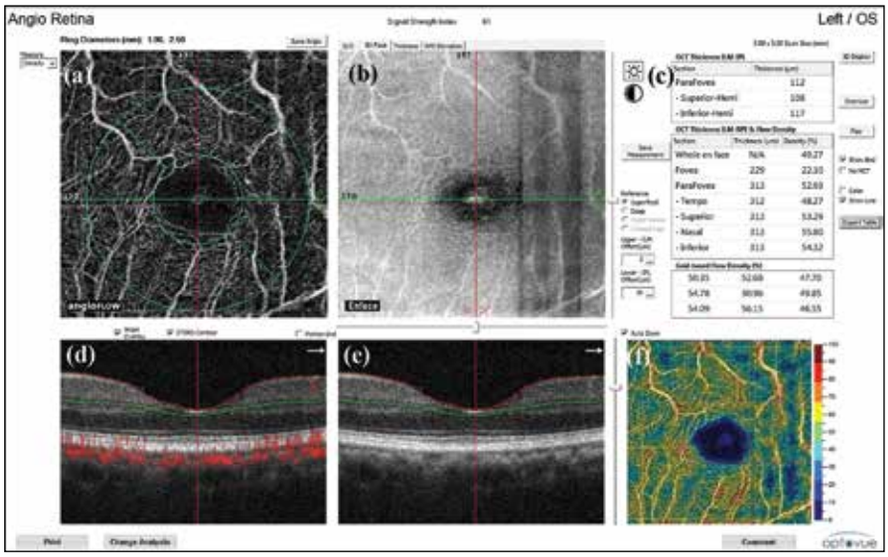

Figure 11: *Macular OCTA scan showing two types of artifacts; motion artifacts, recognized as vertical bands temporally on the en face map (b) and duplication of vessels, recognized inferiorly and nasally on the angiography map (a). These artifacts cause a decrease in vessel density in the temporal sector and increase in vessel density in the nasal and inferior sectors (noted on the heat map [f] and table [c]).*

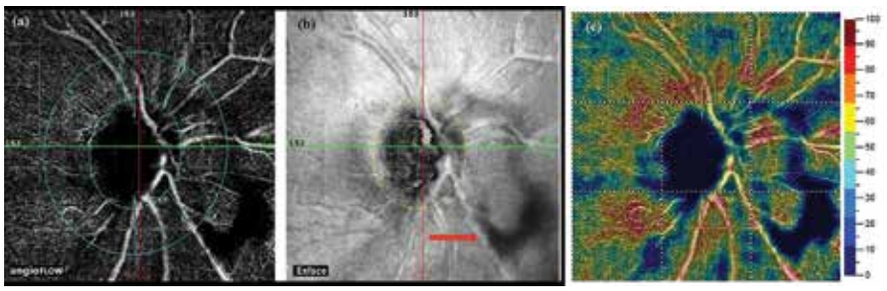

Figure 12: *Vitreous opacity (red arrow on en face map [b]) casting a shadow, as seen on the angiography map (a) and causing a falsely reduced vessel density on the heat map (c).*

FACTORS AFFECTING OCTA MEASUREMENTS

Unlike the neuronal elements, vasculature is affected by multiple factors other than glaucoma. A study evaluated the effect of subject-related (age, gender, systemic hypertension and diabetes), eye-related (refractive error, optic disc size) and technology-related (signal strength index, SSI of the scans) determinants on the peripapillary and macular vessel densities in normal eyes[64]. It found that peripapillary vessel densities were higher in females. Peripapillary vessel densities were lower, while the macular vessel density was higher, in subjects with hypertension. Most of the vessel densities were lower in subjects with diabetes. In addition to these factors, SSI of the OCTA scans showed a significant positive association with the vessel densities of all regions. Vessel densities were higher in scans with higher SSI values. These results should be considered while interpreting the vessel densities in glaucoma.

LIMITATIONS AND RECENT ADVANCES IN OCTA

Motion artifacts are common with OCTA imaging due to the prolonged time required to acquire the scans; in spite of methods available to account for the artifacts (Figure 11). This is true even in research settings and multiple studies have also reported high number of poor quality images with OCTA[65-68]. Two significant improvements incorporated recently to overcome the issue of poor quality scans are (i) real time eye tracking technology, for controlling the motion artifacts more effectively[69] and, (ii) high-density (HD) scanning mode, for improving the resolution of the scans. A recent study has reported that the number of poor quality scans significantly decreased with the incorporation of these improvements[70].

Media opacities, especially vitreous opacities, can significantly affect the quality of OCTA scans and the quantification of vessel densities (Figure 12).

OCTA technology is able to evaluate the superficial retinal vessels well but not the deeper retinal and choroidal vasculature. This is because the signals from the superficial retinal vessels project on to the deeper layers causing artifacts known as the projection artifacts. Detection of CMvD, for example, is affected by the presence of projection artifacts. Newer methods of projection artifact correction have been tried and the newer generations of OCTA (projection resolved OCTA) are likely to evaluate the deeper retinal and choroidal vasculature better[71].

CONCLUSIONS

OCTA has the potential to be useful in the diagnosis and monitoring of glaucoma. However, the technology needs to mature before it becomes a routine part of the glaucoma work-up in our clinics.

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MICROSTENTS IN GLAUCOMA

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Minimally Invasive Glaucoma Surgery or 'MIGS' is a term that encompasses surgeries using shunts, stents and techniques that lower intraocular pressure with less surgical risk than the more established penetrating (trabeculectomy) and non-penetrating procedures (deep sclerectomy, canaloplasty, viscocanulostomy etc.) and setons (Ahmed, Baerveldt, or Molteno).

Microstents are emerging as potential noninvasive alternatives to trabeculectomy, and thus likely to play an important role in future for glaucoma management.

Most surgeons believe that MIGS procedures use an ab-interno approach that leave the conjunctiva intact for trabeculectomy or non-penetrating surgery, in future (if required). Recently, many have started using the term 'MIGS' to include surgery that affects the conjunctiva, such as XEN.

A new term, 'Moderately' Invasive Glaucoma Surgery' has also been suggested to include the conjunctiva incising MIGS and possibly even ExPress Glaucoma Filtration Device.

Broadly, available stents can be divided as:

a) Schlemm's canal stents : iStent®, iStent® inject, Hydrus
b) Suprachoroidal stents: CyPass®, iStent® Supra, and
c) Subconjunctival stents: XEN, InnFocus

INDICATIONS AND CONTRAINDICATIONS FOR MICROSHUNTS

Indications

Solo MIGS

- Patients with mild-moderate glaucoma
- Primary open-angle glaucoma, pseudoexfoliation glaucoma, or pigmentary dispersion glaucoma
- Glaucoma uncontrolled with maximum pharmacologic treatment or there are barriers preventing adequate medication dosing
- Age greater than 18 years

Phaco Plus:

- Patients with clinically significant cataract, as surgery may be performed simultaneously.

All patients must undergo a pre-operative comprehensive eye exam including gonioscopy and a detailed medical history.

Contraindications

Relative contraindications for these shunts include angle-closure glaucoma, secondary glaucoma, moderate-advanced glaucoma, previous glaucoma surgery, or severely uncontrolled IOP. Other considerations include patients with previous refractive procedures as well as monocular patients.

SCHLEMM'S CANAL STENTS

iStent®, iStent® inject

iStent is the first generation trabecular bypass device that is manufactured by Glaukos Inc. The device has CE-mark and was approved in 2012 by the FDA.

iStent inject is a smaller second generation model with radial symmetry.

Mechanism of action: Both the devices connect the anterior chamber with Schlemm's canal.

Device Design: The product has a size of 1×0.3 mm, is made from heparin-coated, non-magnetic titanium. The iStent is delivered in an inserter which consists of a 26-gauge disposable instrument which contains the iStent on the tip. There is a right- and left-eye model which are distinguished by the direction of the foot. Once placed, the long leg of the "L" shaped implant resides in Schlemm's canal with the short leg or snorkel protruding into the anterior chamber.

iStent inject (Figure 1) has a length of only 360 µm and a diameter of 230 µm, and is currently the smallest medical implant approved for use in the human body during surgical procedures. The G2-M-IS injector system contains two stents, allowing the insertion of both stents from one injector during the same surgical procedure.

Hydrus

Mechanism of action: The Hydrus micro-stent dilates Schlemm's canal (SC) in the complete nasal quadrant, allowing aqueous humor to bypass the trabecular meshwork through multiple collector channels

Design: It is also called as "intracanalicular scaffold". Hydrus is about 8mm long and made of Nitinol (nickel-titanium alloy), a shape memory alloy; when deformed, it returns to its original shape after being heated (Figure 2). It straddles 3 clock hours of SC (approximately 90 degrees), it access collector channels, without blocking their ostia and dilates the SC.

