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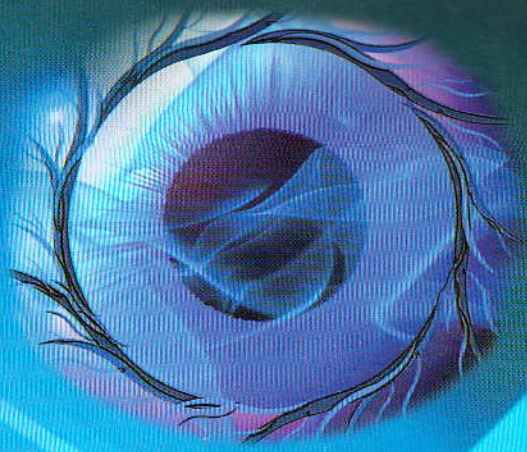

Chief Editor - Dr. Abhishek Chandra

The Scientific Journal of U.P. Ophthalmological Society

U.P. JOURNAL OF OPHTHALMOLOGY

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From the Editor's Desk...

Dear Colleagues,

It is my privilege as Editor, UPJO to bring forth the second edition volume of UP Journal of Ophthalmology in 2016. This time we have included few newer innovations in Ophthalmology such as Argus II retinal prosthesis system and Ray Trace which would apprise our readers about the use of technology in Ophthalmology.

I am happy that this time we got a great response from Ophthalmologists all over the country including those from Karnataka, Maharashtra, Rajasthan and North East. Although I tried to accommodate as many articles as possible, but still I had to refuse almost half of those articles which were not approved by the reviewers. This shows the keen interest people are taking in UP Journal of Ophthalmology. I give my special thanks to the reviewers especially Dr. Kshama Dwiwedi, Dr. Tirupati Nath, Prof. O.P.S.Mauyra, Dr. Shalini Mohan and Prof. S.P.Singh for their comments and help for this journal.

I also express my thanks to the editorial team who have worked hard in the short span of time to bring this issue in time. I would also like to thank various pharma companies especially Pharmatak, who have contributed for this journal and without whose support this issue would not have been possible.

I thank once again all the members of UPSOS and the Ophthalmologists who have contributed for this edition of UPJO. I am sure with their continued support, the UP Journal would continue to grow in readership and quality of research.

(Abhishek Chandra)

Editor, UP Journal of Ophthalmology
Director, Chandra Eye Care
Varanasi

Contents

ARGUS II Retinal Prosthesis System: Which patients will benefit and which will not

Prof. (Dr.) S. Natarajan *

A retinal prosthesis is a biomedical implant intended to restore useful vision to people who have lost their vision due to retinitis pigmentosa (RP), which severely damages the photoreceptors in the eye. In a healthy eye, the photoreceptors (rods and cones) in the retina convert light into tiny electrochemical impulses that are sent through the optic nerve and into the brain, where they are decoded into images. If the photoreceptors does not function correctly the first step in this process is disrupted, and the visual system cannot transform light into images. This lead to blindness in patients with RP.

The first effort to partially restore vision in blind eyes with the help of a prosthesis (connected to the visual pathway) was tried in the first half of the 20th century. Then in 1968, the first long-time implanted device was reported. It was a collection of 80 electrodes implanted in contact with the occipital pole of the right cerebral hemisphere to obtain perception. However, although surface and intracortical stimulation showed promising preliminary results, significant drawbacks were found later. Then the research was focused on devices capable of interacting directly with the retina rather than with the brain.

Thereafter, a number of epiretinal and subretinal implants have been developed. Among these, the Argus II Retinal Prosthesis System (Second Sight Medical Products), originally developed by Mark Humayun, MD, PhD, and colleagues at the Doheny Eye Center at the University of Southern California, aims to provide partial restoration of vision to patients who had lost vision from outer retinal degenerative disease (1). For this innovation, Dr. Mark Humayun received the prestigious National Medal of Technology and Innovation.

In a press release issued by the White House, Obama stated, "Science and technology are fundamental to solving some of our nation's biggest challenges. The knowledge produced by these Americans today will carry our country's legacy of innovation forward and continue to help countless others around the world. Their work is a testament to American ingenuity."

Humayun, who is one of nine recipients of the medal in 2016, was chosen for his lifelong dedication to bridging medical science and engineering to restore sight. He holds more than 100 issued patents and patent applications — most in the area of bioimplants for ophthalmology. His innovative work is best exemplified by the development of the Argus II, the only Food and Drug Administration-approved retinal prosthesis system that allows those with certain blinding diseases to regain some useful vision.(2)

The ARGUS II is a new hope for RP patients. The Argus® II Retinal Prosthesis System ("Argus II") is also known as the bionic eye or the retinal implant. The Argus II was developed by Second Sight Medical Products, Inc. of Lausanne, Switzerland and Sylmar, California, to treat adults with severe to profound RP. RP is a rare, inherited degenerative disease that damages light-sensitive cells in the retina, resulting in decreased vision at night or in low light; loss of side (peripheral) vision; and loss of central vision as the disease progresses. At present, there is no cure for RP (3).

The Argus II is intended to provide electrical stimulation of the retina to induce visual perception in blind individuals with severe to profound retinitis pigmentosa. It provides electrical stimulation of the retina to induce visual perception in blind individuals. A miniature video camera housed in the patient's glasses captures a scene. The video is sent to a small patient-worn computer where it is processed and transformed into instructions that are sent back to the glasses via a cable. These instructions are transmitted wirelessly to an antenna in the retinal implant. The signals are then sent to the electrode array, which emits small pulses of electricity. These pulses bypass the damaged photoreceptors and stimulate the retina's remaining cells, which transmit the visual information along the optic nerve to the brain, creating the perception of patterns of light. Patients need to learn to interpret these visual patterns. (4)

Description of ARGUS II

The Argus II System consists of an active device implanted on and in the eye and external equipment worn by the user.

Director, Aditya Jyoti, Eye Hospital, Mumbai

The implanted portion of the system includes a receiving antenna and an electronics case that are fixed outside the eye with sutures and a scleral band, and an intraocular 6 10 electrode array that is tacked over the macula epiretinally (i.e., on the retinal ganglion cell side). The external portion of the system includes a glasses-mounted video camera and a small video processing unit (VPU) that can be worn on a shoulder strap or belt. The camera collects visual information and sends it to the VPU, which down-samples and processes the image. Several buttons on the VPU allow user control of various image-processing algorithms, for example, enhancing contrast. Data and power are sent wirelessly from a transmitting antenna on the glasses to the internal receiving antenna. The electrodes in the array emit pulses of electricity whose amplitude corresponds to the brightness of the scene in that location. Stimulation of the remaining retinal cells induces cellular responses that travel through the proximal visual system, resulting in visual percepts that subjects learned to interpret.

Surgical Procedure

Subjects received the Argus II Retinal Prosthesis System in the worse-seeing eye. To implant the device, a 360-degree limbal conjunctival peritomy was performed. The rectus muscles were isolated, and the coil was inserted temporally on the globe and centered under the lateral rectus muscle. The electronics package was centered in the superotemporal quadrant. The inferior part of the scleral band was passed under the inferior and the medial rectus muscles, and the superior portion of the band under the superior rectus muscle. The implant was fixed to the eye via sutures passed through suture tabs on the implant in both temporal quadrants, and a Watzke sleeve (Labtician Ophthalmics, Inc, Oakville, Ontario, Canada) and mattress sutures or scleral tunneling were used to secure the scleral band in the nasal quadrants. A core and peripheral vitrectomy were conducted. The array was then inserted through a temporal sclerotomy. The electrode array was placed on the retina in the macular region and then tacked using a custom retinal tack (Second Sight Medical Products, Inc, Sylmar, CA). The extraocular portion of the cable was sutured to the sclera, and all sclerotomies were closed. An allograft (or suitable alternative in countries where allografts were not permitted) was fixed over the device to reduce the likelihood of conjunctival irritation. Finally, the Tenon's capsule and the conjunctiva were closed. (5)

The 5-year results of the Argus II trial support the long-term safety and benefit of the Argus II system for patients blind as a result of retinitis pigmentosa (RP).In this study (6), 30 patients at 10 centres were studied. However, performance data could be gathered only for 20 patients at 5 years. Visual function and functional vision assessments indicated continued efficacy of the Argus II up to 5 years of implantation. Patients are still able to locate objects, determine the direction of moving bar motion and perform an acuity task better with Argus II than when using only residual vision.

Who will benefit from Argus II System?

Argus II is currently approved and intended for use in patients with severe to profound retinitis pigmentosa (RP) who meet the following criteria:

- Adults, age 25 years or older
- Bare light or no light perception in both eyes. (If the patient has no residual light perception, then evidence of intact inner layer retina function must be confirmed.)
- Previous history of useful form vision.
- Aphakic or pseudophakic. (If the patient is phakic prior to implant, the natural lens will be removed during the implant procedure.)
- Patients who are willing and able to receive the recommended post-implant clinical follow-up, device fitting, and visual rehabilitation.

The Argus II is intended to be implanted in a single eye, typically the worse-seeing eye.

Possible Benefits of the Argus II System:

1. The Argus II System may help patient to do tasks visually, rather than by touch.
2. Some subjects can locate lights and windows, follow lines in a crosswalk, or avoid running into things as they walk.

3. Some patients could sort laundry or determine where other people were located in a room.
4. Some patients can read large letters or short words.
5. A few subjects were able to read smaller letters and short words. In addition, many subjects reported enjoying seeing light and motion after being blind for many years and having a greater feeling of connection to their environment and to other people.

Limitations of Argus II System:

1. The Argus II System provides a form of vision that differs from the vision patient used to have.
2. It does not restore normal vision. When the patient is not using the Argus II System, vision will return to its original impaired state.
3. It does not slow or reverse the progression of your disease.
4. It will not replace patient's normal visual aids. (7)

Who will not able to benefit?

1. Some patients who are allergic to Argus II materials
2. Currently the Argus II system is developed only for RP. Patients with other retinal diseases may not able to benefit from Argus II system.

Despite its limitations, Argus II system has brought hopes to hundreds of people living in dark and waiting for a scientific breakthrough which can possible them to see this beautiful world.

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RAY TRACING TECHNOLOGY: A BOON FOR REFRACTIVE SURGEONS

- SONAI MUKHERJEE*

The goal of refractive surgery is to provide the patient with his or her best possible visual performance. To obtain this optical quality, surgery (eg, corneal ablation, IOL implantation, etc.) must change the refracting structures of the eye. Accurate methods of calculation are required to achieve satisfactory surgical outcomes. In ophthalmology, traditional planning methods for IOL power calculations or corneal laser ablation profiles are based on simplified formulas that are derived from paraxial optics. These formulas fail to consider the eye's multiple lenticular structures, or they may incorporate addition theorems for small aberrations in cases where they are not valid. Already somewhat theoretical, such formulations were found to incompletely correct some types of aberrations or to induce errors, specifically in eyes of atypical size or with preexisting aberrations.

Even the planning of refractive treatments using wavefront technology, which is known to measure the entirety of the eye's optical characteristics, is based on an approximation. It is presumed that the total measured wavefront aberration of a multilens system can be compensated for by applying the corresponding correction profile to a single refractive surface of the system without further adjustments of the profile. This is not exactly the case.1 In fact, these assumptions limit the accuracy of today's planning methods and therefore limits their applicability for future fields of interest. Aspects of these calculations, however, can be addressed easily by the ray-tracing method.

RAY-TRACING METHOD

Ray tracing is a computer-based method used to calculate an ablation profile for a refractive laser by incorporating data derived from several types of measurements. By considering all optical surfaces of the eye, such as the back and front surfaces of the cornea and the crystalline lens, ray tracing offers the highest possible accuracy to improve the refractive predictability of corneal laser surgery or lens implantation both in terms of predictability (accuracy) and safety (lines of best-corrected visual acuity (VA) either lost or gained).2

The highest possible accuracy in ablation profile planning can only be achieved by taking all of the optical structures in the patient's eye into consideration. With the advent of partial coherence reflectometry (similar to IOL Master technology for calculating IOL powers) the intraocular structures and dimensions can now be measured with extreme accuracy.

The ray tracing ablation profile is calculated using the following data:

1. Wavefront maps of the optics of the entire eye are collected with a Tscherning Wavefront Analyser.
2. Topographical corneal data is collected with the Pentacam (Oculus GmbH, Germany) or Allegro Oculyzer (WaveLight GmbH, Germany).
3. Posterior corneal surface data is collected by the Pentacam or Allegro Oculyzer.
4. Biometric data such as corneal pachymetry, anterior chamber depth, lens thickness, and axial length are all collected by the Allegro BioGraph (WaveLight GmbH, Germany)

The current ray tracing study protocols use the Scheimpflug principles of the Pentacam and/or Allegro Oculyzer to obtain both anterior and posterior corneal surface data . Based on the Optical Low Coherence Reflectometry (OLCR) measuring principle, the Allegro BioGraph is a multifunctional biometry device used to determine the axial dimensions of the eye, as well as the complete anterior segment. This optical

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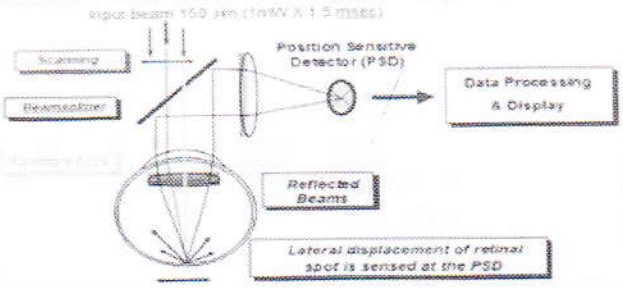
system will combine future technologies with established biometry applications. Its applications include central corneal thickness measurement, anatomic anterior chamber depth measurement, axial length measurement, central lens thickness measurement, retina thickness measurement, keratometry, 'white to white' measurement, and pupillometry (Figure 3). It also measures the patient's visual-optical line to the fovea, which leads to improved VA when compared to calculations based on the theoretically-derived optical axis from the Gullstrand schematic eye.



RAY TRACING ABERROMETRY

Ray tracing concept:

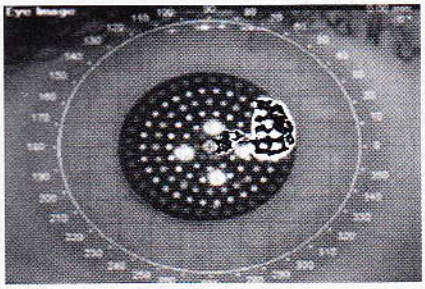
Aberrometry based on the principle of Ray Tracing is, a two-step, serial technique that uses forward projection and which can be used either subjectively or objectively. The ray tracing method uses a laser beam parallel to the line of sight through the pupil. It measures the exact location where the laser beam reaches the retina by means of the retro-reflected light captured by reference lineal sensors X, Y. Local aberrations in the path of the laser beam through the cornea and the internal structures cause a shift in the location on the retina. Once the position 1 has been determined the laser beam is shifted to another position, which is then located in the retina. This process continues until several separated points are projected into the entrance pupil. This way a connection is obtained between the direction that the light beams have taken while entering and leaving, allowing a reconstruction of the real wavefront error. This principle measures «forward» aberrations of the light that goes through the eye. It is more physiological to measure these anterior aberrations as the natural trajectory of the light in the eye is analysed.

The only aberrometer that is commercialised for clinical use is the iTrace (Tracey Technologies, Houston, Tx). The iTrace uses this fundamental principle of Ray Tracing where a sequential series of infrared beams on the order of 100 microns and a 785 nm wavelength each is projected into the entrance pupil parallel to the eye's line of sight.

In Figure 2, a diagram of the Ray Tracing technique developed by Tracey Technologies is shown.

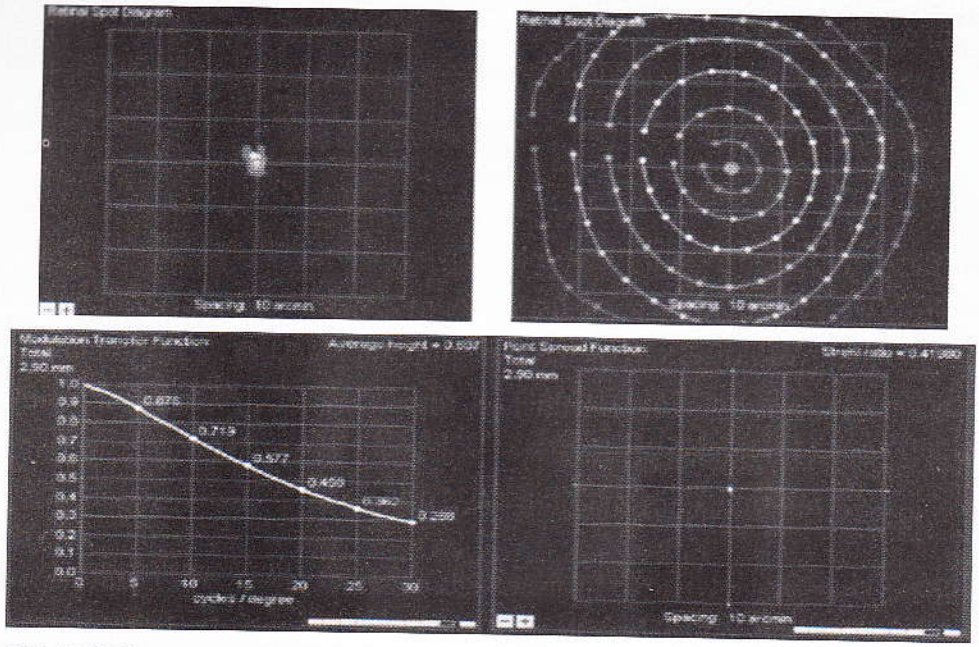
This process continues until 64 laser beams have been projected through the entrance pupil 4 times each (256 points) at high speed (approximately 250 milliseconds). Each of these points represents the entrance of parallel light rays into the eye, which become refracted by the eye's optical power and eventually focus on the retina. If the eye were emmetropic, all 256 points would be concentrated at a single point in the centre of the macula. In other words, the fovea is represented by the conjugate focal point of the system. Generally, local aberrations at the beam's entry point on the cornea or the lens cause a shift in the location on the retina with respect to a position of reference.