Figure 1: *iStent inject with its injector*

Table 1: Scientific evidence for efficacy and safety of iStent and iStent inject

S No.	Author	Study design	MIGS used	Comparator	No. of Eyes	Follow up (Months)	IOP reduction (%) Mean ± SD	Medication reduction at 12 months	Vision loss	Post operative complications	Reoperations needed
Combined iStent (1 iStent)											
1	Arriola-Villalobos, 2012	BEF-AFT Study (Before After)	iStent (1) Combined	None	19	60	11.0 ± 19.2	1.15	None	IOP spike 4/19	None
2	Craven B , 2012	RCT	iSent (1) Combined	Phaco alone	116	24	(iStent + Phaco): 8.6 ± 23.5 Phaco alone): 5.0 ± 24.1	1.20/1.10	None	IOP spike 5/116 Device related 5/116	1/116
3	Fea, 2015	RCT	iSent (1) Combined	Phaco alone	10	48	(iStent + Phaco):17.4 ± 16.8 (Phaco alone):6.6c19.3	1.50/O.80	None	None	None
4	Spiegel, 2009	BEF-AFT	iStent (1) Combined	None	12	12	19.8 ± 23.5	1.20	None	IOP spike 1/58 Device related 7/58	2/58
Combined iStent (2 iStents)											
5	Arriola-Villalobo Se, 2016 (INJECT)	BEF-AFT	(2) iStent Combined (Inject)	None	20	60	16.0 ± 21.7	1.00	None	IOP spikes (3/20) Device related (1/20)	None
6	Belovayf , 2012	NRS	(2) iStent Combined (Inject)	Phaco+3 iStent	28	12	20.2 ± 30.4	1.80	None	None	None
7	Fernandez-Barrientos, 2010	RCT	(2) iStent Combined	Phaco alone	17	12	(2 iStent + Phaco): 27.3 ± 13.8 Phaco alone:6.1 ± 11.6	1.20 / 0.50	None	None	None
8	Gonnermanna, 2017 (INJECT)	NRS	(2) iStent Combined	Trabectome combined	27	12	(2 iStent + Phaco):30.0 ± 23.2 (Phaco + Trabectome): 34.3 ± 22.1	0.67/0.76	None	None	2/27
SOLO iStent (1 iStent / 2 AND 3 iStents)											
9	Katz, 2015	RCT	SOLO iStent	2 and 3 iStent	36	18	iStent :21.2 ± 10.2 2/3 iStents :40.7 ± 10.7	1.52/1.83	None	None	None
SOLO iStent (2 iStents)											
10	Ahmed, 2014	BEF-AFT	iStent Inject Solo	None	39	18	46.9 ± 13.1	1.0	None	Hypotony 1/39	None
11	Donnenfeld, 2015	BEF-AFT	iStent Inject Solo	None	39	36	34.5 ± 14.4	NA		IOP spike 1/39	1/39
12	Fea, 2014 (INJECT)	RCT	2 iStent	2 Medications	94	12	iStent Inject: 38.4 ± 13.6 2 Medications:36.2 ± 13.0	0.96 / NA		IOP spike 1/94 Device related (1/94)	None
13	Lindstrom, 2016 (INJECT)	BEF-AFT	iStent Inject	None	57	18	27.2 ± 12.4	1.00	NA	NA	NA
14	Vold, 2016	RCT	2 iStent	Medication	54	24	2 iStent : 46.3 ± 12.4 Medications :44.6 ± 19.5 0	NA/NA	None	None	None
15	Voskanyan, 2014 (INJECT)	BEF-AFT	iStent Inject	None	99	12	29.0 ± 23.2	NA	None	IOP spike 10/99 Device related 4/99	4/99

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Scientific evidence for efficacy and safety

Table 1 enlists some salient studies highlighting efficacy and safety profile of iStent and iStent inject.

Pfeiffer et al carried out a RCT, where 100 cases were randomised to cataract surgery alone or combined cataract surgery with Hydrus.Glaucoma medications were washed out and the results were presented off glaucoma medications. At 24 months, a significantly greater proportion of the combined surgery cases reached the endpoint of a 20% reduction in diurnal IOP (80% versus 46%, p = 0.0008). The IOP was also significantly lower in the combined surgery group (16.9 ± 3.3 versus 19.2 ± 4.7 mmHg, p = 0.0093), and there was a significant reduction in cases without ocular hypotensive medications in the combined surgery group (73% versus 38%, p = 0.0008).

The HORIZON study is the largest prospective, randomized, controlled trial conducted to date for a MIGS device. The study was conducted at 38 centers in nine countries and enrolled 556 patients. The trial compared reductions in IOP and anti glaucoma medication use in patients having cataract surgery, with and without the Hydrus Microstent.

The 24 month US cohort data (331 patients), showed that 79 percent of Hydrus Microstent patients achieved a > 20 % reduction in IOP, compared to 55 % in the cataract only group. Hydrus Microstent reduced IOP 50 percent more than cataract surgery alone (7.9 mmHg vs. 5.2 mmHg, a difference of 2.7 mmHg). Table 2 shows some studies showing outcome of Hydrus.

SUPRACHOROIDAL STENTS

Targeting suprachoroidal space is likely to be beneficial as prostaglandins, exert their effect via this route. A negative pressure gradient exists that drives aqueous humor in the direction of the suprachoroidal space. Therefore suprachoroidal stents were created to exploit these characteristics.

CyPass

Cypass Microstent (Alcon) is a micro-implantable device made from a biocompatible material (polyimide). It allows for an ab interno surgical approach, which spares the conjunctiva, does not penetrate the sclera and leaves the trabecular meshwork intact.

Mechanism of action: The device is inserted into the supraciliary space, thereby creating a permanent conduit between the anterior chamber and the supraciliary space. It enables aqueous drainage through the uveoscleral pathway.

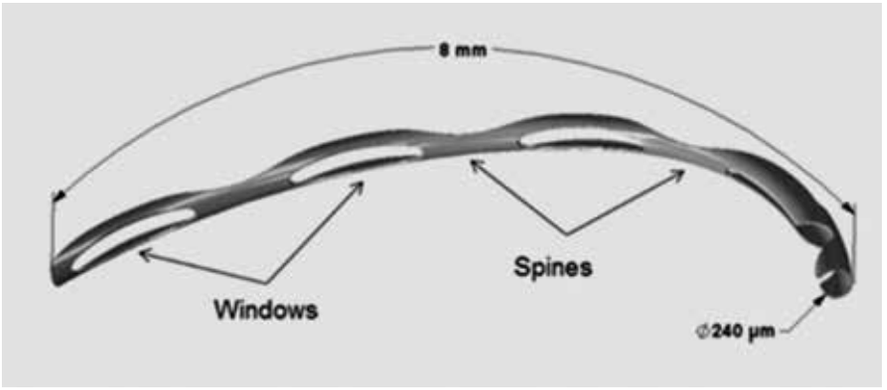

Figure 2: *Hydrus implant*

Figure 3: *CyPass Microstent*

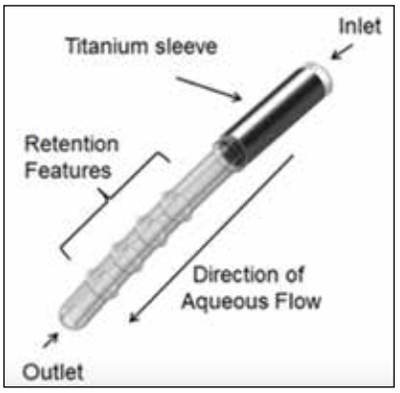

Figure 4: *iStent Supra*

Device Design: This flexible device is 6.3 mm in length and 0.5 mm wide and is introduced by a curved guidewire (Figure 3). It bends to conform to the curved scleral contour during implantation into the supraciliary space. The device has proximal retention rings, that are visible under a goniolens and provide guidance for proper insertion and depth.

Scientific evidence for efficacy and safety

The COMPASS study demonstrated a statistically significant reduction in IOP at two years after cataract surgery combined with the CyPass Micro-Stent implantation vis-a-vis subjects undergoing cataract surgery alone. At two years post-surgery, there was little difference in endothelial cell loss between the CyPass Micro-Stent and cataract surgery-only groups.

The COMPASS-XT study was carried out to gather safety data on the subjects who participated in the COMPASS study for an additional three years, with analysis of the completed data set at five years post-surgery. At five years, the CyPass Micro-Stent group experienced statistically significant endothelial cell loss compared to the group who underwent cataract surgery alone. Therefore, Alcon has recently withdrawn CyPass from global market.

iStent Supra

Device Design: The iStent Supra (Model G3) is made of a biocompatible polymer with a titanium sleeve. It is a 4mm long curved stent with a lumen of 0.165mm (Figure 4).

SUBCONJUNCTIVAL STENTS

The subconjunctival space is the traditional outflow pathway for glaucoma drainage surgery. Continued patency of this pathway for aqueous, and the scarring response in the conjunctiva, determine the successful outcome.

InnFocus

Device design: The InnFocus MicroShunt is made of an ultra-stable synthetic polymer of poly (styrene-block-isobutyl- ene-block-styrene) or SIBS (Figure 5). The MIDI-Arrow or InnFocus MicroShunt, is 8.5 mm long with a 70 mm lumen and a 1.1 mm wide attached fin located 4.5 mm from the anterior tip, which helps secure the device location.

Table 2: Scientific evidence of efficacy and safety of Hydrus

S.No.	Author	Study design	MIGS used	Comparison	No. of Eyes	Follow up	IOP reduction (%) Mean ± SD	Medication reduction at 12 months	Vision loss	Post operative complications	Reoperations needed
Hydrus (Combined)											
1	Pfeiffer, 2015	RCT	HYDRUS combined	Phaco alone	50	24	Hydrus + Phaco: 14.8 ± 23.7 Phaco alone: 14.0 ± 25.5	1.50/ 1.20	None	IOP spikes : 2/50	1/50
Hydrus (Solo)											
2	Gandolfi, 2016	NRS	HYDRUS	Canaloplasty Ab Externo	21	24	37.5 ± 28.0	0.9	None	IOP spike 1/21 Device related 2/21	4/21
3	Fea, 2016	NRS	HYDRUS	SLT	31	12	Hydrus solo: 28.6 ± 24.8 SLT : 31.4 ± 14.2	1.40/ 0.40	None	None	None

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Figure 5: *InnFocus MicroShunt*

Figure 6: *XEN implant in place*

Figure 7: *ExPRESS Glaucoma filtration device*

The InnFocus MicroShunt has been approved in Europe since 2012, but is not yet FDA approved in the USA.

As a fornix-based conjunctival flap and dissection of a shallow scleral pocket is required, it resembles conventional trabeculectomy.

Xen Gel stent

Mechanism of action: XEN is placed in a scleral tunnel created by its beveled needle applicator and terminating just under the conjunctiva. Aqueous humor flows from the anterior chamber through the stent and forms a filtering bleb under the conjunctiva (Figure 6), thus its mechanism of action is akin to trabeculectomy.

Device Design: The Xen Gel Stent is produced from porcine gelatin cross-linked with glutaraldehyde. Three Xen models have been designed, which are all 6 mm in length: Xen140, Xen63, and Xen45 with 140, 63, and 45 mm internal lumen diameters, respectively. The Xen140 offers minimal flow resis- tance and essentially relies entirely on subconjunctival resistance. The Xen63 and Xen45 provide 2–3 mmHg and 6–8 mmHg of outflow resistance, respectively. Xen45 is the primary

Table 3: Some Scientific Evidence for Efficacy and Complications of Xen Implants

S No	Author	Study design	XEN design used	Eyes	Success definition	Complete success	IOP reduction	Medication reduction at 12 months	Vision loss	Intraoperative complications	Post operative complications	Reoperations needed
1	Galal et al.	Prospective, interventional study	XEN45 +MMC : standalone XEN	13	XEN ≥20% IOP reduction without medication/ ≥20% IOP reduction with medication 41.7%	41.7 %	16 ± 4 to 12 ± 3 mmHg (p ≤ 0.01	1.9 ± 1 to 0.3 ± 0.49 (p = 0.003)	None	None	Choroidal detachment (2/13) (transient, resolved at 1 month with medical treatment) Implant extrusion (1/13) (repositioned with conjunctival suturing)	2/13(Trab)
2	De Gregoria et al	Nonrandomised, Prospective, interventional study	XEN45+ MMC Phaco + XEN	41	≤18 mmHg without medication / ≤18 mmHg with medications	80.4 %	16 ± 4 to 12 ± 3 mmHg (p ≤ 0.01)	1.9 ± 1 to 0.3 ± 0.49 (p = 0.003	None	Subcon haem (15/41) Transient ac bleed (10/41) Incorrect position(5/41)	Obstruction/explant (1/41) XEN migration (1/41) Transient hypotony on day 1 (1/41) Transient choroidal detachment with spontaneous resolution at 1 week (1/41)	1/41 (Trab)
3	Fea et al.	Prospective, interventional study	XEN45+ MMC 10: Stand-alone XEN, 2: Phaco + XEN ≤18	12	≤18 mmHg without medication / ≤18 mmHg with medications	50 %	21.8 ± 2.8 to 1414.9 ± 2.1 mmHg (p < 0.001)	2.92 ± 1.16 to 0.50 ± 0.53 (p < 0.001)	None	None	None	1/12 (Trab)
4	Pérez-Torregrosa et al.	Nonrandomised, Prospective, interventional study	XEN45+ MMC Phaco + XEN	30	≤18 mmHg without medication	90 %	21.2 ± 3.4 to 15.03 ± 2.47 mmHg (p < 0.001)	3.07 ± 0.69 to 0.17 ± 0.65 (p < 0.001)	None	Subconjunctival hemorrhage (26/30) AC bleed (26/30) hemorrhage at scleral exit point (27/30) XEN relocation (6/30) XEN reimplantation (1/30)	Encapsulation of filtration bleb (1/30)	None
5	Sheybani et al	Nonrandomised, Prospective, multicentre, cohort trial	XEN140; No MMC Stand-alone XEN	49	≤18 mmHg without medication / ≤18 mmHg with medications	40 %	23.1 ± 4.1 to 14.7 ± 3.7 mmHg (p < 0.001)	3.0 to 1.3 (p < 0.001	None	None	Trace corneal edema (1/13) Shallow AC requiring AC fill (4/49	None

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Table 4: Some Scientific Evidence for Efficacy and Complications for Express Glaucoma Filtration Device

S.No.	Author Year(s) Journal(s)	Study design	Eyes per treatment group	Patient population	EX-PRESS model implanted or trabe-culectomy	Follow up	Success definition, upper limit	IOP success outcomes (complete success without medications)	Visual Acuity results		Post- op Complications	
									Device group	Trabe-culectomy group	Device group	Trabe-culectomy group
1	Dahan 2012 Eye	Prospective, randomized, fellow eye	30	Medically uncontrolled POAG	X-200 Trabe-culectomy	Mean 23.6 ± 6.9 mths	<18 mmHg	Hazard ratio=0.27 (favouring device) P=0.002	Remained stable compared to pre -operative values		Wound leak (7%) Shallow anterior chamber (13%) Hypertony (0%) Hyphema (0%) High avascular bleb (0%) ≥1 complications per eye (20%)	Wound leak (0%) Shallow anterior chamber (20%) Hypertony (20%) Hyphema (7%) High avascular bleb (7%) ≥1 complications per eye(33%)
2	de Jong 2009 Adv Ther, De Jong 2011 Clin Ophthalmol	Prospective, randomized, parallel group	70	Un-controlled open-angle glaucoma; did not have previous ocular surgery (except cataract surgery)	R-50 Trabe-culectomy	3 years 5 years	≤18 mmHg ≤18 mmHg	Device vs trabe-culectomy = 67% vs 41%. P=0.02 Device vs trabe-culectomy = 41% vs 53.9%. P=NS	Improved = 24% Unchanged= 62% Declined= 14%	Improved = 18% Unchanged = 66% Declined = 16%	Shallow anterior chamber (20%) Choroidal detachment (7.5%) Flat anterior chamber (2.5%) Bleb leak (2.5%) Hyphema (0%) IOP spike (0%)	Shallow anterior chamber (12.5%) Choroidal detachment (2.5%) Flat anterior chamber (0%) Bleb leak (5%) Hyphema (5%) IOP spike (2.5%)
3	Beltran-Agullo 2013 Wagschal 2013 J Glaucoma	Prospective, randomized, controlled	64	Un-controlled open-angle glaucoma and trabe-culectomy as planned procedure	P-50 Trabe-culectomy	1 year	NR	Device vs trabe-culectomy = 70% vs 57%. P=NS	Declined in 1st 2 weeks, recovered to baseline at 1 year	Declined wrt baseline	Choroidal effusion (0%) Membrane over tube(3%) Hyphaema (0%) Shunt completely entered AC (3%) Lens opacity (3%) Encapsulated bleb (0%) Epiretinal membrane (0%) CRVO (0%)	Choroidal effusion (3.2%) Membrane over tube (0%) Hyphaema (16%) Shunt completely entered AC (0%) Lens opacity (13%) Encap-sulated bleb (3.2%) Epiretinal membrane (3.2%) CRVO (3.2%)
4	Netland 2014 Am J Ophthalmo	Prospective, randomized, comparative	120	Open-angle glaucoma, history of laser trabe-culoplasty or cataract phaco-emulsion at least 2 months prior to study	P-50 Trabe-culectomy	Upto 2 years	5-18 mmHg	NR	Recovered to baseline in 0.7 months (median time)	Recovered to baseline in 2.2 months (median time)	Shallow AC & choroidal effusion(6.8%) Surgically treated cataract(5.1%) Hyphaema(0%) Early wound leak (3.3%)Dellen (1.7%) Late bleb leak (1.7%) End-ophthalmitis (0%)	Shallow AC & choroidal effusion (11.5%) Surgically treated cataract (11.5%) Hyphaema (9.8%) Early wound leak (4.9%) Dellen (0%) Late bleb leak (1.6% End-ophthalmitis (1.6%)

version utilized worldwide and the only version available in the USA. It softens on contact with water within 1–2 min, meaning that it can bend and conform to tissue, reducing the risk of erosion.