The iTrace uses a pattern of concentric rings (fig. 3).



Retinal Spot Diagram (RSD) Concept. Obtaining PSF and MTF When a set of points is sequentially projected in the entrance pupil a retinal spot diagram (RSD) is created. The RSD contains all the information related to the patient's refraction, aberrations and point spread function (PSF). Analysing the RDS's morphology, we get an idea of the degree of the wavefront's qualitative aberration (fig. 4). The smaller the RSD the higher the concentration of photons that reaches any point of the retina.

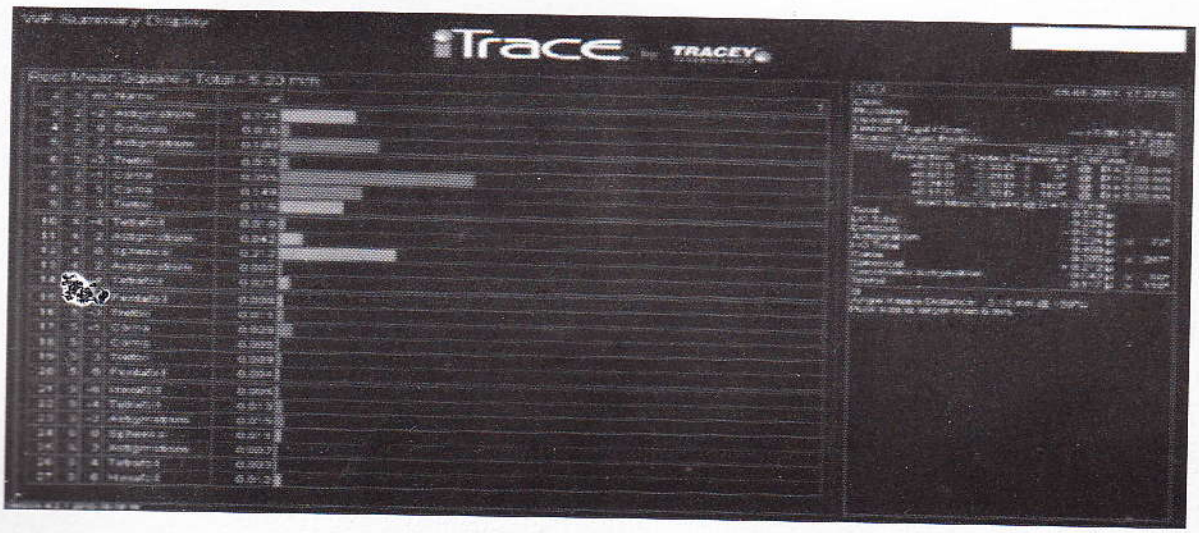
From the RSD we obtain the PSF (Point Spread Function). PSF shows the image obtained in the retina when the patient sees the source of a point of light. The smaller and the sharper the better. The MTF describes how the optical system reproduces detail from the object to the image produced by the lens; therefore, both the MTF and PSF help to describe the optical system's ability.



BASIC DATA GRAPHS WITH THE i-TRACE

– Wavefront map Total and High-order Aberrations (HOA) (Wavefront Total and Wavefront HOA).

– The ***RMS (Root Mean Square)*** is the measurement of the magnitude of the aberration. A total RMS value for the total aberration of the eye and a specific value of RMS for each Zernike term or component of the eye aberrations can be obtained.



– ***Total refractive and HOA refractive maps.***
Emmetropia is represented in green. Myopia in red and hypermetropia

in blue . This map in combination with the topographic one can indicate if the astigmatism is purely corneal or if it has a lenticular component.

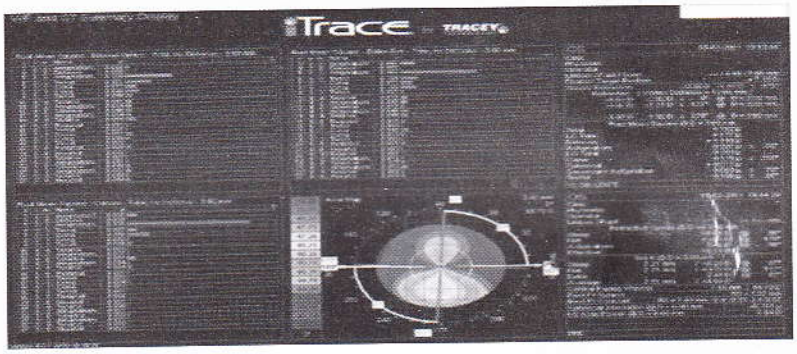
– ***PSF Total and HOA PSF. PSF (Point Spread Function)*** is a figure of merit representing the quality of the image of an optic system, determined by the aberrations to a simple point of light.

– ***Snellen Letter Total and high-order aberrations (HOA).***

The Snellen Letter («E») is a simulation of the iTrace system based on an estimate mathematically derived (convolution) from how the eye «would see» the letter «E» projected in different sizes such as 20/20, 20/40, 20/100 and 20/200.

– ***Zernike polynomials.*** It is a bar graph and a table of the terms or polynomials of Zernike, which show a detailed analysis of the specific aberrations in an eye.

The iTrace shows the Zernike polynomials up to the 6th order (27 terms) and can show the totals for the eye («Total»), only the corneal and the difference between the corneal and the totals (internal optics) figure x)



– **Aberration of internal optics analysis.** Wavefront combined analysis and corneal topography.

This graph provides us with very valuable information unique to the iTrace system. Through corneal topography the corneal aberrations map can be mathematically generated and these aberrations can be adequately subtracted from the total aberrations of the entire eye (fig. x1). The resulting difference obtained by subtracting the corneal aberrations from the total aberrations mainly represents the aberrations of the internal optics; in this way aberrations from the cornea can be separated from those from the interior of the eye. Most of the aberrations of the internal optics are induced by the crystalline lens.

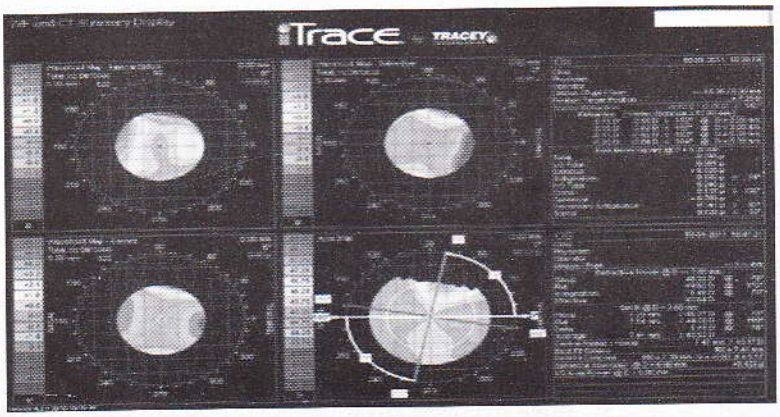


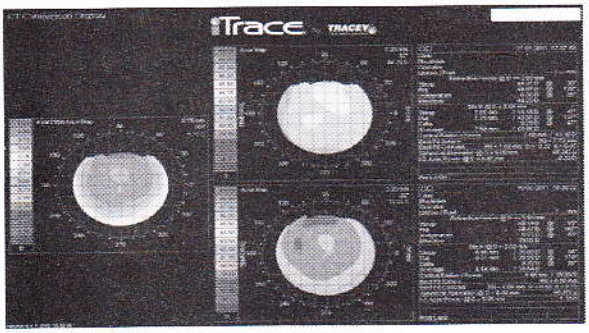
Figure x2 : Analysis of the entire optics of the eye

From a clinical point of view this can help us in certain situations:
If a patient has high total aberrations we can know if the refractive procedure we are planning is better in the cornea or in the crystalline.
If a patient has undergone a phacolensectomy we study the aberrations (induced or compensated) introduced by the IOL with a map before and after (analyzing the aberrations of the internal optics, cornea and total).
Different types of IOL can also be analysed.
We can analyse in an opacified crystalline how many aberrations it is inducing in the total of the eye.

CLINICAL APPLICATIONS :

Lasik

For a 26-year-old patient who underwent surgery 6 months ago optimized Lasik treatment with an aspheric ablation pattern was used.
If we focus on the axial map prior to (top) and post surgery (bottom) as well as the values obtained from them, we see that after Lasik the cornea is more oblate. However, the positive corneal spherical aberration induced after myopic ablation is practically non-existent, i.e. the previous positive value is maintained. It is due to the pattern of spherical ablation produced, taking into account the previous Q value and that expected after Lasik.



A comparison between the total spherical aberration maps (Z 4.0) pre and post Lasik was made. Maintaining the positive spherical aberration of the cornea prevents an increase in total aberration as the patient is young and the lens
compensates with a negative spherical aberration to keep the total close to 0 and to obtain good quality of vision.

Selection of IOLS :

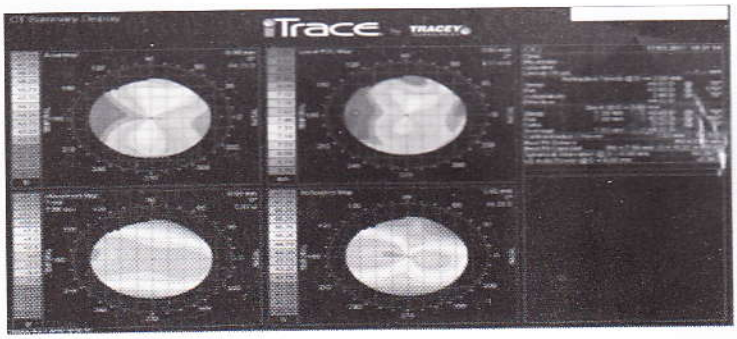
- Example : A patient had a previous myopic LASIK and presented with interest in cataract surgery.
- **High (+) Spherical Aberrations.**
- **The AMO TECNIS® offers _0.27 which is currently the maximum in (_) lenticular aberration correction.**

Therefore, because of the patients high (+) corneal S.A. at 6mm, Tecnis will be the planned IOL for this patient's upcoming cataract surgery to offset the (+) spherical aberration

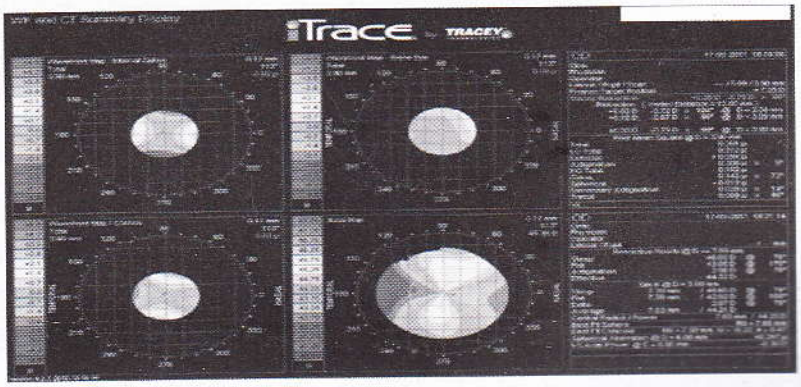
- **Example 2: A patient had a previous hyperopic LASIK procedure some years back. High negative spherical abberation due to LASIK**
- **Resulting highly prolate cornea (Q= _1.03) which is a markedly negative aspheric corneal shape.**
- **Opted to use a traditional spherical IOL which offers a (+) spherical aberration to offset the (_) spherical aberration of the cornea.**

Phakic lens :

A 29-year-old patient with refraction in her RE of –9.00 (–6.00) 175 and VA 0.4. We analysed topography using CT, detecting corneal astigmatism of nearly 3.00 D. The other 3.00 D are therefore derived from the internal optics. Implantation of an anterior chamber phakic toric IOL to compensate overall sphero-cylindrical refraction.



Once this IOL was implanted, we analysed aberrometric status and the visual quality of this patient. Combining the WF with CT we noticed a corneal aberrometric map typical of astigmatism, neutralised by the IOL. It should be noted that both WF maps are symmetrical but present inverted colours, this makes the WF total map very homogeneous, with colours close to green and with a total RMS of 0.361 microns. For a more comprehensive study, we chose the option of decomposing each map into the di#erent Zernike polynomials through a bar graph. The IOL compensates overall corneal astigmatism but to a certain degree also induces this, evident in total refraction (–0.75 to 99°). It also induces a mild comatic aberration.



New frontiers in Anti VEGF Therapy

Dr Mohit Khattri*, Dr Shalini Mohan**, Dr Malay Chaturvedi*

Anti VEGF therapy is one of the most talked and most sought therapy in current ophthalmic clinical practice. It has been seen to have widespread implications along with burgeoning scope of development and research.

HISTORY

In 1983, Senger& colleagues discovered a protein secreted from a guinea pig tumor cell line which induced vascular leakage & named it vascular permeability factor (VPF)

In 1989,Napoleon Ferrara & colleagues identified a molecule in conditioned media from bovine pituitary follicular cells that prompted proliferation of endothelial cell & called it Vascular Endothelial derived Growth Factor (VEGF).

What is VEGF?

VEGF is an angiogenicpeptide derived from a single gene.Four alternatively spliced messenger RNAs code for proteins of VEGF – A 121,165,189 & 206 AA, they are efficiently secreted but differ in their affinity for heparin.

In 1992 VEGF was 1st identified in retina

Physiological roles of VEGF:

- Wound healing
- Vasodilative
- Neuroprotective
- Maintains coronary artery

Pathological roles of VEGF :

- Diabetic Retinopathy
- Retinal Venous Occlusions
- Retinopathy of Prematurity
- Age Related Macular Degeneration
- Neovascular Glaucoma
- Intraocular tumors
- Corneal neovascularization

Evolution of Anti VEGF Therapy

The first commercial use was with Macugen (Pegaptanib sodium, Eyetech/Pfizer) followed by Off-label use of Avastin (Bevacizumab, Genentech) and finally came Lucentis (Ranibizumab, Genentech), widely popular as Accentrix today.

Molecular properties of Bevacizumab and Ranibizumab

- Bevacizumab is a full-length recombinant humanized monoclonal IgG antibody (3 × larger than ranibizumab)[1,2]
- Includes both Fc and Fab regions
- Produced in mammalian expression system (glycosylated molecule)
- Ranibizumab is a recombinant humanized monoclonal antibody fragment(Fab)[3,4]
- Produced in an *Escherichia coli* expression system (and thus not glycosylated)
- Genetically engineered to increase its affinity for binding and inhibition of VEGF
- Shorter systemic half-life than full-length antibody

* Consultant Ophthalmologist, Kanpur
** Associate Professor, Dept. of Ophthalmology, GSVM Medical College, Kanpur

	Ranibizumab	Bevacizumab
Company	Genentech/Novartis	Genentech/Roche
MOA / class	Anti-VEGF-A antibody fragment [targets all VEGF-A isoforms][1]	Anti-VEGF-A full-length antibody [targets all VEGF-A isoforms][4]
Molecular weight	48 kDa[2]	149 kDa[4]
Half-life in the rabbit eye	2.88 days[3]	4.32 days[4]
Systemic elimination half-life	~2 hours[2]	20 days[4]
Licensed indications	Wet AMD, visual impairment due to DME, visual impairment due to ME secondary to RVO (BRVO and CRVO)[1]	Metastatic colorectal cancer, non-small cell lung cancer, glioblastoma, metastatic kidney cancer[4]
Formulation/ administration	Intravitreal injection from a single-use vial[1]	For licensed indications: intravenous infusion from a single-use vial[4]

INDICATIONS

Licensed indications of Ranibizumab are:

1. Neovascular (wet) AMD
2. Visual impairment due to DME
3. Visual impairment due to macular edema secondary to RVO (BRVO and CRVO)
4. Visual impairment due to Myopic CNV

- Ranibizumab is designed and manufactured to the appropriate standards for intraocular use
- It is presented in single use vials for intravitreal injection

Licensed indications of Bevacizumab are:

- Intravenous infusion treatment for patients with metastatic colorectal cancer, non-small cell lung cancer, metastatic renal cell cancer or glioblastoma[5]
- **Bevacizumab is neither licensed nor indicated for any ocular conditions**
- Bevacizumab vials are intended for single use as an intravenous infusion[5]
- For unlicensed intraocular use in neovascular AMD, multiple doses vials[6]
- Vials contain no preservatives and have limited stability[5,7]
- Risk of contamination (particulate or microbial)[8]
- Potential for human error (incorrect dose or incorrect drug)
- **It is not licensed for compounding into smaller doses for ocular use**

Bevacizumab doesn't meet the standards for ophthalmic solutions because of the following

reasons:

- Requirements for particle counts in ophthalmic solutions are clearly defined in US Pharmacopoeia
- USP chapter 789 limits for ophthalmic products: maximum of 50 particles of ≥10 μm permitted in a volume of 1 mL[9]
- USP chapter 788 limits for intravenous medications: maximum of 3000 particles of ≥10 μm per container[10]
- Significant increases in particle density 14 days following preparation have been seen in repackaged bevacizumab from a number of compounding pharmacies ($p<0.03$ for all comparisons)[11]

SIDE EFFECTS

There may be potential adverse effects of anti VEGF action:

- Adverse effects from lack of VEGF signaling, such as:[12]
- Slowed or poor wound healing
- Difficulty growing new blood vessels to replace blocked areas
- There is a theoretical risk of arterial thromboembolic events (ATEs) following intravitreal use of any VEGF inhibitor
- The bevacizumab label states that intravenous use has been associated with serious arterial thromboembolic events (ATEs) including myocardial infarction (sometimes fatal)[13]

Why so much of interest in Anti VEGF?