Scientific evidence for efficacy and safety

Table 3 elucidates several studies that show the efficacy and safety profile of XEN.

Transient hypotony, AC shallowing, and choroidal detachment have been reported in few cases, but these are either self resolving or resolve with medication, without any impact on vision. Conjunctival exposure of the XEN Gel Stent is a serious complication, which can be avoided using a meticulous surgical technique to implant the device.

Where does the ExPress Glaucoma Filtration Device fit?

Ex-PRESS glaucoma filtration device

(Alcon Laboratories, Fort Worth, TX, USA) was created to mimic trabeculectomy's IOP control and improve its safety.

Mechanism of action: This non-valved device drains aqueous fluid from the anterior chamber to the subconjunctival space and forms a filtration bleb.

Device Design: Ex-PRESS glaucoma device is made of biocompatible stainless steel with a spur to prevent extrusion of the device and an external backplate to prevent intrusion. The backplate and spur are designed to conform to angle anatomy, and the distance between them approximates that of the scleral tract created by the device (Figure 7).

Ex-PRESS glaucoma device is currently available in two models: an R-model and a P-model.

R-model: It has a beveled tip, an external diameter of 400 microns (27-gauge), an internal lumen of 50 microns, a total device length of 2.96 mm and a uniform back plate.

P-model: This model has a decreased bevel angle; an external diameter of 400 microns, a total device length of 2.64 mm and a vertical channel back plate. It is available in both a 50-micron and 200-micron internal lumen size.

Scientific evidence for efficacy and safety

Compared with trabeculectomy, the EX-PRESS device eliminates the need for both peripheral iridectomy and removal of a deep corneoscleral tissue block, but these advantages are counterbalanced by the need to align the device properly to avoid contact with either the cornea or the iris.

Table 4 shows the compiled data from the four randomised controlled trials comparing EX-PRESS device with trabeculectomy.

Of the four randomized prospective studies comparing IOP-lowering efficacy of the EX-PRESS device with trabeculectomy, only one demonstrated lower long-term IOP with EX-PRESS device implantation.In that study, there was a significant difference in mean IOP between groups up to 3 years, but this difference was no longer significant at years 4 and 5 of follow-up.

The Ex-PRESS device relies on nonphysiologic subconjunctival flow as its mechanism of IOP lowering. As a result, all of the issues that limit trabeculectomy and the complication profile associated with blebs accompany the Ex-PRESS shunt too, but to a much lesser extent.

In a nutshell, Minimally invasive glaucoma surgeries fill a gap that has existed in the treatment algorithm for glaucoma between medical therapy and laser at one end of the spectrum and traditional filtering glaucoma surgeries at the other.

SUGGESTED READING

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Recent Advances in the Management of Glaucoma

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Glaucoma is the leading cause of irreversible blindness in the world[1]. In India, estimated number of cases of glaucoma is around 12 million, and an equal proportion of open and closed angle glaucoma is seen[2].

Glaucoma is defined as a group of chronically progressive optic neuropathies characterized by atrophy of optic nerve, visual field defects and characteristic optic nerve head changes[3]. Risk factors include advanced age, African race, a positive family history of glaucoma, severe myopia and ocular risk factors, such as increased IOP, morphological features of optic disc and thinness of cornea[4,5,6].

The established treatment protocol has been concentrated on lowering IOP to a level at which the progression of glaucomatous damage can be delayed or halted. In recent years, however, a more aggressive treatment approach has been adopted. This change is due to both the availability of more powerful ocular hypotensive agents as well as to the increased understanding of the need to achieve the lowest possible pressure to preserve the visual field.

ADVANCES IN THE MEDICAL MANAGEMENT OF GLAUCOMA

Latanoprostene bunod

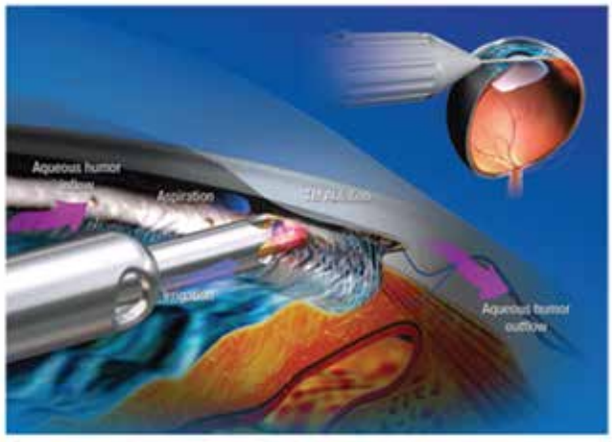
Latanoprostene bunod (LBN) is a nitric oxide (NO) donating prostanoid FP receptor agonist. It is rapidly metabolized in the eye into lataoprost acid, a F2α prostaglandin analogue, and butanediol mononitrate, which subsequently releases NO in conjunction with butanediol, an inactive metabolite[7,8]. Latanoprost acid causes remodelling of the extracellular matrix in the ciliary body, thereby increasing aqueous humor outflow through the uveoscleral pathway and thus decreases the IOP[9,10,11,12]. NO causes relaxation of the trabecular meshwork and Schlemm's canal, resulting in increased aqueous humor outflow[13,14,15,16].

The VOYAGER study, a well-controlled phase 2 study in 413 patients with open angle glaucoma (OAG) or ocular hypertension (OHT) demonstrated a significantly greater reduction in mean diurnal IOP after 28 days of treatment with LBN 0.024% compared with latanoprost 0.005%[17].

Another randomized controlled study (APOLLO study) demonstrated that LBN 0.024% resulted in significantly greater IOP lowering compared with Timolol 0.5%[18].

Rho kinase inhibitor

Rho kinase (ROCK 1 and ROCK 2) is a serine/ threonione kinase that serves as an important downstream effector of RhoGTPase, and plays a role in the regulation of contractile tone of smooth muscle tissue in a calcium independent manner. Modulation of ROCK activity within the aqueous humor outflow pathway using selective inhibitors can be used in the treatment of glaucoma.



The Trabectome tip, moving through Schlemm's canal, ablates trabecular and juxtacanalicular tissues to improve aqueous access to outflow channels and lower IOP.

Figure 1: *Glaucoma surgery using Trabectome*

Inhibitors of ROCK and Rho kinase increase aqueous humor drainage through the trabecular meshwork, leading to decrease in IOP. Further they have been shown to increase the ocular blood flow, retinal ganglion cell survival and axonal regeneration.

A double masked randomized controlled trial in 89 patients with OAG or OHT demonstrated a statistically significant ocular hypotensive effect of 0.05%, 0.1% and 0.25% AR12286, a Rho kinase inhibitor[19].

Another phase 2 randomized clinical study of a Rho kinase inhibitor, K-115, showed a significant ocular hypotensive effect in OAG and OHT[20].

Sustained release drugs

Daily application of topical medications have a negative impact on patient compliance due to poor bioavailability and other long term side effects such as allergy and intolerance to medications, which leads to suboptimal medical management of the disease resulting in poor IOP control[21]. The use of liposomes as biocompatible nanocarriers allows delivery of lipophilic as well as hydrophilic drug molecules, due to its physical structure of a polar core and lipophilic bilayer[22]. Topical application of liposomes have demonstrated poor penetration into the eye[23]. Subconjunctival injections, however, have shown limited sustainability[24].

A study by Natrajan JV et al has revealed that a single subconjunctival injection of latanoprost-loaded Egg PC liposomes effectively lowered IOP in rabbit eyes for at least 90 days[25].