- We still don't have an ideal anti VEGF
- Global market of anti VEGF is 10 billion US$ per year
- Annual Accentrix sale in India last year was Rs 96 crores.

UPCOMING AGENTS

Few upcoming anti VEGF agents are:

AFLIBERCEPT (Bayer, Regeneron)

- Eylea, instead of being an antibody to VEGF molecule, is a fusion protein consisting of portion of VEGF receptors fused with Fc portion of IgG1.
- Recommended dose is 2 mg (0.05 ml)
- Specially used for cases refractory to Avastin or Lucentis
- Supported by VIVID, VISTA and PROTOCOL T trials

ANECORTAVE ACETATE Retaane (Alcon labs)

- It inhibits the expression of urokinase plasminogen activator (uPA) and matrix metalloproteinases (MMP)
- It prevents the breakdown of basement membrane and extracellular matrix, preventing the migration of VECs
- 15 mg suspension tried as posterior juxtascleral depot
- Also found safe with PDT
- Trials mainly done for wet AMD

Anti PDGF drug FOVISTA (Ophthotech)

- In a large phase 2 study, combination of Fovista and Ranibizumab was 62% more efficacious than Ranibizumabmonotherapy.
- It targets PDGF and causes pericyte stripping from the newly formed blood vessels
- The dose is 1.5 mg

DARPin (Designed Ankyrin Repeat Proteins) Allergan

- Drug developed with Molecular Partners, showed efficacy in treating wet AMD as monotherapy in a phase 2a study.
- The priority now is to combine the DARPin with an anti-PDGF in a dual-acting combination therapy.
- The DARPin is also being tested in combination with Ranibizumab.
- Abiciparpegol 2 mg is the latest drug being worked upon.
- Phase 3 trials started in 2015

Allegro Ophthalmics' **Integrin peptide** (ALG-1001 Luminate)

- Integrin Peptide Therapy turns off the production, reduces the leakage of and inhibits the growth of aberrant blood vessels by acting against integrin alpha(v) and beta(3&5)
- This new approach has the potential as a monotherapy or used in combination with existing drugs
- The drug showed good efficacy in DME and AMD

KALA's **MPP** (Mucus-Penetrating Particle)

- Kala's product candidate KPI-121 is a novel nanoparticle formulation of loteprednoletabonate for the treatment of ocular inflammation, dry eye and meibomian gland disease.
- Kala is also advancing small molecule receptor- tyrosine kinase inhibitor (RTKi) for topical treatment of wet age-related macular degeneration (AMD)

Pill for Dry AMD

- Acucela's drug Emixustat (formerly known as ACU-4427) entered a phase 2/3 trial for the treatment of dry AMD.
- It works by inhibiting RPE65 and reducing A2E
- Results announced on 25.5.2016 for phase 3 (ENVISION)

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THE ASSOCIATION BETWEEN PAX6 GENE AND CONGENITAL CATARACT

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AIM: To determine association of PAX-6 gene in congenital cataract patients in a cross sectional hospital based study over a period of 1 year.

METHODS: During the study 17 patients and 33 parents were recruited from Ophthalmology, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi after informed consent.All cases underwent Visual acuity using Snellen's chart (if possible),Vision with pin hole (if possible),Retinoscopy under mydriasis,Refraction by autorefractor and best corrected visual acuity,Slit lamp examination,Distant direct ophthalmoscopy,Indirect ophthalmoscopy And Ultrasonography B Scan of both eyes.

RESULTS: The mean age of male and female patients affected with congenital cataract who came in OPD of SS Hospital was 4.3±0.888194 and 4.75±1.258306 respectively.No polymorphism in patient affected with congenital cataract was observed.

CONCLUSIONS: Our study found no link between PAX6 gene polymorphisms and patient affected with congenital cataract in this part of population screened in eastern U.P.

Congenital cataracts are one of the most common treatable causes of visual impairment and blindness during infancy and are responsible for nearly 10% of all vision loss in children worldwide.Its occurrence,depending on the regional socioeconomic development,is of 1 to 6 cases per 10,000 live births in industrialized countries[1-3], and of 5 to 15 per 10,000 in the poorest areas of the world[4].

Congenital cataract is visible at birth or during the first decade of life. About 20,000 to 40,000 new cases of bilateral congenital cataract are diagnosed each year in India[4].

The cataract is usually seen as an isolated abnormality but may occur in association with other ocular developmental or systemic abnormalities.If a cataract goes undetected in an infant, permanent visual loss may ensue.If a lenticular opacity is in the visual axis, it is considered visually significant and may lead to blindness. If the cataract is small, in the anterior portion of the lens, or in the periphery, no visual loss may be present[5].

Congenital cataracts occur in a variety of morphologic configurations, including lamellar, polar, sutural, coronary, cerulean, nuclear, capsular, complete, membranous and are often confined to a portion of the lens, and may be static or progressive.[6] In general, the more posteriorly located and dense an opacity, the greater the impact on visual function.[7]

Congenital cataract is both clinically and genetically heterogeneous; isolated congenital cataract is usually inherited as an autosomal dominant trait although autosomal recessive and X linked inheritance are seen less commonly.[8]

Unilateral cataracts are usually isolated sporadic incidents. They are usually the result of local dysgenesis and may be associated with other ocular dysgenesis such as persistent fetal vasculature (PFV), posterior lenticonus or lentiglobus, persistent hyperplastic primary vitreous, anterior segment dysgenesis, posterior pole tumors, trauma, or intrauterine infection, particularly rubella.

Bilateral cataracts are often inherited and associated with other diseases. They require a full metabolic,

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infectious, systemic, and genetic workup. The common causes are hypoglycemia, trisomy (eg, Down, Edward, and Patau syndromes), myotonic dystrophy, infectious diseases (eg, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex [TORCH]), and prematurity.

It is known that different mutations in the same gene can cause similar cataract patterns, while the highly variable morphologies of cataracts within some families suggest that the same mutation in a single gene can lead to different phenotypes[9].

To date, more than 25 *loci* and genes on different chromosomes have been associated with congenital cataract[10].Mutations in distinct genes, which encode the main cytoplasmic proteins of human lens, have been associated with cataracts of various morphologies[11], including genes encoding crystallins (CRYA, CRYB, and CRYG)[12], lens specific connexins (Cx43, Cx46, and Cx50)[13], major intrinsic protein (MIP) or aquaporine[14], cytoskeletal structural proteins[15], paired-like homeodomain transcription factor 3 (PITX3)[16], avian musculoaponeurotic fibrosarcoma (MAF)[17], and heat shock transcription factor 4 (HSF4)[18].

Paired box protein Pax-6 also known as **aniridia type II protein** (AN2) or **oculorhombin** is a protein that in humans is encoded by *PAX6* gene.[19]

Pax6 is a transcription factor present during embryonic development. The encoded protein contains two different binding sites that are known to bind DNA and function as regulators of gene transcription. It is a key regulatory gene of eye and brain development. Within the brain, the protein is involved in development of the specialized cells that process smell. As a transcription factor, Pax6 activates and/or deactivates gene expression patterns to ensure for proper development of the tissue. Mutations of the Pax6 gene are known to cause various disorders of the eyes. Two common disorders associated with a mutation are: aniridia, the absence of the iris, and Peter's anomaly, thinning and clouding of the cornea.[20-25]

The human eye malformation aniridia results from haploinsufficiency of PAX6, a paired box DNA-binding protein.The characteristic paired DNA binding domain of Pax6 utilizes two DNA-binding domains, the paired domain (PD), and the homeodomain (HD). These domains function separately via utilization by Pax6 to carry out molecular signaling that regulates specific functions of Pax6.[26]Because the gene has been sequenced, prenatal diagnosis of aniridia is now possible. In addition, some evidence suggests that *PAX6* may be expressed by damaged eye tissue to induce limited regeneration; artificial upstream regulation of *PAX6* may eventually be used to induce such regeneration. Finally, some cancers, including alveolar rhabdomyosarcoma, may be caused by *PAX* mutations.[27]

These findings suggest potential therapeutic applications for*PAX6* research and may lead to a more complete understanding of its role in eye development.[28]

METHODS- The present study was undertaken to evaluate the association of PAX6 gene polymorphisms in congenital cataract patients in eastern U.P. during the period of July 2015 and June 2016.Ethical approval was obtained for the study. A written consent was taken by the patient mentioning the pros and cons of the treatment, study and duly signed by a witness also. The study is based on data having sporadic cases of congenital cataract as no family history could be elicited. During the study 17 patients and 33 parents were recruited from Ophthalmology, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi after informed consent.

INCLUSION CRITERIA:-

- All cases of congenital cataract as per history and clinical evaluation.
- Patient and guardian consent.

- All patients less than 15 years of age.

EXCLUSION CRITERIA:-

- Unwilling guardians.
- Patients with history of trauma.
- Patients with history of use of steroids.
- Patients with history of previous radiation therapy.
- Patients with history of previous laser therapy.
- Patients with posterior segment pathology.
- Patient receiving treatment for some disease.
- Low birth weight or extremely malnourished child.

Data collected from the patients' records included patients' age, gender, duration of cataract, age at onset of cataract, presence or absence of other associated complaints, use of any medication, antenatal, natal and perinatal history, developmental history and immunization history. All patients undergone biological workup including complete blood count, renal function test, serum electrolytes, liver function test, blood sugar (both fasting and post prandial).

All the patients underwent the following tests on the first day of visit and then at regular follow up at 7th postop day and 4 weeks:

- Visual acuity using Snellen's chart (if possible)
- Vision with pin hole (if possible)
- Retinoscopy under mydriasis
- Refraction by autorefractor and best corrected visual acuity
- Slit lamp examination
- Distant direct ophthalmoscopy
- Indirect ophthalmoscopy
- Ultrasonography B Scan of both eyes.

GENETIC ANALYSIS:

3 to 5 ml of peripheral venous blood was collected from patient along with parents in EDTA coated vials from the subjects and stored at -20 degrees Celsius for less than 3 months before DNA extraction.

DNA isolation was done by "Salting Out" method and dissolved in tris- EDTA (TE) buffer. Primers used for PCR amplification were designed using Primer3 software version 0.4.0 (http://frodo.wi.mit.edu/primer3/) (Rozen S et al., 2000) for PAX6 gene exon5 using sequences from the NCBI Gene (Reference GRCh38.p2 Primary Assembly NC_000002.12) and they were amplified by Thermocycler (Applied Bio system). *In silico* PCR analysis and Blast searches were performed using the UCSC Genome Bioinformatics website (website http://genome.ucsc.edu/).

List of Primers of PAX6

PAX6 Exon		Sequence (5' >3')	Length	Product Length (bp)	Tm
Exon 5	FP	CCTCTTCACTCTGCTCTCTTC TC	23	254	59.87
	RP	AAGAGAGGGCGTTGAGAGTG	20		59.39

PCR was used to amplify DNA with candidate gene primers for sequencing. Primers were purchased from NEB and prepared from dry oligonucleotides to make up a working concentration of 5pmol/µl. Gel electrophoresis was used to enable us to find out if the desired region of the DNA was amplified during PCR reaction. By separating PCR products by size, it allowed us to estimate the size of the amplified product.

DNA Sequencing

Sequencing was used to screen the candidate gene in the relevant affected individuals. PCR products were first purified using the EXOSAP protocol. Purified PCR products were then added to the reaction mixture for sequencing amplification. Sequencing reactions were analysed using 3130*xL* Genetic Analyzer (Applied Biosystems®). Sequencing files obtained from the 3130*xL* Genetic Analyzer (Applied Biosystems®) were analysed using FinchTv viewer.

RESULTS-

A total of 135 children were admitted to Sir Sunderlal Hospital during the period of one year from July 2015 to June 2016 in Department of Ophthalmology.

During July 2015 to June 2016 different cases of congenital cataract were recruited from different districts in and around eastern Uttar Pradesh. These patients hailed not only from Varanasi but also other nearby districts; Chandauli, Jaunpur, SantRavidas Nagar, Ghazipur, Mirzapur and Sonbhadra of Uttar Pradesh.

Of this 135, 17 were affected with congenital cataracts. These comprise of 11 males (77%) and 6 (23%) females, a sex ratio of 1.83:1.The mean age of male and female patients affected with congenital cataract who came in OPD of SS Hospital was 4.3±0.888194 and 4.75±1.258306 respectively. During the study according to religion the patients were categorized into two categories Hindu (14) and Muslims (3). We observed that maximum patient suffering from congenital cataract were Hindu in this part of country.

The study also includes the type of cataract during one year period. The type of cataract included zonular, nuclear and total. During the period zonular (14 or 82.3%), nuclear (2 or 11.7%) and total (1 or 5.8%) were the major type of cataract encountered in our study. As the percentage of zonular cataract was maximum in our study; hence we also checked the distribution pattern of zonular cataract according to sex. We observed that the percentage of male candidate were maximum in zonular cataract.

Our study also recorded preoperative visual acuity and retinoscopy values of all the cases. We found that most of our cases had vision of range between 6/60 to 6/18 (14, 82.3%) followed by 2 cases having vision of < 6/60 (11.7%) and 1case having vision of > 6/18 (5.8%). In retinoscopy done at one arm distance we found that 15 (88.2%) of them had values between range of + 2.50 DS to + 5.00 DS in both meridians while one each had value < +2.50 DS and > +5.00 DS values in both meridians respectively.

The study also recorded preoperative fundus details of patients among which in 10 (58.8%) of them we could easily see all the fundus details very clearly through cataract while in 3 (17.6%) of them we had some difficulty in visualizing fundus details. We could barely see fundus in remaining 4 (23.5%) of them. Subsequently, these 4 cases underwent Ultrasound B Scan of their eyes which were found to be absolutely normal.

Our study also looked for preoperative axial length of cases for planning of surgery and prediction of postoperative visual outcomes. We found majority of our cases had axial length between 20 – 22 mm (88.2%) and one each had axial length less than 20 and greater than 22 mm.

All our 17 cases underwent cataract extraction followed by intraocular lens implantation. Subsequently, post-operative visual acuity was also calculated after one month of surgery. Majority (14, 82.3%) of our cases developed visual acuity ranging between 6/9 – 6/18 and two of them obtained visual acuity of 6/9.One case attained visual acuity of < 6/18 after surgery.

PCR-Genotyping:

We examined exon5 of PAX6 gene for novel polymorphisms that could be used to detect an association of

	Tm
	59.87
	59.39

PAX6 gene with congenital cataract patients and their parents. The amplified products for exon5 were subjected to 2% agarose gel electrophoresis (Fig.1).

Figure 1: 2% Agarose Gel Electrphoresis (AGE) amplified product of congenital cataract family sample (360, 361, 362, 363, 364, 365, 366, 393, 394, 395) of PAX6 Exon5.

We were unable to detect any polymorphism in patient affected with congenital cataract.

DISCUSSION- A cross sectional hospital based study was done involving patient from different parts of eastern Uttar Pradesh that were referred for treatment in SS Hospital, BHU. In our study, it was observed that during the last 1 year the male to female ratio was 1.83:1. However, the ratio is very high this may be due to an underestimation of the true situation since; in India many people do not come to hospital if a girl child has this type of disease. This needs a door to door study of a location. In our study we did observe that the occurrence of zonular cataract was most prevalent and that of nuclear, total, sutural were least. We conclude that zonular or lamellar cataract is the most common type of congenital cataract as also demonstrated in other studies.

The distribution according to religion showed maximum number of affected patients belong to Hindu religion as in Indian scenario majority belongs to Hindu community.Study involving more cases from the general population may confirm the same.

Majority of our cases had preoperative visual acuity between 6/18 – 6/60. This is due to the fact that zonular cataract demonstrates different grades of opacities in different areas of lens with possibly clear area in between zones. One of them who had visual acuity of < 6/60 may have been due to total cataract in which whole lens was opaque thus did not allow any light to pass through.

Majority of the cases who underwent retinoscopy with eye ointment atropine at one arm distance revealed a hypermetropic fundus. This correlates well with age of presentation of disease. As majority of these patients are children their eye ball is in continuous phase of development hence have a hypermetropic fundus till age of 8 years. One of them who demonstrated a myopic fundus may have been due to lenticular myopia induced by cataract. Axial length also followed the same rule of hypermetropia as majority of fundus demonstrated axial length ranging from 20-22 mm.

Fundus details could be deciphered in majority of cases as zonular cataract usually allow for fundus examination through clear portion of lens. In cases where details could not be appreciated were possibly due to greater density of cataract and involvement of all the zones of lens in cataract. Following surgery majority of our patients developed visual acuity of 6/9-6/12 with two of them having visual acuity of 6/6. One patient developed 6/18 vision which may have been due to central nuclear nature of cataract which did not allow any light to pass through thereby producing stimulus deprivation amblyopia.