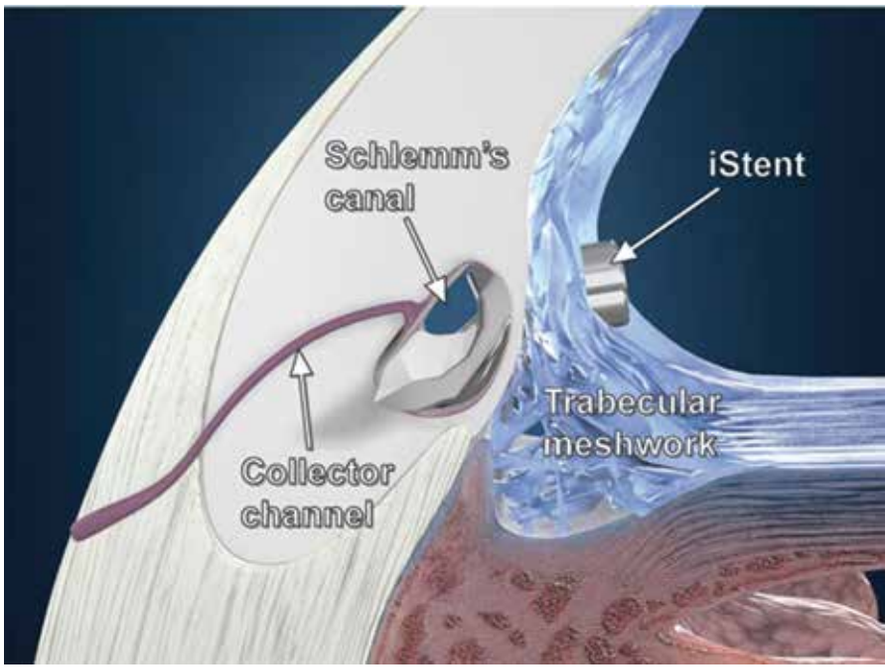


Figure 2: *Glaucoma surgery showing iStent*

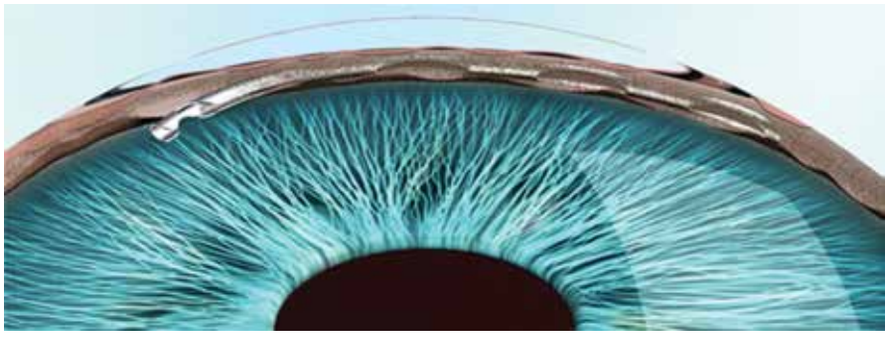


Figure 3: *Hydrus microstent placed in the Schlemm's canal*

Nicotinamide

Recently, the differences in gene expression and total NAD levels have been proposed to affect the functioning of retinal ganglion cells. Williams et al hypothesized that reduced levels do destabilize metabolism during periods of stress and that the age-dependent decline in NAD levels, when combined with stress from elevated intraocular pressure, has a negative effect on mitochondrial function. This compromise in function leads to increases in the metabolism of fatty acids and the generation of free radicals, and thus an impaired response to metabolic stress, which in turn leads to loss of retinal ganglion cells. To test the "NAD-deficit" hypothesis, Williams et al. supplemented the mouse diet with nicotinamide (the amide of vitamin B3 and a precursor to NAD+) to enhance cellular energy production. At the lowest dose studied (equivalent to about 2.5 g per day for a person weighing 60 kg), the authors found that nicotinamide prevented the structural and functional loss of retinal ganglion cells despite the continued elevation of intraocular pressure[26].

ADVANCES IN SURGICAL MANAGEMENT OF GLAUCOMA

Microinvasive Glaucoma Surgery (MIGS)

Traditionally, invasive surgical management of glaucoma is recommended when medication and or laser trabeculoplasty fail to control IOP. Filtering procedures such as trabeculectomy and glaucoma drainage devices, are effective in lowering IOP, but are associated with significant adverse effects and high rates of failure.

MIGS procedures have a higher safety profile with a fewer complications and a more rapid recovery time than other invasive techniques.

MIGS APPROACHES

1. Increasing trabecular outflow
   - Trabectome
   - Istent
   - Hydrus stent
   - Gonioscopy associated transluminal trabeculotomy
   - Excimer laser trabeculotomy
2. Suprachoroidal shunts
   - Cypass microstent
3. Reducing aqueous production
   - Endocytophotocoagulation
4. Subconjunctival filteration
   - XEN gel implant

TRABECTOME

The Trabectome system performs a trabeculotomy via an internal approach. Under the guidance of intraoperative gonioscopy, a disposable 19.5-gauge handpiece with an insulated footplate containing electro cautery, irrigation, and aspiration functions is inserted into the anterior chamber and then through the TM into Schlemm's canal. The device moves along the TM, removing both a strip of TM and the inner wall of Schlemm's canal. Thus a pathway for aqueous outflow from the anterior chamber directly into the collector channels is created[27].

Maeda et al evaluated the outcome of surgeries using Trabectome in 80 eyes of 69 patients. A mean preoperative IOP of 26.6 ± 8.1 mmHg was found to decrease to a mean postoperative IOP of 17.4 ± 3.4 mmHg within 6 months after the surgery. Average number of medications also decreased from 4.0 ± 1.4 to 2.3±1.2 at 6 months[28].

ISTENT IMPLANT

The iStent is a trabecular micro-bypass product that directly connects the anterior chamber to Schlemm's canal and creates a permanent opening into Schlemm's canal. The device is composed of a heparin-coated, non-ferromagnetic, titanium stent, approximately 1×0.3 mm in size, that connects at a right angle to the canal-implanted portion, which has a pointed end. It comes with an inserter, which is guided into a corneal wound, at least 1.7 mm in size, and into the anterior chamber under ophthalmic viscoelastic device (OVD). With the help of a surgical gonioscopy lens, it is implanted into Schlemm's canal with a sideways sliding technique. Like the Trabectome, the iStent reduces resistance in the juxtacanalicular TM.

A prospective randomized clinical trial demonstrated a significant reduction in the mean diurnal IOP and the number of medications[29].

Figure 4: *Gonioscopy assisted transluminal trabeculotomy*

phacoemulsification combined with XEN45 implant surgery in 30 eyes and reported a significant decrease in IOP and the number of medications over a period of 12 months[32].

MINIATURIZED HIGH INTENSITY FOCUSED ULTRASOUND

The ciliary body ablation is still considered as a last resort treatment to reduce the intraocular pressure (IOP) in uncontrolled glaucoma. Several ablation techniques have been proposed over the years, all presenting a high rate of complications, nonselectivity for the target organ, and unpredictable dose-effect relationship. These drawbacks limited the application of cyclodestructive procedures almost exclusively to refractory glaucoma. High-intensity focused ultrasound (HIFU), proposed in the early 1980s and later abandoned because of the complexity and side effects of the procedure, was recently reconsidered in a new approach to destroy the ciliary body.

Several mechanisms of action were proposed to explain the final IOP lowering after HIFU, such as localized destruction of the ciliary-pigmented and nonpigmented epithelium, atrophy of the ciliary muscle, cyclodialysis cleft, and scleral thinning[33,34,35]. Despite encouraging initial evidence, the ultrasound cyclodestruction was used only in advanced and refractory glaucoma, because of the significant risk of complications (scleral staphyloma, corneal thinning, persistent hypotony, phthisis bulbi, and loss of the visual acuity).

Ultrasound circular cyclocoagulation (UC3), by using miniaturized transducers embedded in a dedicated circular-shaped device, permits to selectively treat the ciliary body in a one-step, computer-assisted, and non-operator-dependent procedure. UC3 shows a high level of safety along with a predictable and sustained IOP reduction in patients with refractory glaucoma. Recent studies in patients with refractory glaucoma report encouraging results after UC3 in terms of both IOP reduction and safety of the procedure[36,37,38].

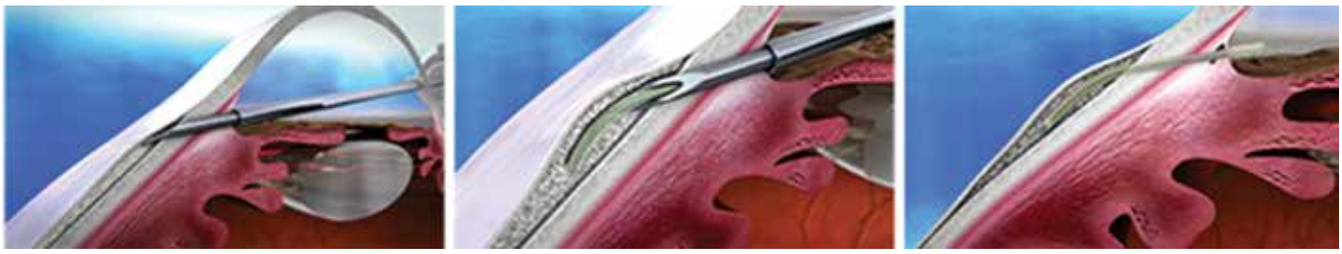


Figure 5: *Placement of a XEN GEL implant in the eye*

HYDRUS IMPLANT

The device is inserted into the Schlemm's canal via a 1-1.5mm clear corneal incision. It dilates the canal by 4-5 times the natural width, thus maintaining patency and establishing outflow.