Genetic studies have contributed to the idea that genes involved in early onset cataract are also implicated in age-related cataract. In particular, mutations in some genes *(MIP* and *yC-crystalliri)* result in progressive cataracts,[29,30] whilst familial adult onset pulverulent cataracts has been linked to the CAAR locus.[31] It may be suggested that mutations in certain genes may have a detrimental effect on eye lens development resulting in congenital cataract.

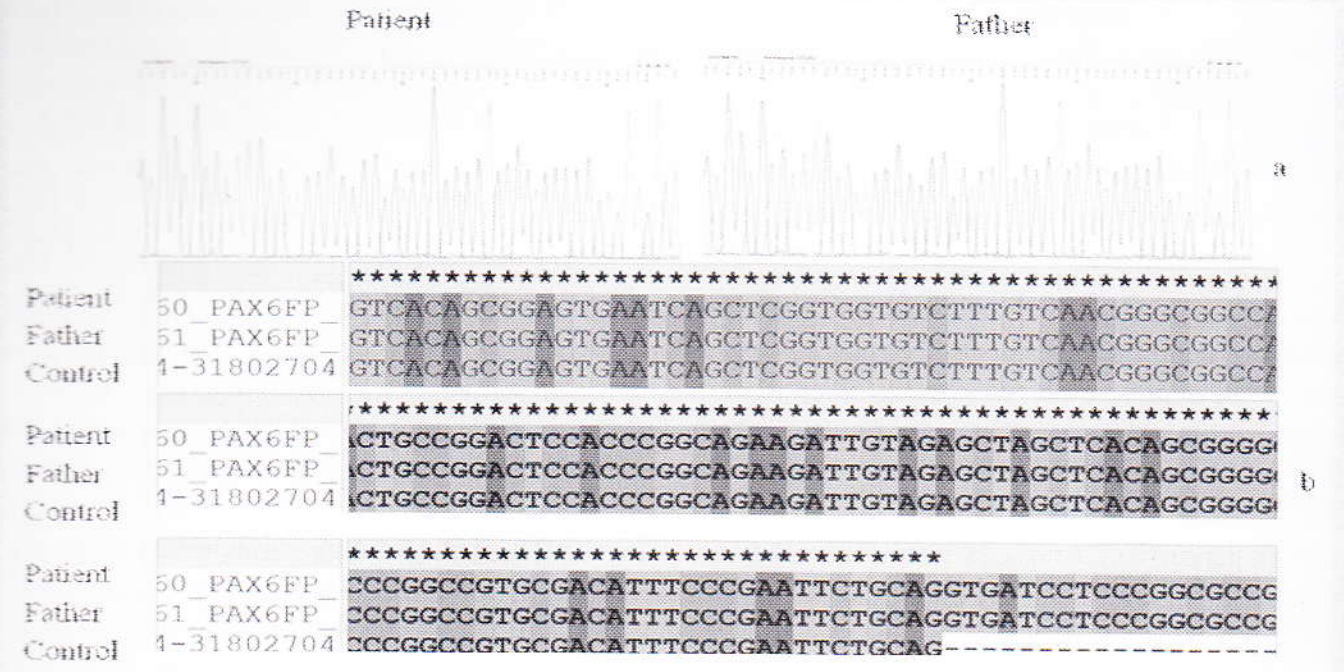
PAX 6 gene encodes paired box gene 6, one of many human homologs of the gene found in *Drosophila Melanogaster* named " prd ". In addition to the hallmark feature of this gene family, a conserved paired box domain, the encoded protein also contains a homeo box domain. Both domains are known to bind DNA, and function as regulators of gene transcription. This gene is expressed in the developing nervous system, and in developing eyes. Mutations in this gene are known to cause ocular disorders such as aniridia and Peter's

anomaly. Alternatively spliced transcript variants encoding either the same or different isoform have been found for this gene. There are around 40 mutations known to cause congenital cataracts, of which only 1 is caused by mutations in the pathogenesis of the independent occurrence of ADCC (G18W), the mutation interfering with the target gene PAX6 binding, and reduce its transcriptional activation function located in the 11p13. A novel PAX6 gene mutation was identified in a Chinese aniridia family.This mutation may also contribute to congenital cataracts in these aniridia patients.[132-135].

Glaser T et al.*, 1994**[35] found that PAX6 is located on human chromosome 11p13, and mutations in this gene lead to a variety of hereditary ocular malformations of the anterior and posterior segment, including aniridia,[36] coloboma of the iris,[37] keratitis,[138] congenital cataracts,[35] Peter's anomaly,[39] and optic nerve defects.[40] ***Fucheng Cai et al.*, 2010**[41] identified a novel deletion mutation of *PAX6* in a Chinese family with aniridia and congenital cataract. This finding expands the mutation spectrum of *PAX6* and is useful and valuable for genetic counseling and prenatal diagnosis in families with aniridia accompanied with congenital cataract. ***Dansault et al. [42] reported 14 affected members carrying a p.S74G mutation in exon 6 of PAX6 gene. All of them were suffering from diverse congenital ocular abnormalities including congenital cataracts, diverse neurological manifestations and variable cognitive impairments. Recently, ***Chien et al.*** [43] had identified a p.R317X PAX6 mutation in a patient (familial case) suffering from cataract, aniridia, nystagmus and was developmentally delayed. ***Manel Chograni et al.***[44] reported no mutation in the four genes of congenital cataract and its flanking regions. Only variations that did not segregate with the studied phenotypes (ARCC associated to Mental retardation (MR), ARCC associated with MR and microcephaly) were reported.He detected three intronic variations in PAX6 gene: IVS4 -274insG (intron 4), IVS12 -174G>A (intron12) in the four studied families and IVS4 -195G>A (intron 4) in two families.

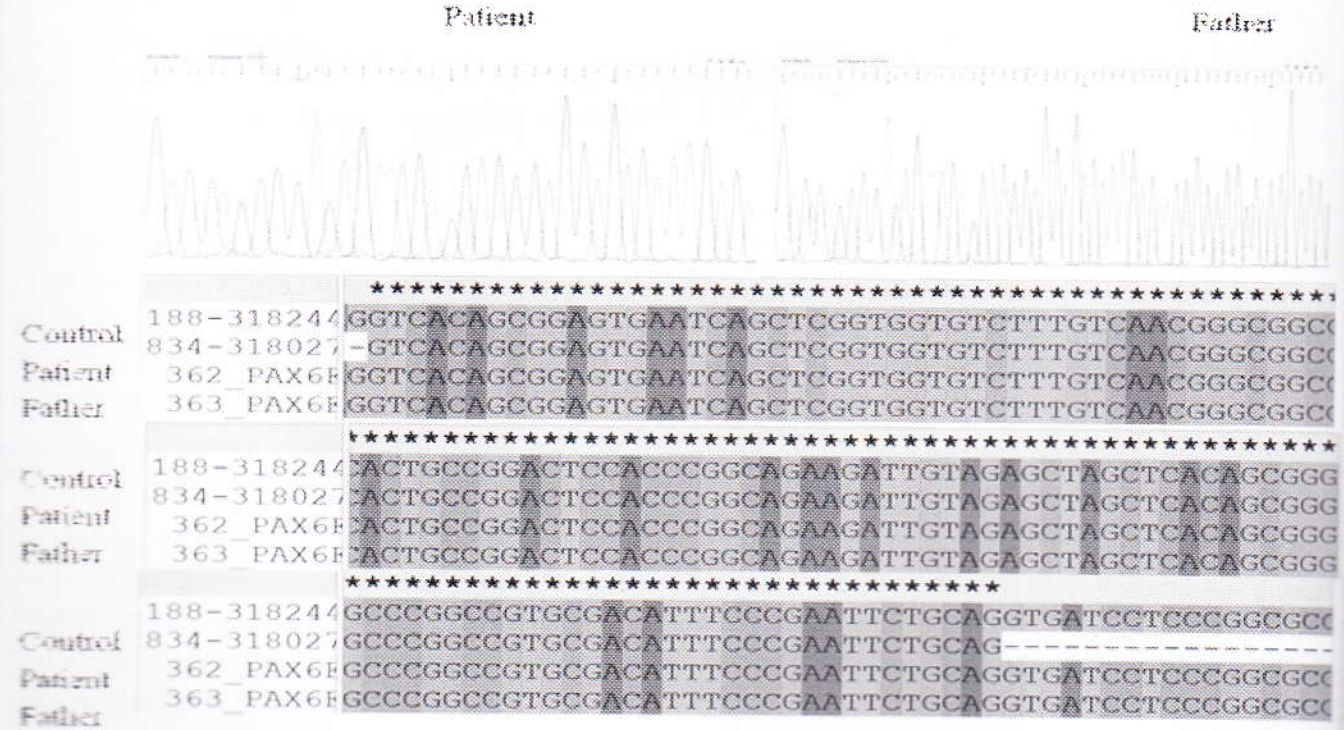
Manel Chograni et al.[45] identified a novel nonsense mutation (p.Q89X) in exon 6 of PAX6 gene in a Tunisian family with aniridia and congenital cataracts. Additionally, he highlighted the predicted pathogenic effect of the reported nonsense mutation, p.R240X, in a second Tunisian family with aniridia, congenital cataracts and variable ocular anomalies. These two mutations lead to truncated proteins and added to the large spectrum of nonsense mutations associated with aniridia. ***Li Wang et al.***[46] identified a novel missense mutation (c.1147A>T) in exon 12 of *PAX6* gene associated with autosomal dominant congenital aniridia and cataract in a Chinese family. It gives further evidence of genotype heterogeneity in congenital aniridia associated with *PAX6*. ***Noriyuki Azuma et al.***[47] ascertained a novel missense mutation in four pedigrees with Peter's anomaly, congenital cataract, Axenfeldt anomaly, and/or foveal hypoplasia, which, to our knowledge, is the first mutation identified in the splicevariant region. A TrA transition at the 20th nucleotide position of exon 5a results in a ValrAsp (GTCrGAC) substitution at the 7th codon of the alternative splice region. Tom Glaser ***et al.***[48] characterized two PAX6 mutations in a family segregating aniridia and a milder syndrome consisting of congenital cataracts and late onset corneal dystrophy.

Very little work has been performed to correlate an association between PAX 6 gene and congenital cataract. PAX6 plays an important role in development of eye. It is emphasized that it may play an important role in congenital cataract too. We could not demonstrate any polymorphisms of PAX 6 gene in our subjects possibly due to smaller sample size and non familial cases. But further work in this study is required and may possibly let us a peep into the role of PAX6 in the development of eye and its association with the congenital cataract in this part of the country.



a. Figure representing the chromatogram for family 360-361.
b. Multiple sequence alignment show that no change was observed

SEQUENCING RESULTS FOR FAMILY 360-361



a. Figure representing the chromatogram for family 362-363.
b. Multiple sequence alignment show that no change was observed

SEQUENCING RESULTS FOR FAMILY 362-363.

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DRY EYE IN DIABETES

- Kshama Dwiwedi*

DRY EYE SYNDROME - Recognised as a lacrimal function unit (LFU) dysfunction disease by the international dry eye workshop in 2007. LFU comprises of- cornea, conjunctiva, lacrimal gland, meibomian glands, lids and the neuronal connection between them. Diabetes mellitus has known ocular complications e.g diabetic retinopathy and cataract, but dry eye syndrome is also common in them.

DEWS [DRY EYE WORKSHOP] 2007 defined Dry Eyes as -

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort,visual disturbance,tear film instability with potential damage to ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.

MAGNITUDE OF PROBLEM

Diabetes is a global academic. According to international diabetes federation in 2016 the magnitude of problem is as follows

China – largest no. 98.4 million

India - 2nd no. -65.1 million

USA - 3rd no.- 24.4 million

Relationship in diabetes and dry eye is not yet established, but DES is known to occur more in diabetes than in non-diabetic, that too more in uncontrolled ones than in controlled ones. Prevalence of DES is 54% [both symptomatic and asymptomatic] in DM[1]. Incidence of DES is correlated with the level of HBA1C, higher the HBA1C-higher the incidence of DES[2]. Beaver Dam Eye Study revealed that approximately 20% of dry eyes occurred in individuals with Type 2 diabetes. Hom and De Land reported that 53% with diabetes or borderline diabetes had self-reported, clinically relevant dry eyes[3]. A hospital based study revealed significant associations between DR and DES[4]. Out of the patients of DMDES (Diabetes Mellitus Dry Eye Syndrome) - 17.1% had mild NPDR, 17.1% had moderate NPDR, 11.1% had severe NPDR and 25.1% had PDR. DR has been shown to be more prevalent in individuals with DR ±CSME group as compared to non-DR group[5].

ETIOLOGY OF DMDES

Hyperglycemia can affect any component of LFU, which in turn is reflected on entire lacrimal due to the neuronal connections – hence causing DE by various pathways[6]. Some of which are-

1. LFU dysfunction
2. Abnormal tear dynamics
   - Abnormal enzyme metabolism
   - Decreased mucin secretion
3. Diabetic neuropathy
4. Tear film dysfunction

LFU DYSFUNCTION – DM is a risk factor for corneal epithelial abnormalities. It causes epithelial barrier dysfunction which can result in superficial punctate keratitis, trophic ulcers, persistent epithelial defects and recurrent corneal erosions. Diabetes with HbA1C are more predisposed to impaired barrier function in corneal epithelium[7].

ABNORMAL ENZYME METABOLISM – High glucose levels in cells of lacrimal gland triggers the polyol pathway, causing activation of aldose reductase which in turn leads to accumulation of sorbitol within cells. It

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Hence resulting in decreased tear secretion

DECREASED MUCIN SECRETION – Corneal and conjunctival epithelial damage by the above mechanism leads to reduction of number of goblet cells, causing decrease in mucus production. Hence the hydrophillicity of the ocular surface is lost , and the tear film becomes unstable[8]

In humans mucosal and ocular surface are covered and protected by a high molecular weight,heavilyglycosyalted protein, which is secreted by goblet cells and exogenous glands. About 20 basic type of mucins have been identified throughout the human body, atleast 7-8 types are present in ocular surface

Tear mucin is secreted by conjunctival goblets cells and corneal epithelial cells and contributes to the mucous layer. It serves two purpose 1.protective function 2. Forms the glycocalyx that contributes to cell adhesion molds the tear film hydrophilic.

DIABETIC NEUROPATHY – hypoglycemia causes corneal epithelium barrier dysfunction and corneal neuropathy,hence the trophic changes are seen[9]. DES is common in patients with type 2 diabetes mellitus complicated with polyneuropathy. Impaired corneal neurons and reduced corneal sensitivity have been reported in diabetic patients with polyneuropathy. MyelinatedA delta and unmyelinated c fibres are the main neural components of human cornea.

TEAR FILM DYSFUNCTION

Tear lipid thickness [especially the lipid layer of the tear film],stability,corneal sensitivity and tear quantity were significantly decreased in patients with diabetes. Tear film stability was inversely associated with the total neuropathy score

PATHOGENESIS

1. Insulin is critical for proliferation of acinar lacrimal gland and cornea epithelial cells
2. High glucose level in diabetic patients leads to increased expression level of advanced glycolated end products modified proteins which may be used as biomarkers
3. Hyperglycemia initiates an inflammatory cascade that generates innate and adaptive immune response of LFU
4. Hyperglycemia causes tear film hyperosmolarity inducing hyperosmolarity of the ocular surface epithelial cells-stimulating a cascade of events that involve MAP-Kinase and NFKB signaling pathways
5. The expression of apoptosis related proteins has been reported to be increased

CLINICAL FEATURES

They are essentially the same as non-diabetic DES. Grittiness being the most common symptom, soreness, difficulty in vision, photophobia, itching and tearing are the other common symptoms. Signs e.g. decrease in Schirmer and TBUT values, decrease in corneal sensitivity, decrease in tear meniscus height, staining of the ocular surface etc.

WHY EARLY DIAGNOSIS IS CRUCIAL

1. Severe DMDES leads to ulcer- secondary bacterial infections- corneal scarring- visual impairment.
2. DM has a synergistic effect on keratitis.
3. It not only leads to occurrence of dry eye but simultaneously aggravates the ocular surface- causing a persistent epithelial defect.

METHODS OF DIAGNOSIS

These objective tests lack sufficient sensitivity and specificity, so they are not adequately reproducible. SYMPTOMS AND SIGNS ARE NOT ALWAYS DIRECTLY PROPORTIONAL TO THE RESULTS OF THESE TESTS. There is battery of investigations available for evaluating different aspects of tear function. We

diagnosis.

OSDI QUESTIONNAIRE-

It has a Likert design. It assesses frequency of ocular subjective symptoms [soreness, blurred vision], difficulty with vision related function [TV,visual display unit, driving,reading] and discomfort due to environmental triggers [low humidity, high wind].The patient answers 12 questions with higher scores representing greater disability .Score range: 0-12 no disability, 13-22 light dry eye, 23-32 moderate dry eye and 33-100 severe dry eye.

SCHIRMER TEST

It is invasive and indirect test. It measures changes in volume of tears in the tear reservoir. Schirmer 1 measures the total secretion whereas Schirmer 2 measures the basal secretion.Strip is folded at notch and placed at junction of middle and lateral third of eyelids and allowed there for 5 minutes with normal blinking. Values of less than 5 mm is abnormal, 6-10 mm is borderline whereas more than 10 mm is normal.