A study by Pfeiffer et al compared Hydrus microstent with concurrent cataract surgery and cataract surgery alone, and reported that 86% of Hydrus patients had a 20% reduction in the washed out IOP compared to 46% of patients undergoing cataract surgery alone[30].

GONIOSCOPY ASSISSTED TRANSLUMINAL TRABECULOTOMY (GATT)

GATT is a sutureless and conjunctival sparing technique. Under the guidance of gonioscopy lens, a goniotomy is made in the nasal trabecular meshwork through which a microcatheter is inserted. Microsurgical forceps are used to advance the microcatheter in the Schlemm's canal circumferentially 360 degrees. The catheter is then externalized to create a 360 degree trabeculotomy.

Grover et al reported a significant IOP decrease in patients with primary OAG and secondary glaucoma[31].

XEN GEL IMPLANT

It is an ab interno gelatin stent implanted via a clear corneal incision without conjunctival dissection. The stent follows Poisueille's law of laminar flow where the length and the inner diameter of tube manages the rate of flow.

Perez-Torregrosa et al performed

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Secondary Glaucoma After Blunt Trauma

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Summary: *Secondary glaucoma after closed globe injury is a frequently encountered condition. The rise in intraocular pressure after blunt trauma has multiple causes which can be classified as early and late onset. We describe two different scenarios highlighting the early and late causes of raised intraocular pressures. The patients should be examined thoroughly for the underlying etiology and managed accordingly.*

The reported incidence in literature varies from 2-10%, the Indian studies reporting a figure of 4.5%[1,2]. Glaucoma following a closed globe injury can present with raised intraocular pressure (IOP) in early or late postoperative period. The various reasons for early onset IOP rise are inflammation, hyphema, damage to trabecular meshwork, secondary to organisation of blood/inflammatory products, alterations in lens position, phacoanaphylactic glaucoma, increased episcleral venous pressure whereas the various causes of late onset IOP rise are steroid induced, secondary angle closure, angle recession, ghost cell, hemolytic, hemosiderotic, lens subluxtion, lens particle, lens induced uveitis etc[3].

The early identification of underlying etiology is important for appropriate management of raised intraocular pressures and delay/prevent the irreversible glaucomatous damage. We present 2 cases projecting different causes of post-traumatic raised intraocular pressure.

CASE PROFILE

Case 1

A 30 year old male presented with history of trauma to right eye 14 days back followed by acute, painful, diminution of vision. His best corrected visual acuity (BCVA) was hand motion close to face in right eye and Snellen 6/6 in left eye. The IOP was 40 mmHg and 14 mmHg in right and left eye respectively on Tab.Acetazolamide 250 mg, G.Brimonidine 0.2% and G.Timolol Maleate 0.5% in right eye. Slit lamp examination revealed subconjunctival haemorrhage in nasal, temporal and inferior quadrants (Figure 1a). The cornea was clear, with presence of 2 + pigmented cells in anterior chamber (Figure 1b). The pupil was 'D shaped' with multiple sphincter tears (Figure 1a). There was presence of post- traumatic posterior subcapsular cataract (Figure 1c and d).

Gonioscopy revealed angle recession in nasal quadrant and iridodialysis extending about 2 clock hours (11-1 o' clock) in superior angle. The ciliary processes were visible through iridodialysis (Figure 2).

The media was hazy due to cataract but the disc was healthy with cup disc ratio of 0.3. The left eye examination was within normal limits. The patient was given injection Mannitol 2g/kg b.w i/v over 30 minutes. He was started oral steroids (1 mg/kg body weight) with slow tapering every 3 days. He was also given topical steroids, cycloplegic (G. Atropine sulphate) and continued oral and topical antiglaucoma medication. The IOP lowered down in susbsequent visits as the inflammation settled down and the antiglaucoma drugs were gradually tapered over a period of 3 months.

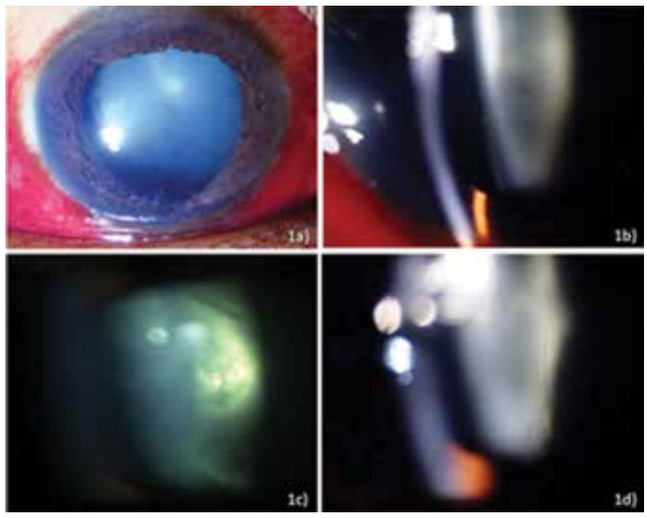

Figure 1

Figure 2

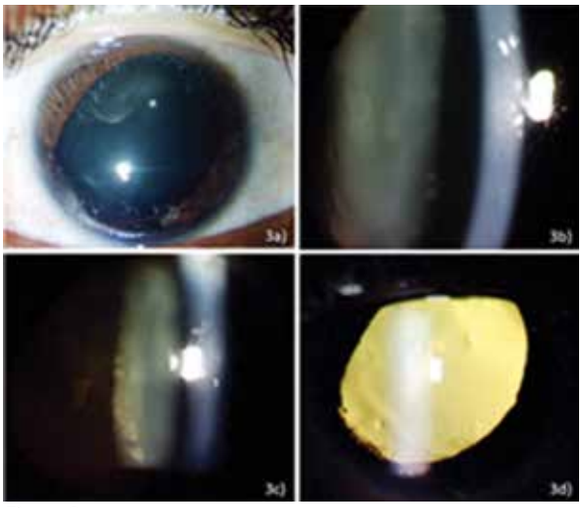

Figure 3

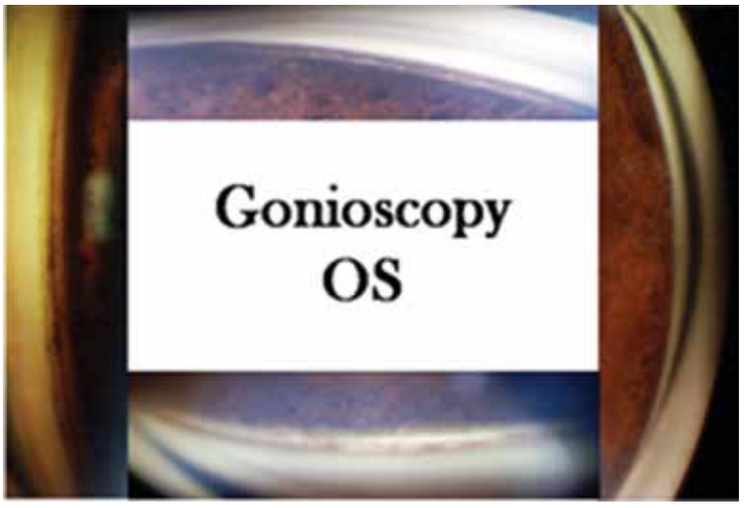

Figure 4

Case 2

A 23 year old male was referred three months after blunt trauma with raised intraocular pressures. His BCVA was Snellen 6/6 in right eye and hand motion close to face in left eye. The IOP was 14 and 50 mmHg in right and left eye respectively on Tablet Tab.Acetazolamide 250 mg, G.Brimonidine 0.2% and G.Timolol Maleate 0.5% in right eye. On slit lamp examination, the conjunctiva was normal. The cornea was clear. The pupil was dilated, non reactive, irregular with presence of multiple sphincter tears and phacododensis (Figure 3a). The anterior chamber depth was non uniform with 3 plus pigmented cells in anterior chamber (Figure 3b). Posterior subcapsular cataract was seen (Figure 3c). On retroillumination, yellow glow was appreciated (Figure 3d).

Gonioscopy revealed pigmented angles and angle recession in 2 quadrants (superior and inferior) (Figure 4).

Ultrasound examination showed the presence of pin point and dense hypereflective echoes suggestive of vitreous hemmorhage. A provisional diagnosis of Khaki cell glaucoma (ghost cell glaucoma) was made. The patient was taken up for L/e Pars plana lensectomy and vitrectomy. The IOP lowered down and the antiglaucoma medication was weaned off in next two months.

COMMENT

Secondary Glaucoma following closed globe injury occurs due to coup-countercoup injury. Thorough clinical examination in case of trauma includes evaluation of 'seven rings of trauma': pupillary tears, iridodialysis, angle recession, cyclodialysis, meshwork tears, ruptured zonules and retinal dialysis. Increased pigmentation of the angle, elevated baseline IOP, hyphema, lens displacement and angle recession of more than 180 degrees are some of the early predictors which are significantly associated with the occurrence of chronic glaucoma after closed globe injury[4]. In a study comparing the outcome of glaucoma after penetrating and closed globe injury, 58% of the eyes with history of penetrating trauma required glaucoma surgery, whereas only 12% of the eyes in the group with blunt trauma in history underwent a glaucoma surgery during follow up. The time of surgery in the eyes with a penetrating trauma in history was after sixth month of follow-up. But in 64% of eyes in the group with blunt trauma in history, early surgical intervention were needed[5]. Early onset raised IOP is more commonly due to trabeculitis and need to be managed with steroids and cycloplegic agents. For late onset IOP rise, patient should be thoroughly examined for underlying etiology and managed accordingly.

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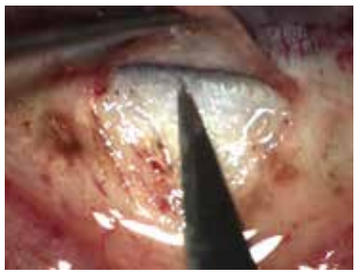
DOS Times Quiz 2018-19

Episode-3

Last date: Completed responses to reach the DOS Office by e-mail or mail before 5 pm on 28th February 2019

Q1. What is the external surgical landmark and its corresponding internal angle structure for the site of entry into the anterior chamber in trabeculectomy surgery?

A) Gray zone, trabecular meshwork
B) Gray-white junction, Scleral spur
C) Just anterior to blue gray junction, Schwalbe's line
D) Blue zone, Trabecular meshwork
E) White sclera, Ciliary body band

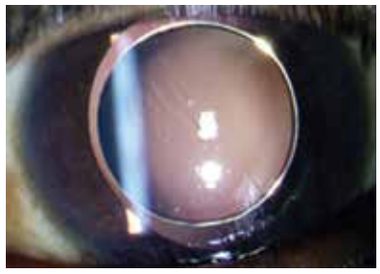


Q2. Which of the following antiglaucoma drug is used as a treatment for nystagmus?

A) Timolol B) Brinzolamide C) Latanoprost D) Brimonidine E) Pilocarpine

Q3. Which of the following is true about the condition shown in the picture?

A) Laser PI may not be helpful in this condition
B) This condition is associated with deep anterior chamber
C) It is always familial and associated with systemic abnormalities
D) Miotics if given in this condition can cause inverse glaucoma
E) It is associated with hypermetropia and subluxation



Q4. Identify the finding and the conditions associated?

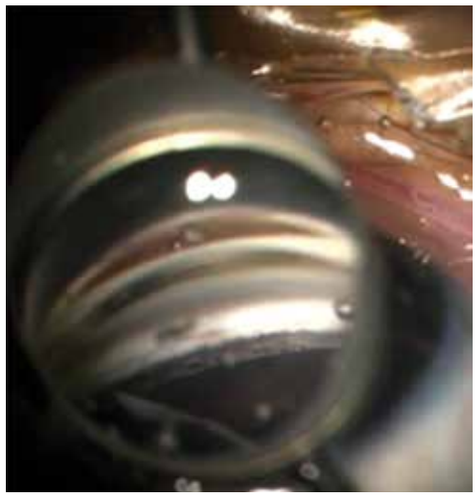
Q5. What is the treatment of choice of the condition shown in the left eye of the photograph below?

A) Cyclodestructive procedures
B) Goniotomy
C) Trabeculotomy with trabeculectomy
D) Glaucoma Drainage device
E) Medical management

Q6. All of the following are true about Frequency doubling perimetry except?

A) It is done to diagnose early defects of glaucoma.
B) It tests the M subtype of retinal ganglion cells, which constitute 15 % of the total RGCs.
C) Test area is divided into squares.
D) Time taken for the test to be completed is faster than standard automated perimetry.
E) Test stimulus involves high spatial frequency sinusoidal grating with a low temporal frequency.

Q7. Identify the lens and the procedure?



Compiled by:
Dr. Madhuri Akella
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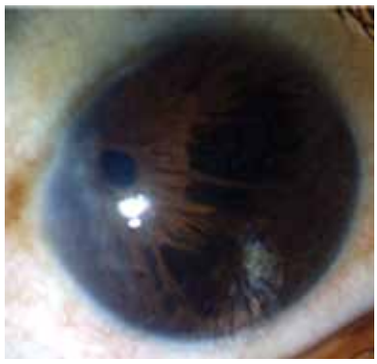
Q8. A 61 year old female presents with the following finding on optic disc evaluation. Which of the following statement is true?

A) This finding is most commonly seen in eyes with ocular hypertension
B) It is specific for glaucoma and indicates progression
C) IOP control is not likely to be beneficial in the management and systemic BP should be monitored
D) Visual field defects are more likely to be present closer to the fixation point in the superior hemifield
E) It is most commonly seen on the temporal aspect of the disc and precedes diffuse neuroretinal rim loss and peripapillary atrophy.

Q9. Which of the following is a conclusion of tube versus trabeculectomy study (TVT)?

A) Tube shunt surgery was associated with a greater IOP reduction than trabeculectomy with MMC
B) Higher early post-operative complications were seen with Trabeculectomy with MMC as compared to tube shunt surgery
C) Additional glaucoma surgery was needed more commonly after tube shunt surgery than trabeculectomy with MMC
D) Trabeculectomy with MMC was associated with higher success rate than tube shunt surgery
E) The rates of reoperation for complications and cataract extraction were observed to be higher in the trabeculectomy group.

Q10. Which of the following gene has been associated with the condition shown in the image



A) PITX2
B) CYP1B1
C) TIGR
D) PAX6
E) LOXL1

DOS Times Quiz Rules

1. DOS Times Quiz will now feature as **5 Episodes** (Episode 1: July-August, Episode 2: September – October, Episode 3: November – December, Episode 4: January – February, Episode 5: March – April). Entries will have to be emailed before the last date mentioned in the contest questions form. Late entries will not be entertained.
2. Please email (as scanned PDF Only) completed responses for the quiz along with details of the contestant **filled in and signed** to dostimes10@gmail.com (with cc to dosrecords@gmail.com) or mail to DOS Times Quiz, Dr. Subhash Dadeya, Room No. 114, 1st Floor, OPD Block, Guru Nanak Eye Centre, Maharaja Ranjit Singh Marg, New Delhi.
3. Nonmembers may also send in their entries but will be required to send along with their completed entries, the completed membership application (with the required documents) to enroll as member. Failing this their entries into the contest will not be considered.
4. Contestants are requested to attempt all the 5 episodes of the Quiz contest and send in their applications within the date specified. No entries will be entertained after the last date. The scores of each contestant for all 5 episodes together will be compiled at the end of episode 5 and the winner will be announced in the DOS Annual Conference in April 2019. In the event of more than one winning contestants, a draw of lots will decide the winner. Winner of each episode will also be published in the next episode along with the previous episode answers.
5. Please write to dostimes10@gmail.com or dosrecords@gmail.com for further clarifications if any.