TFBUT

It assesses tear film stability. No anaesthesia is required. Apply a flourescein strip after moistening it with a drop of normal saline to the lower tarsal conjunctiva. The time lapse between the last blink to the appearance of the first random dry spot was taken.Less than 5 seconds is considered severe dry eye, whereas 6-10 seconds is moderate dry eye. More than 10 seconds is considered to be normal.

TEAR OSMOLARITY MEASUREMENT

It is assessed by freezing point depression technique, and has been proposed as the gold standard test for the diagnosis of DES. However it is technically difficult, costly, time consuming; and requires tear volume much higher than those collectable in several forms of DES. It can also induce excessive reflex tearing during tear sampling. Sample size of 0.1 µL is required.

TEAR MENISCUS HEIGHT MEASUREMENT (MENISCOMETRY)

It is used to diagnose aqueous tear deficiency. A rotatable projection system with a target comprising black and white stripes is projected onto the lower central tear film meniscus. Images are recorded and transferred to computer in order to calculate the radius of curvature. Several alternative methods have been proposed to achieve the same e.g. using a video slit lamp biomicroscope, measurement after instillation of fluorescein etc. Cut off is 0.18 mm (Farell et al 2003).

OTHER FACTORS WHICH MAY EFFECT THE RESULTS are social context, environmental conditions, race, ethnicity and season. Time of day, temperature, humidity, air speed and illumination are assumed to influence the results. So they should be kept constant at all follow ups.

PREVENTION AND TREATMENT

Tear film dysfunction increases the incidence of dry eye and also aggravates the ocular surface, which induces a corneal defect. Treatment protocol of dry eye whether diabetic or non-diabetic is essentially the same. Artificial tears are drug of choice for symptomatic relief of dry eye.

Anti-inflammatory drugs are required to stabilize the ocular vsurface and block the inflammatory cascade e.g corticosteroids, non steroidal anti- inflammatory drugs, cyclosporine A, tacrolimus, autologous blood serum etc. Lower concentration of milder steroids are recommended for shorter duration (1-2 weeks). It suppresses the cellular infiltration and increased synthesis of lipocortin[10]. But it also predisposes to infectious keratitis. Hence cautious use is advised.

Non – steroidal anti-inflammatory drugs are safer alternative e.g bromfenac. Immunomodulator e.g cyclosporine eye drops and tacrolimus ointment are also used. They increase tear production, suppress immune response and reduce damage to goblet cells by inflammation but they reduce the corneal sensitivity so usage in DMDES should be with precaution

Autologous blood serum eye drops containing immunoglobins, vitamin A, fibronectin, growth factors and anti-

inflammatory cytokines which are essential components present in natural tears[11]. 50% of autologous serum is very helpful in severe dry eye and persistent corneal epithelial defect. However it is non-preserved, so carry potential risk of infection.

Secretogogese: Rebamipide [quinolone derivative mucin secretogoge] and others are undergoing clinical trials. Gene therapies are undergoing research.

CONCLUSION

In addition to DR, increasing prevalence of DMDES, is of real concern. It predisposes to keratitis,persistent epithelial defects and also reduces the quality of vision in normal cornea. Hence ocular surface examination must be a compulsory part of diabetic ocular examination-whether he/she is symptomatic or not. Preservative free artificial tear and anti-inflammatory drugs are recommended to improve the hyperosmolar state of tear and decrease the local inflammatory reaction.

KEYWORDS

DR: Diabetic retinopathy

DES: Dry eye syndrome

DMDES: Diabetes mellitus associated dry eye syndrome

DM: Diabetes mellitus

LFU: Lacrimal function unit

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A STUDY OF CALOTROPIS INDUCED OCULAR TOXICITY IN WESTERN RAJASTHAN

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INTRODUCTION

Calotropis procera (Fig. 1) belonging to Asclepiadaceae family grows generally in desert areas and is ubiquitous across Rajasthan. In India, it is found mainly in Assam, West Bengal, Rajasthan, Punjab, particularly in the wastelands. It is called Ak in Hindi and Akonda in Bengali and also known as Sodom apple or Madar shrub. It produces copious amounts of thick milky sap which profusely exudes out on breaking the leaves or stalk of the plant also called milkweeds. it is common to get ocular injuries caused by accidental contact or inoculation of the latex while cutting it or plucking flower for worship of lord shiva and children during playing.

We report the spectrum of ocular toxicity following accidental inoculation of latex of Calotropis procera in 15 eyes between july 2015 and july 2016. All patients underwent complete examination including visual acuity assessment, slit lamp examination, fundus evaluation, tonometry and fluorescein staining. Pachymetry and specular microscopy was carried out in some cases to confirm presence of corneal oedema and evaluate endothelial cell count and morphology.

calotropis fig.1

OBJECTIVE- The latex of *Calotropis procera* causes significant ocular morbidity which may be preventable by simple health education like importance of washing hands after handling its flower and leaves.

METHODOLOGY-

Prospective clinical study; Most of the patients in our study were male and they got injured while cutting wood. One child who was playing with plant stem and two females while plucking flowers got injured. All patients reported a burning sensation and watering immediately after the accidental splashing of Calotropis latex associated with blurring of vision within few hours. There was mild discomfort although none of the patients reported any significant pain. There was no history of ocular trauma, surgery, or any other ophthalmic problem in any of the patients. The visual acuity was variably reduced in all eye while in the uninvolved eyes, the best corrected visual acuity (BCVA) was 6/6. On slit lamp examination all eyes showed mild conjuctival and circumcorneal congestion and there was corneal odema and descemet folds present.

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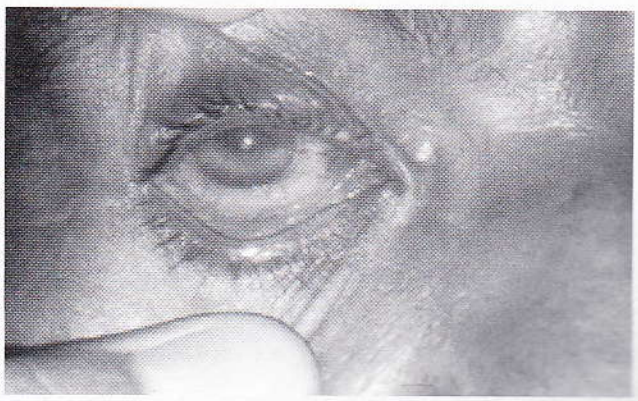
On fluorescein staining seven out of fifteen cases showed corneal staining suggestive of epithelial defect and and four cases showed conjuctival staining in form of triangle from lower fornix. There were no keratic precipitates (KPs). Anterior chamber showed no cells or flare. Iris, pupil, lens were normal. Fundus examination was normal. Intraocular pressure was with in normal range 10-14 mmhg. Specular microscopy was performed in four cases but on presentation reading can't be taken due to epithelial defect and in one case there was significant difference in central corneal thickness and endothelial count.

All patients immediately washed their eyes with water and presented to our department within few hours. All patients were prescribed topical corticosteroid , cycloplegic , tear supplement except the patient who had epithelial defect treated with plain antibiotic drop and after healing of defect topical steroid was given. Patients were followed after five and fifteen days. All patient recovered within a period of 5 to 10 days.

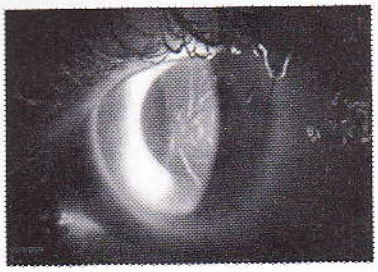
Demography and visual acuity in all patients

Case no	age	Sex	Eye involved	Time of presentation after injury	Visual acuity at presentation	Visual auity after 5 days	Visual acuity after 15 days
1	18	Male	RE	17hours	6/24	6/9	6/6
2	21	Male	RE	22hours	6/24	6/6	6/6
3	6	Male	LE	24 hours	6/36	6/9	6/6
4	32	Female	RE	18 hours	6/9	6/6	6/6
5	22	Female	RE	4 hours	6/18	6/9	6/6
6	18	Female	LE	22 hours	6/24	6/6	6/6
7	25	Male	RE	6 hours	6/18	6/6	6/6
8	21	Male	RE	16 hours	6/9	6/6	6/6
9	50	Male	RE	2 hours	6/18	6/6	6/6
10	30	Male	LE	24 hours	6/36	6/9	6/6
11	32	Male	RE	9 hours	6/60	6/18	6/9
12	40	Male	RE	12 hours	6/36	6/9	6/6
13	40	Female	LE	24 hours	6/60	6/18	6/9
14	18	Female	LE	22 hours	6/18	6/9	6/6
15	25	Male	RE	12 hours	6/24	6/6	6/6

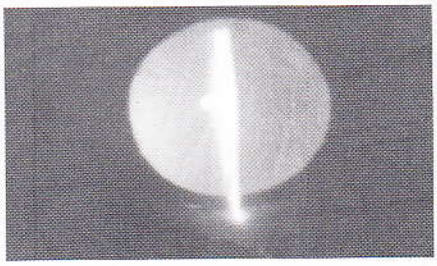


Flurosceien staining of and conjunctiva following calotropis milk inury

There was a case of post calotropis induced corneal ulcer due to delayed presentation at hospital and treatment taken by some local quack resulting in poor visual prognosis.



slit lamp examination of corneal odema and descemet folds



Slit lamp exmination of descemet fold on retroillumination

DISCUSSION -

The sap of C. procera is **acidic** in reaction and turns blue litmus red . On keeping for some time the latex separates into a white coagulum and clear serum. Latex contains several alkaloids like **calotropin, catotoxin, calcinin, gigantin, strychnine**. The serum is highly toxic. **Gigantin** a white crystalline substance isolated from the serum has been found to be 15-20 times as poisonous as **strychnine**[1]. Previous reports showed that accidental contact of *Calotropis* latex into the eye caused violent keratoconjunctivitis with associated corneal edema and gross dimness of vision but without any pain. In this series, all patients presented with sudden dimness of vision with photophobia due to corneal edema with Descemet's folds. Ocular manifestation may be due to either acidic nature of milky latex or toxin present in latex. A study done by Col Shrikant Waikar , Brig V.K. Srivastava showed two stages of calotropis toxicity –

(1) stage of acid injury (2) stage of toxicity

Stage 1 manifest immediately with burning sensation, pain and photophobia. There is staining of cornea and conjunctiva due to epithelial defects as a result of acid injury.

In **Stage 2** toxic effect manifests after a few hours with diminution of vision. The noticeable cause of this was corneal oedema with folds in Descemet's membrane. It probably occurs because of toxicity to corneal endothelium[1-4].

CONCLUSION

1. Initial first six hours of injury are critical , if patient comes with in six hours of injury then visual prognosis is good as compare to the patient who comes later.
2. Immediate wash with normal saline or plain water can prevent severe visual loss.
3. Topical steroid with cycloplegic in form of homatropine is effective drug modality with supportive treatment in form of lubricant and analgesics.
4. Local treatment is not advisable.
5. Immediate wash of hands after contact with sap to avoid contact with eyes.

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Association of Apolipoprotein E (*APOE*) gene in Primary Open- Angle Glaucoma (POAG).

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Aim : To investigate the association between Apolipoprotein E (*APOE*) gene and primary open-angle glaucoma (POAG) in a cross sectional study of eastern Uttar Pradesh and eastern Bihar subjects.
Methods: 23 cases (17 men, 6 women) and 27 control (21 men , 6 women) were undergone systematic examination of optic disc, visual field examination with automated static perimetry , Intraocular pressure (IOP) measurement with Goldmann applanation tonometry. Spectral domain HD OCT used to measure RNFL thickness. Cases and control were genotyped with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: The mean ages were 54.00±14.190 and 52.26±12.424 years in POAG and control groups, respectively . No Polymorphism in cases affected with POAG was observed. Intraocular pressure (IOP), cup/disc ratio (C/D) and RNFL thickness were compared among cases and control . p value <0.05 was considered as statistically significant.

Conclusions: Our study found no link between polymorphisms in *APOE* gene and POAG in eastern Uttar Pradesh and eastern Bihar patients, although a larger sample is required to elucidate the association of APOE gene polymorphisms in the pathogenesis and course of primary open-angle glaucoma (POAG) .

Introduction

Glaucoma is chronic progressive optic neuropathy, characterized by optic nerve head (ONH) changes and visual field loss. Elevated intraocular pressure (IOP) is generally accepted as the major modifiable risk factor for glaucoma, however, factors other than IOP also play role in the pathogenesis and progression of glaucoma, particularly in subjects with normal tension glaucoma (NTG).

Glaucoma is the leading cause of irreversible blindness worldwide and has become one of the most challenging health issues currently being confronted by mankind[1]. It is the second leading cause of blindness worldwide, estimated to affect about 70 million people, with 6.7 million of these being bilaterally blind [2]. *It is the third leading cause of blindness in India .12 million people are affected accounting for 12.3% of the countries blindness due to glaucoma* [3]. Primary open-angle glaucoma (POAG) is the major type of primary glaucoma in most populations. POAG is a genetically heterogeneous disorder and at least 22 genetic loci have been mapped for POAG of which only *GLC1A* (myocilin, *MYOC*), *GLC1E* (optineurin, *OPTN*), *GLC1G* (WD repeat domain 36, *WDR36*), and *GLC3A* (*cytochrome P4501B1, CYP1B1*) have been characterized[4,5]. However, mutations in these genes account for less than 10% of POAG cases. It appears that POAG is a complex trait and multiple genes, each with allelic variations, and environmental factors contribute to the pathogenesis and phenotype and increase individual's susceptibility to glaucomatous optic neuropathy, with no particular gene having a single dominant effect . Currently, several genes have been reported to be associated with POAG, and the apolipoprotein E (APOE) gene has received increasing attention[6,7].

Apolipoprotein E (*APOE*), which is the major apolipoprotein in the central nervous system, plays an important role in neural function and repair after injury. APOE is up-regulated in response to oxidative stress and is endowed with antioxidant properties[8]. The APOE gene has been mapped to the 19q13 region, and its common polymorphism has three alleles in exon 4, namely, ε2, ε3, and ε4. These three alleles define the

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following six APOE phenotypes:ε2/ε2, ε3/ε3, ε4/ε4, ε2/ε3, ε2/ε4, and ε3/ε4[9]. ApoE isoforms may have different effects on defective arterial constriction or dilation in vascular dysregulation because of their differential roles in lipid transport in the blood circulation. Atherosclerosis may restrict blood supply to the retina, and ApoE4 is associated with atherosclerosis. Lipid oxidation associated with atherosclerosis can be protected by the anti-oxidation properties of ApoE[10]. ApoE2, followed by ApoE3, has been shown to be more effective than ApoE4 in inhibiting hydrogen peroxide-induced cytotoxicity in cultured B12 cells[11]. Oxidative stress, due to reactive oxygen species, is a cause of retinal ganglion cell death, thus leading to neurodegeneration in glaucoma[12]. It is likely that the *ApoE* genotype is associated with protective properties against oxidative neurogeneration in glaucoma, E4 more susceptible to oxidative damages than E2 or E3.

In the rat eye, it has been shown to be synthesized by Müller cells, secreted in the vitreous, absorbed by the retinal ganglion cells (RGC), and transported down the optic nerve[13]. Its possible role in RGC metabolism, together with its documented effect on neuronal survival following ischemic and traumatic insults, has led to the hypothesis that particular APOE isoforms could be related to neuronal damage in glaucoma patients[14]. Given the potential similarities between the cellular events leading to degeneration in both Alzheimer's disease and glaucoma, the higher incidence of glaucoma in Alzheimer's disease[15,16]. And APOE ε4 allele as a risk factor for Alzheimer's disease. APOE seems to be a pliable candidate for glaucoma susceptibility.

METHODS

The present study was undertaken to evaluate the association of *APOE* gene polymorphism in Primary open angle glaucoma in Eastern Uttar Pradesh & Eastern Bihar patients. The study was done after approval from Departmental Research committee (DRC) and Ethical committee of Banaras Hindu University . Written informed consent was obtained from each patients. 50 patients (23 case and 27 control) were enrolled with age equal or greater than 35 and less than 80.

Before going through ocular examination a detailed history was taken. Personal interview was conducted to determine profile, exposure to the risk factors of glaucoma like family history of glaucoma, ocular trauma, past eye surgery, past treatment for glaucoma. History was taken and general checkup was done to rule out diabetes, anemia and hypertension.

All subjects underwent full clinical and ophthalmologic evaluation, IOP measurement by Goldman applantation tonometry, Slit lamp biomicroscopy, Zeiss 4 mirror Gonioscopy, Automated Perimetry (Humphrey 30-2), OCT & Pachymetry was used the measurement of central corneal thickness (CCT) .

Visual field examination with Humphrey field analyser using SITA standard 30-2 was performed within 3 months. Subjects were excluded If fixation loss greater than 20% and false positive and false negative errors greater than 33%. Patients were excluded who had history of Blunt ocular injury, severe Uveitis, Exofoliation Glaucoma, Diabetes Mellitus, intraocular surgery and laser treatment.

An additional exclusion criterion includes refractive error higher than ±4.00 D .

Best corrected visual acuity measured from 6 meter distance with Snellen's visual acuity chart. The visual acuity of each eye, both with and without corrections was noted. Refraction was carried out manually using Streak retinoscope followed by subjective corrections. Anterior segment was examined both by torch light and slit-lamp. A provisional diagnosis of suspected glaucoma was made when the subject had one or more of the following conditions: intralobular pressure (IOP) ≥ 21 mmHg in either eye, vertical cup-to-disc ratio (VCDR) ≥ 0.7 in either eye or cup-to disc ratio (CDR) asymmetry ≥ 0.2, and focal thinning, notching, or a splinter hemorrhage.

Genetic analysis: Venous blood was obtained from the subjects and stored at -20 °C for less than three months before DNA extraction. DNA isolation was done by "Salting Out" method and dissolved in Tris-

EDTA (TE) buffer. The genotypes of *APOE* polymorphisms were determined by the PCR-RFLP method. *APOE* gene polymorphisms were investigated using the primer sequences 5'-GAA CAA CTG ACC CCG GTGGCG-3' (forward) and 5'-GGA TGG CGC TGA GGC CGC GCT-3' (reverse). The amplified product for exon4 were subjected to 2% agarose gel electrophoresis and 3.5% Agarose Gel Electrophoresis for Restriction digestion of ApoE gene using HhaI overnight at 37 °C.

The statistical analysis was done using SPSS for Windows version 16.0 software. For comparing two groups of mean Student's 't' test was used. For categorical data Chi-square and Fischer's Exact test was used. The critical value of 'p' indicating the probability of significant difference was taken as <0.05 for comparison.

RESULTS-

During the period July 2015 to June 2016 total 50 samples were collected. Of this 50 samples, 23 were cases (46%) and 27 control (54%). These 23 cases comprises of 17 male & 6 female (sex ratio 2.83:1) where as in 27 controls 21were males & 6 females (sex ratio 3.5:1) . During the study we obtained 2 cases (8.6%) with family history .

The mean age of cases and control who came in OPD of SS Hospital was 54.00±14.190 and 52.26±12.424 respectively .All cases in both eye had higher IOP (>21 mm of Hg) as compared to controls. The level of IOP in right & left eye were statistically significant $p<0.05$. With a mean deviation found in cases right eye (24.61±3.100), left eye (23.13±4.742) and control right eye (14.07±1.796), left eye (14.81±1.594). All cases in both eye had higher C:D ratio as compared to control had in normal range (0.2-0.5) which was statistically significant $p<0.05$. With a mean deviation found in cases right eye (0.7152±0.13604), left eye (0.648±0.1904) and control right eye (0.4259±0.12586), left eye (0.433±0.1144) . Majority of the cases in both eye had lower RNFL (Retinal nerve fiber layer) Thickness as compared to control had in normal range (90±8 µm) which was statistically significant $p<0.05$. With a mean deviation found in cases right eye (57.65±17.809), left eye (64.52±23.245) and control right eye (91.19±6.697), left eye (90.63±4.617).Majority of the cases in both eye had lower CCT as compared to control had in normal range (550±10 µm) which was statistically significant $p<0.05$. With a mean deviation found in cases right eye (530.74±5.065), left eye (531.26±4.484) and control right eye (548.11±4.799), left eye (548.78±5.337).

APO E Genotyping

Exon4 of APO E gene for novel polymorphisms/mutations case and control used to detect an association of APO E gene with POAG cases and control. The amplified product for exon4 were subjected to 2% agarose gel electrophoresis and 3.5% Agarose Gel Electrophoresis for Restriction digestion of ApoE gene using HhaI .

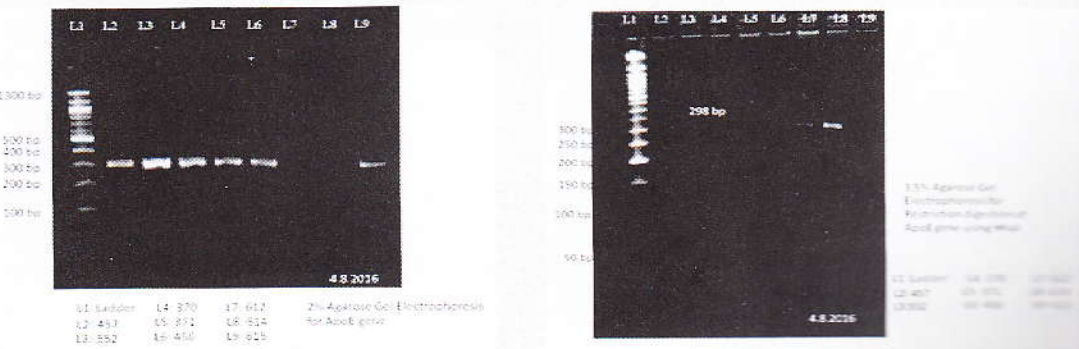

Figure 1,2: 2% Agarose Gel Electrophoresis (AGE) amplified product & 3.5% Agarose Gel Electrophoresis (AGE) for restriction digestion of APO E gene using Hhal amplified product of POAG cases sample (370, 371, 456, 457, 552, 612, 614, 615) of APO E Exon4

We were unable to detect any polymorphism in patient affected with Primary open angle glaucoma.

Discussion

Genetic factors are receiving increasing attention for their role in many forms of glaucoma[17,18]. It is also well known that patients with POAG or their family members have a much higher tendency toward a rise in intraocular pressure (IOP) with use of steroids, indicating a possible hereditary association between steroid response and glaucoma. In addition, the prevalence and severity of POAG, particularly in older age groups, is greater in black and Hispanic Americans compared to whites, which may indicate an increased genetic susceptibility to POAG in these population[19,20].

The high prevalence of POAG, variability in age of onset, and variable penetrance (variable phenotypic expression of a disease despite carrying the genetic mutation) in some pedigrees that have been reported argue strongly that in most cases POAG is inherited as a "complex" trait that does not demonstrate simple Mendelian inheritance. It appears likely that there is interplay between various environmental and genetic factors, or between multiple genes, resulting in a high degree of variability in phenotypic expression and severity of disease. The most frequently mentioned genes with regard to open-angle glaucomas (OAGs) are myocilin (MYOC) (1q23-q24)[21] and optineurin (OPTN) (10p13)[22]. The pathophysiolology of POAG is not precisely known but is felt to be multifactorial[23,24] and polygenetic in etiology. A positive family history, especially among first degree relatives, is a well-known risk factor for POAG.

Our understanding regarding the genetics of POAG is incomplete, and the molecular biology of glaucoma in general is currently a subject of intense investigation. Our study have investigated the APO E polymorphisms involved in oxidative stress, neurotrophic mechanism, and cell morphogenesis in Indian patients with POAG. Single-nucleotide polymorphisms (SNPs) have important implications in human genetic studies, as the presence of a specific SNP allele can be implicated as a causative factor of a genetic disorder. Identification of SNPs allow location and identification of genes of functional importance, which can be used as genetic markers in genetic mapping studies. In addition, understanding the associated polymorphisms may provide an increased understanding of the molecular mechanism of a disease.

In this study, we could not show an association between APOE genotypes/alleles and POAG. Althrough, APOE is a 36-kDa glycoprotein that plays an essential role in lipid and cholesterol transport[25,26]. There is strong evidence that the prevalence of POAG is greater in Alzheimer's disease (AD) patients, and an association between POAG and Alzheimer's disease exists[27,28]. It has also been reported that AD and glaucoma share some common features and that AD patients exhibit widespread axonal degeneration of the optic nerves and the loss of retinal cells, especially ganglion cells[29,30]. Previous studies have shown that the *ε4* allele has been linked to central nervous diseases, such as Parkinson disease, Alzheimer disease, and amyotrophic lateral sclerosis[31,32,33]. In fact, POAG can be considered a neurodegenerative disease as wel[34].

Ressiniotis et al[35]., Lake et al[36]., and Zetterberg et al[37]. have shown that the APOE genotype or alleles do not constitute a risk factor for POAG and NTG, comparable with our results. In the study of Ressiniotis et al[35]. in English population, the frequency of the ε3 allele was 72.6% in POAG group and 76% in control group and the frequency of the APOE ε4 allele in their control population was 13.3%, which was not different than the glaucoma group (14.6%). In their study, Lake et al[195] found no significant difference in frequency of APOE ε3 and ε4 alleles between the normal tension glaucoma group (73.9% and 17.1%, respectively) and the control population (76.5% and 15.5%, respectively). In addition, comparing those patients with progressive NTG disease to the controls revealed no association between APOE genotype and

the disease progression. In the study of Jia et al[38]., ε2,ε3, and ε4 frequencies were found to be 8.75%, 82.25% and 9%, respectively, in Northern Chinese, which were not statistically different between POAG patients and control group. In contrast to these studies, Junemann et al[39] have shown a significant association between the level of IOP and the APOE ε2 allele in German patients, and Vickers et al[40] showed that the APOE ε4 allele was associated with elevated risk for NTG in the Tasmanian population. In a recent study[41], the frequency of the APOE ε4 allele in POAG group was significantly higher, whereas the frequency of the APOE ε2 allele was found to be significantly lower than those in control group in Chinese population. In contrary, Mabuchi et al[42] found a significantly lower frequency of the APOE ε2 and ε4 alleles in Japanese patients with OAG, and Lam et al[43] found lower frequency of the ε4 allele in patients with NTG, but not with high tension glaucoma in Chinese, indicating a protective effect of the ε4 allele against glaucoma. In a study by Fan et al[44] APOE ε4 carriers were found to have a decreased NTG risk (p=0.007).

Song et al[45]conducted a meta-analysis based on nine case-control studies to evaluate the association between the APOE gene ε2/ε3/ε4 polymorphism and the risk of POAG. Corder et al., who claimed that the effects of the ε4 allele dose are associated with increased risk for Alzheimer Disease[46]. Similarly, Schmechel et al. also noted that patients with two ε4 alleles exhibited a distinct neuropathological phenotype compared with other patients[47]. Copin et al. reported that the *APOE* promoter gene polymorphism affected visual field loss and optic nerve damage[48].

Wang et al[49] evaluated only the genetic models of the allele ε2 versus allele ε3, allele ε4 versus allele ε3, ε2 carriers versus allele ε3, and e4 carriers versus allele ε3, and ignored the functions of the genotypes of the APOE gene & indicated no association between the APOE gene and the POAG risk. Yaun et al[50] reported that the ε4 allele may be a latent risk factor in developing primary glaucoma in the Chinese population. Liew et al[51] found a weak association between *APOE* ε4 and retinal microvascular degeneration.

As shown above, there is no consensus whether APOE alleles constitute a risk factor or are protective against glaucoma. There are several possible explanations for these discrepancies. APOE might have a more obvious effect in populations exposed to different environmental factors or with a different genetic background. The pathogenesis and genetic risk factors for glaucoma are not fully understood yet. Genetic polymorphisms in APOE have been investigated in several studies in different populations. Polymorphisms have important implications in human genetic studies and screening for such alleles helps in the detection of a genetic predisposition to disease. However, there are conflicting results about the association of these polymorphisms with glaucoma development and phenotype. The main problem in identifying the gene variants associated with susceptibility to common diseases is that the observed results are not replicated in subsequent studies that used different populations and/or larger numbers of cases versus controls. This discrepancy in the literature may reflect sampling bias, as some of the studies have small number of subjects or it could be attributed to ethnic disparity. Also in glaucoma studies, the inclusion of a normotensive glaucoma group, which has risk factors other than elevated IOP and therefore has a different pathogenesis, may make a study more sensitive to underlying neurodegenerative risk factors.

This is the first population based study in India POAG patients for APOE gene polymorphisms that might be associated with POAG. Our study found no link between polymorphisms in APOE gene and POAG in eastern Uttar Pradesh & eastern Bihar subjects, although a larger sample is required to identify the role of these polymorphisms in the pathogenesis and course of glaucoma if their effects are mild.

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Glaucoma Drainage Implants

- DR RAKESH JAISWAL, DR TIRUPATI NATH, DR Shalini Mohan

Abstract

Purpose of review

The purpose of this review is to critically compare the various glaucoma drainage implants in regular use.

Recent findings

Glaucoma drainage implants are being increasingly utilized in the surgical management of glaucoma. Comparisons between the various drainage implants are difficult because most clinical data are derived from retrospective studies with different study populations, follow-up periods, and criteria defining success. The type of glaucoma under treatment is a major factor influencing surgical outcomes. The resistance to aqueous flow through glaucoma drainage implants occurs across the fibrous capsule around the end plate, and the major determinants of the final intraocular pressure are capsular thickness and filtration surface area. The use of antifibrotic agents as adjuncts to drainage implant surgery has not proven effective in modulating capsular thickness. Valved implants appear to reduce, but do not eliminate, the risk of hypotony. Bleb encapsulation is more frequently seen with the Ahmed valve implant than other drainage implants. Diplopia was a common complication with the Baerveldt glaucoma implant after its introduction, but design modifications have markedly reduced the incidence of this complication.

Summary

There are several glaucoma drainage implants that are currently available, and all have been shown to be safe and effective in reducing intraocular pressure. Greater pressure reduction may be achieved with implants with larger end plates, and valved implants appear to reduce

the risk of postoperative hypotony.

Keywords

Antifibrotic, drainage implants, glaucoma, intraocular pressure, surgical

Introduction

The use of glaucoma drainage implants has increased in recent years, especially relative to other surgical glaucoma procedures such as trabeculectomy [1,2]. The increased utilization of drainage implants is related to a greater experience and appreciation of the efficacy of aqueous shunts, and a growing concern about late complications associated with standard filtering surgery [3].

Only a handful of glaucoma drainage implant types are commercially available and in common use. Comparisons between the various implant types are, however, difficult because most clinical data are derived from retrospective studies with different study populations, small sample size, limited follow-up, and varied criteria for defining successful outcomes. In addition, the types of glaucoma for which drainage implants are being used has expanded to include eyes with major retinal or corneal surgery and glaucomas associated with pseudophakia, aphakia, uveitis, trauma, epithelial and fibrous downgrowth, aniridia, and iridocorneal endothelial syndrome.

These refractory glaucoma types can be effectively managed with glaucoma drainage implants, albeit with differing levels of success that affect comparative efficacy results between the varying types of glaucoma drainage implants.

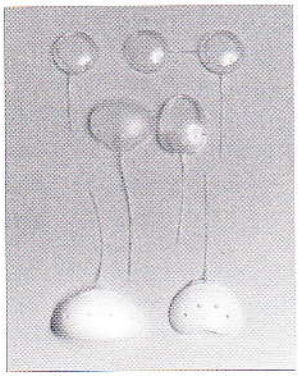
Current glaucoma drainage implants

All modern glaucoma drainage implants consist of a tube that shunts aqueous humor to an end plate (or explant) located in the equatorial region of the globe. Drainage implants differ in their design with respect to the size, shape, and material from which the end plate is constructed. They may be further subdivided into valved and nonvalved implants, depending on whether or not a valve mechanism is present that limits flow through the tube to the plate if the intraocular pressure (IOP) becomes too low. The implants currently in common use include the Ahmed glaucoma valve (New World Medical, Rancho Cucamonga, California, USA), the Baerveldt glaucoma implant (Advanced Medical Optics, Santa Ana, California, USA), the Krupin slit valve (Hood Laboratories, Pembroke, Massachusetts, USA), and the Molteno implant (Molteno Ophthalmic Limited, Dunedin, New Zealand). Fig. 1 shows these popular glaucoma drainage implants, and Table 1 reviews the major design features for each implant.

Ahmed glaucoma valve

The Ahmed glaucoma valve has a scarab-shaped end plate made of polypropylene (models S2, S3, and B1)

Figure 1 Glaucoma drainage implants in common use



Single-plate and double-plate Molteno implants (top row). Krupin slit valve and Ahmed glaucoma valve (middle row). 350-mm2 and 250-mm2 Baerveldt glaucoma implants (bottom row).

Table 1 Design features of current glaucoma drainage implants

Implant type	Size	Material	Valved/ nonvalved
Ahmed glaucoma valve	96 mm^2 (S3) 184 mm^2 (S2) 364 mm^2 (B1) 96 mm^2 (FP8) 184 mm^2 (FP7) 364 mm^2 (FX1)	Polypropylene Silicone	Valved
Baerveldt glaucoma implant	250 mm^2 350 mm^2	Silicone	Nonvalved
Krupin slit valve Malteno implant	183 mm^2 134 mm^2 (single-plate) 268 mm^2 (double-plate)		

or silicone (models FP7, FP8, and FX1). Fenestrations have been added to the plate of the silicone models. Different sizes of the Ahmed valve are available, including those with a surface area of 96 mm2 (S3 and FP8) or 184 mm2 (S2 and FP7). A double-plate version has a surface area of 364 mm2 (B1 and FX1). Aqueous humor passes from the anterior chamber tube through two thin membrane-like elastomer sheets that theoretically restrict flow until a pressure of greater than 8–12 mmHg is exerted upon them.

Baerveldt glaucoma implant

The Baerveldt glaucoma implant is a nonvalved implant. The end plate is made of barium impregnated, rounded silicone with surface areas of 250- or 350-mm2. The plate has fenestrations, which allow fibrous bands to develop that reduce the profile of the bleb. Krupin slit valve The Krupin slit valve consists of an anterior chamber tube connected to an oval silastic disc with a surface area of 183 mm2. Alternatively, the tube end may be connected to a #220 silastic band. The distal end of the tube contains horizontal and vertical slits that function as a unidirectional and pressure-sensitive valve.

Molteno implant

The Molteno implant has a round polypropylene end plate with a surface area of 134 mm2 for the singleplate implant and 268 mm2 for the double-plate implant. The plates of the double-plate implant are connected by a 10 mm silicone tube.