Q. No. Completed Responses for DOS Times Quiz: Episode 3

1. _____ 6. _____
2. _____ 7. _____
3. _____ 8. _____
4. _____ 9. _____
5. _____ 10. _____

Contestant Details

Name: _____ Degree: _____

Designation:_____ Address:_____

_____ State _____ Pin _____

Mobile No: _____ DOS Membership no: _____

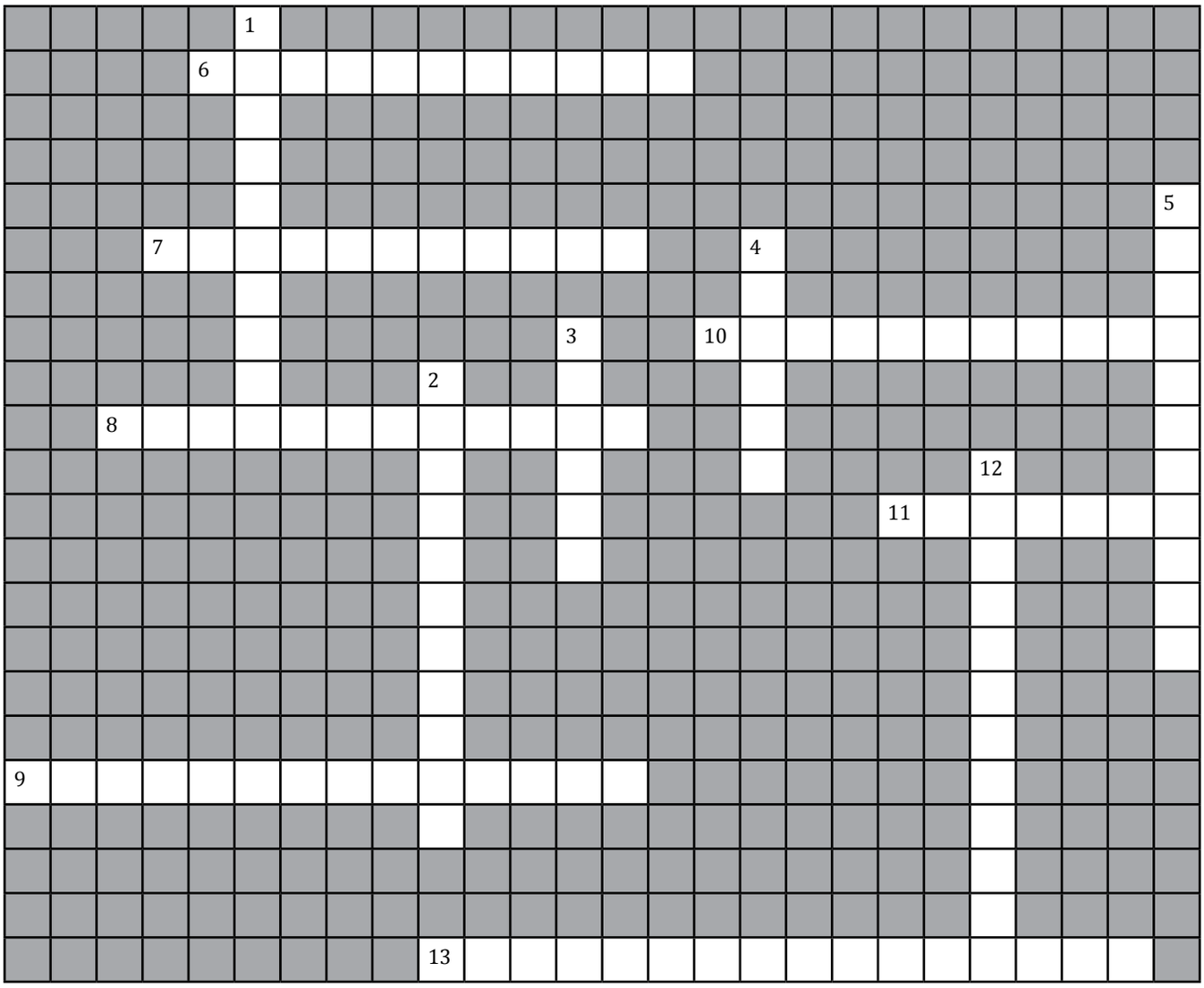
Email ID: _____Signature: _____

DOS Crossword

Episode-3

Correspondence to:
Dr. Madhuri Akella
Senior Resident, PGIMER, Chandigarh, India

Fill the boxes below with the most appropriate answers by using the hints below



ACROSS

6. A syndrome associated with nodular pigmented iris lesions(11)
7. Double hump sign is seen in this condition(11)
8. Pigment deposition at lens periphery in PDS(12)
9. A component of "Vogt's triad"(14)
10. Drug with maximum propensity to cause allergic conjunctivitis(11)
11. A tonometer used in children(7)
13. A condition characterised by white eye and recurrent attacks of unilateral raised IOP with mild anterior chamber inflammation(16)

DOWN

1. A drug which can cause secondary angle closure glaucoma(10)
2. A condition associated with unilateral redness, ipsilateral glaucoma and hemiplegia(11)
3. MIGS implant withdrawn from market recently(6)
4. Translucent tissue like membrane thought to be present in angles in primary congenital glaucoma(6)
5. Anatomical structure thought to be a dividing point between structures of aqueous outflow and inflow(11)
12. A mechanism of glaucoma in uveitis(12)

Newer Antiglaucoma Medications

Name of drug	Class of drug	Mechanism of action	Dosage	Mean IOP lowering effect in phase II/III trials	Adverse effects
Rhopressa™ (Netarsudil ophthalmic solution 0.02%) [AR 13324; Aerie Pharmaceuticals, North Carolina, USA]	Rho kinase inhibitor and norepinephrine transporter (NET) inhibitor	Improved outflow through the trabecular meshwork and the uveoscleral pathway, decreasing episcleral venous pressure, and decreasing aqueous production	OD (Bedtime)	5.5 mm Hg	Conjunctival hyperemia, conjunctival hemorrhage, and cornea verticillata.
Roclatan™ (Fixed-dose combinations of netasurdil with latanoprost 0.005%)	Rho kinase inhibitor and norepinephrine transporter (NET) inhibitor plus prostaglandin analogue	Improved outflow through conventional and uveoscleral pathway	OD (Bedtime)	Average reduction in IOP of 1.8mmHg greater than those receiving latanoprost, and 2.7mmHg greater than those receiving Rhopressa.	Conjunctival hyperemia, Instillation site pain, cornea verticillata.
Glanatec™ (Ripasudil 0.4%; K-115, Kowa Ltd, Nagoya, Japan)	Rho-associated coiled-coil-forming protein kinase (ROCK) inhibitor	Selective inhibition of the actin cytoskeleton contractile tone of smooth muscle in the trabecular meshwork; resulting in increased aqueous outflow directly through the conventional pathway.	BD	2.7-3.7 mm	Conjunctival hyperemia
Trabodenoson (INO 8875) (Inotek Pharmaceuticals, USA)	Adenosine A1 receptor agonist	Alters ECM turnover by TM cells and increases conventional outflow facility	500mcg	4.1mm Hg	Conjunctival hyperemia
CF-101 (Can-Fite Biopharma)	Adenosine receptor A3 agonist.	Stimulate secretion of (MMPs) in the endothelial cells lining the trabecular meshwork causing cell volume shrinkage and extracellular matrix remodeling, which ultimately facilitates conventional aqueous outflow.	1 mg BD oral	1.1. (12 weeks)	Constipation Headache Palpitations
DE-117 (Santen Pharmaceutical, Japan)	EP2 agonists Prostanoid receptor agonist	Relaxation of endothelial cells in the Schlemm's canal→ Facilitating uveoscleral outflow. Increase conventional outflow by decreasing cell contractility and collagen deposition	OD	Phase III ongoing 7.1 ± 1.8 mmHg	Conjuntival hyperemia ocular hyperaemia, photophobia

Name of drug	Class of drug	Mechanism of action	Dosage	Mean IOP lowering effect in phase II/III trials	Adverse effects
Taprenepag isopropyl (PF-04217329)	EP2 agonist	Facilitates uveoscleral outflow by decreasing cell contractility and collagen deposition	BD	Phase II; 30-50 % decrease in mm hg	Conjunctival hyperemia dose-related iritis Increased corneal thickness
ONO-9054; 0.003% (Ono Pharmaceuticals, Japan)	EP3 agonist and FP receptor agonist	Facilitates uveoscleral outflow	OD (Evening) 30mcg/ml	7.3 mm Hg 28-31% IOP reduction	Hyperemia Dry eye
Bamosiran (SYL040012) (Sylentis, Spain)	Small-interfering RNA	Specific gene silencing and causes beta-2 adrenergic receptor blockade→ Decreasing aqueous production	OD 600 µg/eye/day	Phase IIb 20% reduction of IOP in individuals with a higher baseline IOP	Darkening of the iris color, lash growth, periocular pigmentation, and hyperemia
Vyzulta™ (Latanoprostene Bunod, 0.024%)	Prostaglandin F2-alpha analog and nitric oxide	Enhances uveoscleral outflow by upregulating MMP's and remodeling of the ciliary muscle's ECM Linked to an NO-donating moiety enhances conventional outflow by inducing cytoskeletal relaxation via the soluble guanylyl cyclase-cyclic guanosine monophosphate (sGC-cGMP) signaling pathway	OD	7.5 -9 mm Hg (22 % IOP reduction)	Conjunctival hyperemia (5.9%), Eye irritation (4.6%); Eye pain (3.5%).
Mikeluna™ (OPC-1085EL; Otsuka Pharmaceutical Co., Ltd.)	Carteolol hydrochloride 2%, and the prostaglandin analog, latanoprost 0.005%	Reduce aqueous production and increase uveoscleral outflow	OD (Morning dose)	Phase III (3.5 mm Hg)	Conjunctival hyperemia, Blepharal pigmentation, and punctate keratitis

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