Surgical results

Attempts at comparing the surgical results achieved with the various glaucoma drainage implants are made difficult because of differences in study populations, followup period, and criteria by which success is defined. Case series studying glaucoma drainage implants have reported success rates ranging from 22% to 78% for neovascular glaucoma [4–16], 75% to 100% for uveitic glaucoma [9–11,17,18,19], 44% to 100% for developmental glaucoma [4,5,8–11,20–32, 33], 50% to 88% for eyes that have undergone cataract surgery [4,5,8,10,11,14,15,34,35], and 44% to 88% for eyes with failed glaucoma filtering surgery [4,5,8,11,15, 35]. The poorest surgical results are observed in neovascular glaucoma. As with trabeculectomy, attrition over time results in a trend toward lower success rates among studies with longer follow-up periods.

Pathophysiology

Following implantation of a glaucoma drainage device, a fibrous capsule forms around the end plate over a period of several weeks. A feature common to all glaucoma drainage implants is construction of the plate from materials to which fibroblasts cannot adhere. Aqueous humor pools in the potential space between the end plate and surrounding, nonadherent fibrous capsule when flow occurs through the anterior chamber tube. Aqueous then passes through the capsule via the process of passive diffusion and is absorbed by periocular capillaries and lymphatics. It is the fibrous capsule around the end plate that offers the major resistance to aqueous flow with drainage implants. Therefore, the degree of IOP reduction observed following glaucoma drainage implant surgery is dependent on capsular thickness and the total surface area of encapsulation. Lower postoperative IOP is expected with a thinner capsule and larger surface area of encapsulation.

Table 2 Surgical result with glaucoma drainage implant in eyes with neovascular glaucoma

Author	Procedure	Success rate	IOP Success (mmHg)	Follow-up (months)	
				Mean	Range
Hodkin et al. (4)	Baerveldt	43%	-	18.3	
Minckler et al (5)	SP Molteno	47%	≤21	20.2	
Krupin et al (6)	Krupin long valve	77%	≤21	20.2	12-36
Ancker and Molteno(7)	SP Molteno	67%	<20	18	6-55
Lloyd et al (8)	SP Molteno	22%	≤21and >5	33.8	7-70
Seigner (9)	Baerveldt	71%	≤21and >5	13.6	4-37
Freedom and Rubin(10)	SP Molteno	76%	≤21	35	6-88.9
Mills(11)	SP/DP Molteno	50%	≤22	24	6-66
Sidoti(12)	Baerveldt	61%	≤22and >5	15.7	6-28
Mastropasqua(13)	Krupin Denver valve	36%	≤22and >5	58.4	10-108
Huang(14)	Ahmed	68%	≤22and >5	13.4	4-44
Broadway(15)	SP Molteno	53%	≤22and >5	28	
Krishna(16)	Baerveldt	78%	≤22and 30% reduction	24	

DP;double-plate;IOP;intraocular pressure;SP;single- plate

Table 3 Surgical result with glaucoma drainage implants in eyes with glaucoma

Author	Procedure	Success rate	IOP Success creiteria (mmHg)	Follow-up (months)	
				Mean	Range
Seigner (9)	Baerveldt	91%	≤21and >5	13.6	4-37
Freedom and Rubin(10)	SP Molteno	80%	≤21	48	0.5-13.9
Mills(11)	SP/DP Molteno	75%	≤22	69	42-96
Damata(17)	Ahmed	100%	≤21	24.5	
Molteno(18)	SP Molteno	83%	≤21and >6	85.2	20-240
Ceballos(19)	Baerveldt	92%	≤21and >5	20.8	

DP;double-plate;IOP;intraocular pressure;SP;single- plate

Table-4 Surgical result with glaucoma drainage implants in eyes with developmental glaucoma

Author	Implant	Age (years)	Success rate	IOP Success criteria (mmHg)	Follow-up (months)	
					Mean	Range
Moltino (20)	SP Molteno	≤36	95%	<20	66	12-114
Goldberg(21)	DP Molteno	<13	100%	<20	18.4	6-24
Minckler(5)	SP Molteno		54%	≤21	22.8	
Billson(20)	DP Molteno	<21	78%	<21	41.3	12-84
Hill(23)	SP/DP Molteno		62%	<22 and >5	22.7	6-59
Freedom and Rubin(10)	SP Molteno		50%	≤21	37	16-51
Munoz(24)	SP Molteno	<12	68%	≤21	18	6-36
Nesher(25)	SP/DP Molteno	≤13	59%	≤21	20	6-36
Lloyd(8)	SP/DP Molteno	<13	44%	<21 and >5	49.1	7-76
Netland and Walton(26)	Molteno , Baeveldt	≤10	80%	≤21	25	8-41
Hodkin(4)	Baeveldt	<13	100%	≤21	19.2	
Seigner(9)	Baeveldt		80%	<21 and >5	13.6	4-37
Fellenbaum(27)	Baeveldt	<21	83%	<21 and >6	15	6-25
Mills(11)	SP/DP Molteno	<18	50%	≤22	36	10-99
Coleman(28)	Ahmed	<18	71%	<22 or 20% reduction	16.3	
Eid(29)	SP/DP Molteno,Schocket, Baeveldt		44%	<21 and >5	47.3	14-80
Englert(30)	Ahmed	<18	85%	≤21	12.6	3-31
Djodeyre(31)	Ahmed	<15	69%	≤22	12.6	0-37.9
Pereira(32)	SP/DP Molteno,Schocket, Baeveldt	≤3	60%	≤22	50	
Budenz(33)	Baeveldt	<18	71%	<22 and ≥5	23.4	1-106

DP:double-plate;IOP;intraocular pressure;SP;single- plate

Table 5 Surgical result with glaucoma drainage implants in aphakic/pseudophakic eyes

Authors	Implant	Eyes	Success rate	IOP	Follow-up (months)	
					Mean	Range
Minckler et al (5)	SPMolteno	A/P	63%	≤21	16.2	7-30
Freedom and Rubin (10)	SPMolteno	A/P	83%	≤21	22	8.1-53.3
Lloyd et al (8)	SP/DPMolteno	A/P	56%	≤21->5	48.6	7-78
Heuer(34)	SP/DPMolteno	A/P	50/75%	≤21->6	14.9	6-29
Hodkin(4)	Baeveldt	A/P	74%	≤21	16.4	7-30
Mills(11)	SP/DPMolteno	A/P	58%	≤22	16.3	6.1-26.1
Huang(14)	Ahmed	A P	88% 70%	≤22->5	45 13.4	6-107
Broadway(15)	SP/DPMolteno	A P	70% 66%	≤21->5	43	4-44
Roy et al(35)	Baeveldt	A	75%	≤21->6	37.6	12-68

DP;double-plate;IOP;intraocular pressure;SP;single- plate

Table 6 Surgical result with glaucoma drainage implants in eyes with failed filters

Author	Implant	Success rate	IOP Success creiteria (mmHg)	Follow-up (months)	
				Mean	Range
Minckler et al (5)	SP Molteno	70%	≤21	12.3	6-25
Lloyd et al (8)	SP/DP Molteno	75%	<21 and ≥5	41.4	15-64
Hodkin et al. (4)	Baerveldt	75%	≤21	16.1	7.1-26.1
Mills(11)	SP/DP Molteno	44%	≤22	42	8-78
Broadway(15)	SP/DP Molteno	58%	<22 and ≥5	43	
Roy et al(35)	Baerveldt	89%	<21 and ≥6	37.6	12-68

DP;double-plate;IOP;intraocular pressure;SP;single- plate

Implant size and intraocular pressure reduction

The surface area of encapsulation around a glaucoma drainage implant is directly proportional to the end plate size. Therefore, the degree of IOP reduction achieved postoperatively is also directly proportional to implant size. In other words, glaucoma drainage implants with large plates produce a larger surface area of encapsulation and greater degree of pressure reduction. There is good clinical evidence to support this premise. In a prospective randomized clinical trial comparing single-plate and double-plate Molteno implants, Heuer and colleagues found a higher success rate and greater IOP reduction with the double-plate implant presumably because of its larger surface area [34].

There appears to be an upper limit to plate size beyond which an increase in surface area may not improve pressure control, and may even detrimentally affect surgical outcome. In a prospective study comparing the 350-mm2 and 500-mm2 Baerveldt glaucoma implants, Lloyd et al. found no significant difference in surgical success and visual outcomes between the different implant sizes [36]. With longer follow-up, Britt et al. reported lower success with the 500-mm2 Baerveldt compared to the 350-mm2 implant [37]. Adjunctive use of antifibrotic agents Surgeons have attempted to modulate capsular thickness with the various glaucoma drainage implants by applying antifibrotic agents intraoperatively in much the same manner as with standard filtering surgery. Perkins et al. compared 21 patients who received adjunctive mitomycin C (MMC) at the time of Molteno implantation with 18 patients who received buffered saline solution [38]. After 3 years follow-up, 35% of MMC–treated patients were considered successes versus 17% of the non–MMC–treated group. Cantor et al. randomized 25 consecutive patients to receive either 5FUC or balanced saline solution during placement of a Molteno implant. No significant IOP difference was noted between the two groups [39]. Costa et al. prospectively randomized 60 eyes with refractory glaucoma to receive intraoperative MMC or buffered saline and found no effect of the MMC on IOP lowering at 18 months [40]. No clear benefit of antifibrotic agents as adjuncts to glaucoma implant surgery has been observed, and a higher incidence of hypotony, flat anterior chambers, choroidal effusions, and conjunctival melts has been reported with their use [38,41,42].

Studies comparing different implant types

Prospective randomized clinical trials comparing glaucoma drainage implants of differing size, but of the same type (that is, double-plate versus single-plate Molteno implants [34] and 350-mm2 versus 500-mm2 Baerveldt implant [36,37]) have offered important insight into the role of implant plate surface area and IOP lowering.Unfortunately, no prospective studies comparing different implant types have been reported. Current data regarding the role and efficacy of different glaucoma drainage implant designs are limited to retrospective case series, which have selection bias inherent to any retrospective study design. Differences in the familiarity of surgeons with each of the implants (that is, the number of each type used in the study), differences in the glaucoma type (that is, neovascular, uveitic, postkeratoplasty, etc.), follow-up periods, and other factors make direct comparisons in these retrospective studies difficult. In addition, some of these comparative study results for the Ahmed valve may not be valid to current practice with the change from the polypropylene to the silicone Ahmed implant by many surgeons. The results of a recently initiated prospective study comparing the new silicone Ahmed to the Baerveldt [the Ahmed Baerveldt Comparison (ABC) study] glaucoma drainage implant will provide important clinical insight into the comparative efficacy of these two widely used glaucoma drainage devices (D. Budenz, personal communication).

Baerveldt versus Ahmed

Retrospective comparative studies between the Ahmed and the Baerveldt glaucoma drainage implants demonstrate similar good IOP lowering capacity with high success rates. At 1 year follow-up, the Ahmed and Baerveldt implants had relatively similar rates for IOP control and success end points [43,44].

Similar results were observed in an Asian population with a shorter mean follow-up period [45]. Several differences are notable with regard to the Ahmed implant, however, which had a higher hypertensive phase rate with increased IOP typically 1–2 months after implantation and a higher rate of bleb encapsulation [43,44]. With regard to hypotony and choroidal effusions, our experience has been that the Baerveldt implant has a higher risk of these complications after the ligature dissolves 4–6 weeks after shunt implantation, whereas the Ahmed implant has a higher risk in the first week after shunt implantation, probably due to poor valve function. Syed et al., however, found a higher hypotony rate for Baerveldt glaucoma drainage implants within the first 2 days of implantation [44], which may reflect their greater experience with Ahmed compared to Baerveldt glaucoma drainage implants.

Baerveldt versus double-plate Molteno

Smith et al. retrospectively compared 18 eyes that underwent implantation of a 350-mm2 Baerveldt implant to 19 eyes that received a double-plate Molteno [46]. The double-plate Molteno and the 350-mm2 Baerveldt glaucoma drainage implants had relatively similar reduction in IOP (greater than 44%), success rates, and visual outcomes with almost 1 year of follow-up. Whereas the Baerveldt had a slightly higher risk of anterior chamber shallowing, the Molteno was associated with a higher corneal graft failure rate, although the study numbers were small.

Ahmed versus double-plate

Molteno In a retrospective study, 30 patients implanted with the Ahmed device were compared to 30 patients who received the double-plate Molteno implant [47]. The double-plate Molteno produced a statistically significant lower IOP at 12 and 18 months compared to the Ahmed. The Ahmed had a significantly greater risk of developing a hypertensive phase (83.5%) compared with the double-plate Molteno (43.5%), albeit with ultimate success rates that were similar (approximately 50%) at 24 months.

Ahmed versus Krupin eye valve with disk versus double-plate Molteno

Taglia et al. performed a nonrandomized retrospective review of 27 patients who received a double-plate Molteno implant, 13 patients who had a Krupin eye valve with disk, and 13 patients who underwent placement of an Ahmed glaucoma valve, with adjunctive MMC [48]. The double-plate Molteno was more likely to produce a lower IOP, but it also had a higher rate of hypotony.

Complications

Comparison of the various glaucoma drainage implants requires not only an assessment of their efficacy, but also an evaluation of their surgical complications. Drainage implants have similar operative and postoperative complications as encountered with trabeculectomy, but there are other unique complications associated with their use. Differences exist in the incidence of hypotony, diplopia, and bleb encapsulation with the glaucoma drainage implants in current use.

Hypotony

Nonvalved implants initially had a relatively high rate of postoperative hypotony until techniques were developed to temporarily restrict aqueous flow through the device until encapsulation of the end plate occurred. Methods for flow restriction with single-stage implantation include tube ligation with 8-0 polyglactin (Vicryl; Ethicon, Somerville, New Jersey, USA) or prolene suture, or tube obstruction with a collagen plug or luminal suture. Additionally, a two-stage implantation technique may be used in which the implant is attached to sclera in the first stage of the procedure, and the tube is later inserted into the anterior chamber after a period of several weeks during the second stage.

Temporary restriction of aqueous flow makes the implant nonfunctional in the immediate postoperative period. Reinstitution of medical therapy frequently provides adequate pressure reduction until the tube opens and the implant becomes functional. Tube fenestration may also be performed intraoperatively, and this technique has been shown to effectively decrease IOP in the early postoperative period with nonvalved implants [49,50]. We prefer to fenestrate the tube with a TG-140 or TG-160 needle (Ethicon) anterior to a Vicryl ligature near the tube–plate junction, and 1–3 fenestrations are placed along the tube depending on the preoperative IOP level. Alternatively, an orphan trabeculectomy may be performed in conjunction with glaucoma drainage implant placement for early postoperative pressure control.

Diplopia

Transient diplopia is not uncommon following glaucoma drainage implant surgery, but it generally resolves as the postoperative periocular edema improves. Persistent restrictive strabismus may occur because of scarring between the rectus or oblique muscles and the implant [51], or due to a crowding effect from a large bleb with limitation of extraocular motility [52,53]. Although diplopia may occur with any of the drainage implants, it was particularly common following the introduction of the Baerveldt glaucoma implant [54]. The manufacturer of the Baerveldt implant subsequently discontinued the 500-mm2 size implant and included fenestrations in the end plate, which allows the growth of fibrous bands through the plate to reduce bleb height. These design modifications have markedly reduced the incidence of diplopia with the Baerveldt glaucoma implant.

Bleb encapsulation

Failure to control IOP after glaucoma drainage implant surgery may occur secondary to encapsulation of the bleb around the end plate. This complication is analogous to an encapsulated bleb that develops after trabeculectomy, and it is generally treated in a similar fashion with antiglaucoma medications. The incidence of bleb encapsulation has been estimated to be between 40% and 80% with the Ahmed glaucoma valve, and between 20% and 30% with the Baerveldt and double-plate Molteno glaucoma implants [55]. Several possible explanations have been offered for the higher incidence of bleb encapsulation with the Ahmed glaucoma valve compared with other implants. Some authors have suggested that immediate aqueous filtration with inflammatory factors may stimulate a fibrotic response in the subconjunctival space when the Ahmed implant is used, and delayed flow with a ligated, nonvalved implant may elicit a less fibrous reaction [43]. Others have speculated that differences in the rate of bleb encapsulation may be related to the biomaterial, shape, and consistency of the end plate [56,57].

Future glaucoma drainage implants

Several glaucoma implants are in development, and early clinical use shows variable levels of promise. These new glaucoma implants have a similar goal of shunting aqueous fluid out of the anterior chamber and bypassing the trabecular meshwork to increase outflow and lower the IOP.

MIGS has been defined as IOP-lowering surgery with the

following characteristics that distinguish it from traditional glaucoma

surgery:

- Minimally traumatic
- Via an ab-interno conjunctiva-preserving approach
- High safety profile
- Rapid recovery

Frequently combined with cataract extraction

Provides more modest IOP lowering than trabeculectomy

It is generally accepted that MIGS uses an ab-interno approach that leaves the conjunctiva intact for potential later trabeculectomy or non-penetrating surgery. MIGS procedures form a heterogeneous group of techniques: they may bypass trabecular meshwork (TM) resistance to aqueous flow with stents into Schlemm's canal (iStent, Hydrus), via drainage into the suprachoroidal space (Cypass, iStent Supra) or by excision of TM itself (Trabectome).

Conclusion

Several different types of glaucoma drainage implants are currently available, and all have been shown to be safe and effective in reducing IOP in glaucoma patients. A paucity of studies exists which compare different glaucoma drainage implant types, and these are all limited to retrospective case studies. The Ahmed Baerveldt Comparison (ABC) study is the first multicenter randomized clinical trial comparing different implant types and promises to yield valuable information that will guide surgical decision-making (D. Budenz, personal communication). We generally prefer the Baerveldt glaucoma implant because it optimizes surface area and ease of implantation as a single-plate implant. A Vicryl suture is used to ligate the tube at the time of implantation, and we routinely fenestrate the tube for early pressure control. We use valved implants in the rare situations where aqueous hyposecretion may be present with uncontrolled glaucoma, such as uveitic glaucoma or eyes with prior cyclodestruction. In these settings, the valve mechanism should serve to minimize the risk of postoperative hypotony.

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RETINOPATHY OF PREMATURITY

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Introduction

Retinopathy of prematurity (ROP) is a vasoproliferativedisorder of the retina among premature babies. In almost all terminfants, the retina and retinal vasculature is fully developed, and ROPcannot occur; however, inpreterm infants, the development of the retina, which proceeds from the optic nerve head anteriorly during the course of gestation, is incomplete, with the extent of the immaturity of the retina depending mainly on the degree of prematurity at birth.

ROP begins to develop between 32 and 34 week after conception, regardless of gestational age at delivery and has two distinct phases

[1]. During the acute first phase, the normal vasculogenesis of the retina is disturbed by the relative hyperoxia of the extrauterine environment. This causes vaso-obliteration and non-vascularization of some areas of the anterior retina

[2]. The subsequent hypoxia causes a second chronic phase, characterized by the proliferation of vascular and glial cells, arteriovenous shunt formation, occasionally leading to involution or permanent cicatricial changes and visual impairment.

In its more severe forms, it results in severe visual impairment or blindness, both of which carry a high financial cost for the community but also a high individual cost by affecting the normal motor, language, conceptual, and social development of the child.

Staging of ROP is described based on the

1) location of retinal involvement by zone

2) extent of retinal involvement by clock hour, and

3) stage of the disease at the junction of the avascular and vascular retina.

Location of the disease-

Zones are centered around the optic disc and not the macula.

Zone I (innermost) is a circle, the radius of which extends from the center of the optic disc to twice the distance from the center of the optic disc to the center of the macula.

Zone II extends centrifugally from the edge of zone 1 to the nasal ora serrata.

Zone III is the residual crescent of retina temporal to zone 2.

Extent of the disease-

The extent of the retinal involvement is recorded as hours of the clock or as 30 degrees sectors.

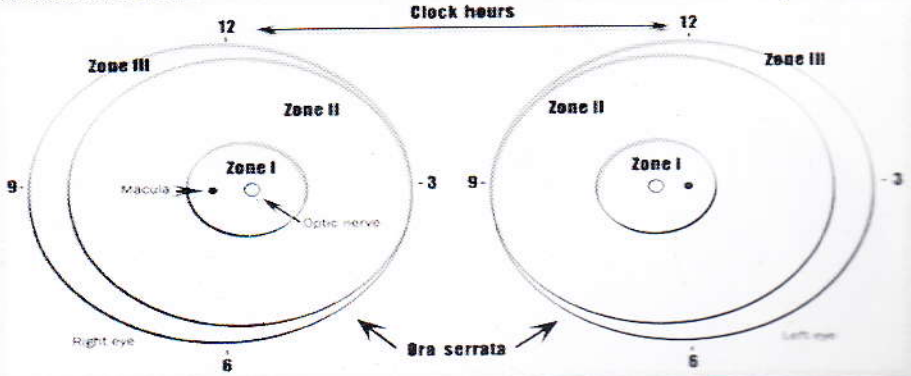

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FIGURE 1

Scheme of retina of the right and left eyes showing zone borders and clock hours used to describe the location and extent of ROP. Diagrammatic representation of the potential total area of the premature retina, with zone I (the most posterior) symmetrically surrounding the optic nerve head (the earliest to develop). A larger retinal area is present temporally (laterally) rather than nasally (medially)

(zone III). Only zones I and II are present nasally. The retinal changes discussed in recommendation 4 are usually recorded on a diagram such as this one.

Stage of the disease-

The clinical appearance of the stages of ROP is related to the appearance of the retinal vessels at the avascular-vascular junction. More than one stage may be present in the same eye; staging then is determined by the most severe manifestation present. Immature or incompletely vascularized retina: this is seen prior to the development of ROP and is characterized by dichotomously branching retinal vessels of normal caliber.

Stage 1- A flat demarcating line is seen delimiting vascularized retina from the anterior avascular retina. Abnormal branching or arcading of vessels is seen leading up to the demarcation line.

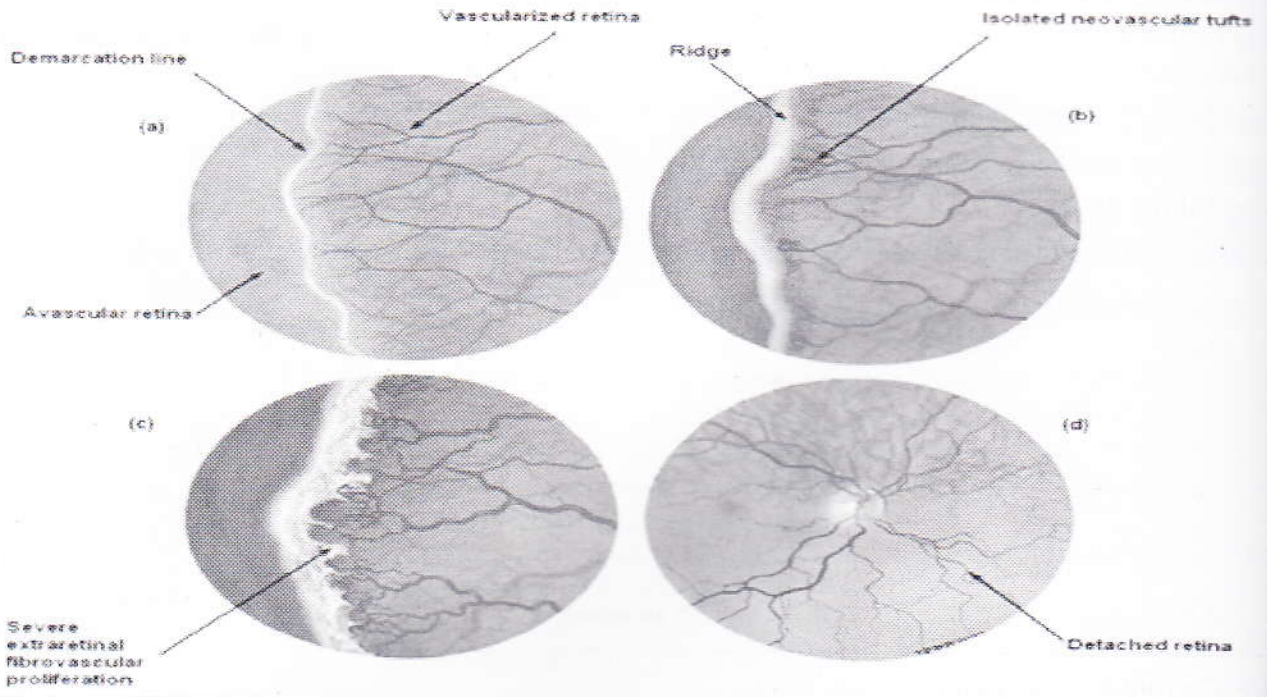
Stage 2-The demarcation line develops into a ridge. This ridge is raised and has volume.

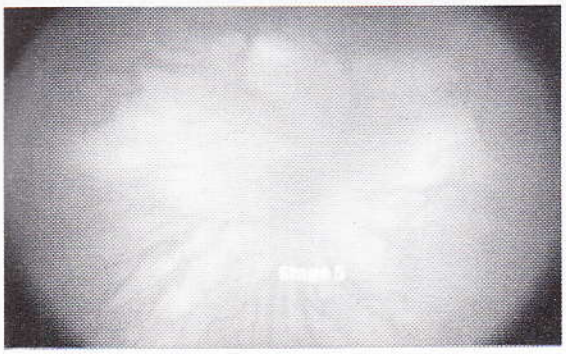
Stage 3- Extra-retinal neovascularization into the vitreous is seen with the development of abnormal shunt vessels at the ridge.

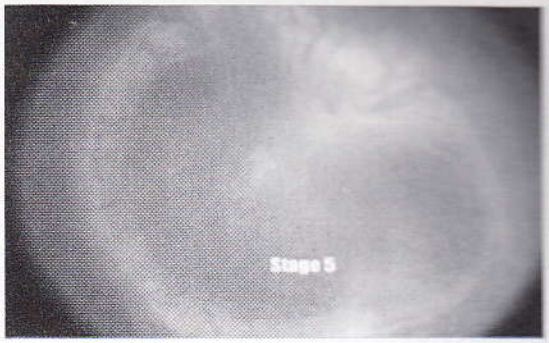
Stage 4- ROP associated with retinal detachments are classified into

stage 4A (partial retinal detachment, not involving the macula) and stage 4B (involving the macula).

Stage 5- Total retinal detachment is usually tractional and funnel shaped and presents as a leucocoria or white pupillary reflex.

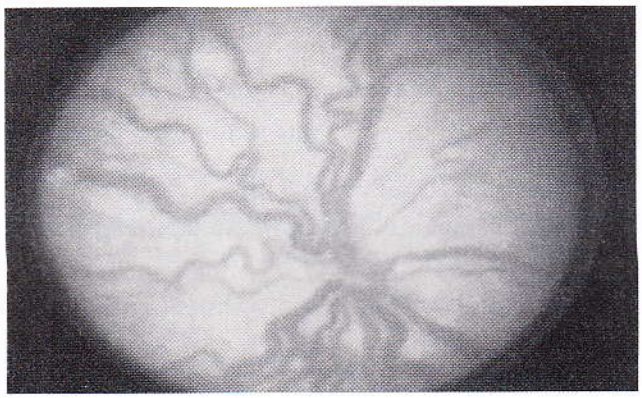




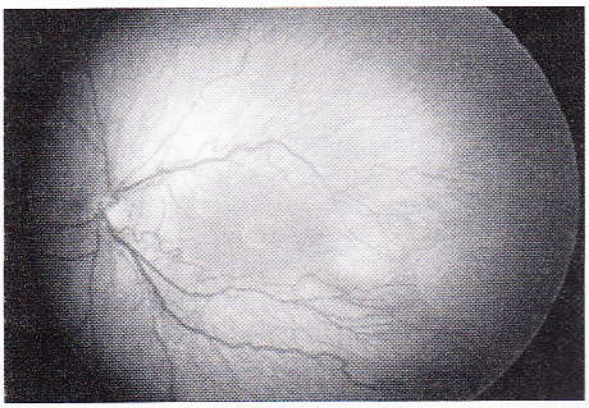


Special Conditions:

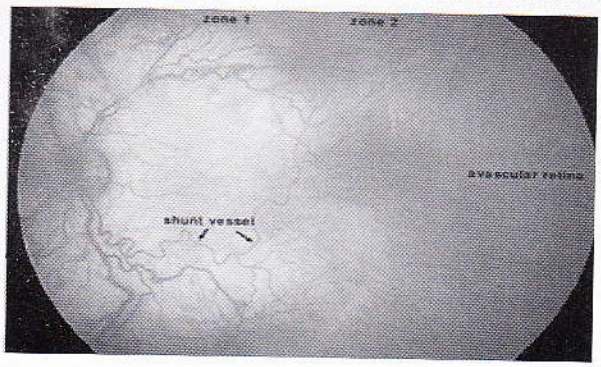
Plus disease: refers to venous dilatation and arteriolar tortuosity of the posterior retinal vessels in at least two quadrants of the eye. Engorgement of iris vessels, pupillary rigidity and vitreous haze may also be seen. A plus symbol is added to the ROP stage number to designate the presence of plus disease.



Pre-plus: is the term used to denote vascular abnormalities of the posterior retina that are insufficient for the diagnosis of plus disease, but that cannot be considered normal.



Aggressive-posterior ROP (AP-ROP): (previously called type II ROP and "rush disease"): is a rapidly progressing, severe form of ROP which if untreated progresses to stage 5 ROP. The features include posterior location (zone I and sometimes posterior zone II), prominence of plus disease, ill-defined nature of the retinopathy, flat network of neovascularization and hemorrhages. The earliest phase of this disease shows abnormal closed-loop vessels (and not the normal dichotomous branching pattern) with mild tortuosity that can develop into the full-blown picture in less than a week. The disease does not proceed from the classical stages of 1 through 3. Diagnosis can be made on a single visit and does not require evaluation over time.



SCREENING GUIDELINES

Recommendations based on review of data from the CRYO-ROP and LIGHT-ROP studies

— **Whom to screen**

1. BW < 1500 g or
2. Gestational age < 30 weeks or
3. Infants with an unstable clinical course who are at high risk (as determined by paediatrician)

Initial screening should be performed by 31 wks PCA or 4 wks CA, whichever is later.

In Indian Scenario

— BW < 2000 g

— GA < 34-35 weeks

— Initial screening recommended between 20-30 days of life.

— Early screening (i.e. < 20 days of life) is strongly recommended for babies < 30 weeks of GA.

Treatment

The goal of treatment in ROP is prevention of retinal detachment and any scarring with optimization of visual outcome.

Indication of treatment

Ablation treatment should be considered for

Type I ROP

- Zone I, any stage ROP with plus disease or
- Zone I, stage 3, with or without plus disease or
- Zone II, stage 2 or 3 ROP, with plus disease

Continued serial examination should be considered for

Type II ROP

- Zone I, stage 1 or 2 with no plus disease or
- Zone II, stage 3 with no plus disease

Table 2: treatment guidelines for ROP adapted from the current ETROP guidelines[1]

Zone I	NO PLUS	Stage 1	Follow	Zone II	NO PLUS	Stage1	Follow
		Stage 2	Follow			Stage2	Follow
		Stage 3	Treat			Stage3	Follow
	PLUS	Stage 1	Treat		PLUS	Stage1	Follow
		Stage 2	Treat			Stage2	Treat
		Stage3	Treat			Stage3	Treat

Available treatment modalities

Treatment involves ablation of the peripheral avascular retina.

Diode laser therapy has largely replaced cryotherapy[2,3] although it is indicated[3] in cases where there is poor fundus visibility, unavailability of laser and physician's unfamiliarity with indirect laser photocoagulation.

Laser photocoagulation

At present the standard of care in ROP is diode laser (810nm). It can be done under local or general anesthesia or sedation. Laser treatment has supplanted cryotherapy as it has better structural[4] and visual outcomes[1]. Its advantages over cryotherapy are its ease of treatment, portability, less postoperative pain, less damage to the adjacent tissues, lesser chances of exudative retinal detachment, vitreoretinal traction and vitreous hemorrhage due to reduced breakdown of blood retinal barrier. It minimizes the risk of missing areas, as laser spots are visible during the treatment. Treatment includes ablation of the entire avascular retina from the ora serrate up to the ridge with near confluent burns spaced one to half burn width.

Materials and preparation for laser treatment

Materials required for laser ablation are- pediatric (alphonso's speculum), pediatric scleral depressor, sterile cotton tipped applicator, topical anesthetic eye drops and dilating[5] along with sterile Ringer Lactate in a syringe. Preparation requires pupils should be dilated and autoclaved instruments should be used. If topical anesthesia is used the child should be fed and burped at least 30 minutes prior to the treatment. The treatment should be carried out in a Neonatal intensive care unit (NICU) or in a setting where suction and resuscitation equipment are readily available.

Postoperative care

The child should be after 30 minutes of the procedure and should be under the care of a neonatologist. Postoperative hypothermia and hypoglycemia should be prevented. Counseling should be done regarding postoperative chemosis and conjunctival hyperemia to avoid alarm. Topical steroids should be started thrice a day to manage postoperative inflammation and prevent formation of post laser posterior synechiae.

Follow up after laser

In patients with zone II disease, re-evaluation should be done within 7 days and signs of regression should be looked for. If adequate regression has not occurred laser treatment is done to the skipped areas and around the active areas. With zone I or APROP cases, one session is usually inadequate for regression, hence, re-evaluation and complete ablation should be done every 3-4 days until complete regression is seen.

Table 1: Follow up schedule for screening/treatment[5]

How frequently to examine	
1. Mature retina	Follow-up 3 months – 1year
2. Immature retina	Follow-up bi-weekly
3. Immature Zone I retina	Follow-up weekly
5. Prethreshold ROP	Follow-up 3-7 days
6. Threshold ROP	Early treatment within 72 hours
7. Retinal Detachment in ROP	Early surgical treatment

Treatment of Retinal detachment associated with ROP

Stage 4 or 5 ROP is a high risk of irreversible blindness. It requires vitreoretinal surgical intervention with lens sparing vitrectomy. It has shown promising results in stages 4A and 4B[6]. The results of surgical intervention are poor in stage 5 ROP[7].

Role of anti-VEGF

Anti VEGF have been used in severe forms of ROP, however its role is controversial. According to BEAT ROP Bevacizumab showed promising results in zone I stage 3+ ROP but not in zone II[8]. In zone I, recurrence rates after laser treatment is higher when compared to Bevacizumab. Since systemic absorption may cause delayed vascular development in other organs, it is not recommended as the first line therapy[9].

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Evolution of Preservatives in Topical Ophthalmic Medications

Dr Neetu Saharan, Dr Tirupati Nath, Dr S k Satsangi

Preservatives are an important component of ophthalmic preparations, providing antimicrobial activity in the bottle and preventing decomposition of active drug. Often under recognized, however, are the significant cytotoxic effects of preservatives associated with long-term therapy and especially use of multiple preserved drugs. The most common preservatives in ophthalmic preparations for glaucoma and surface eye disease-benzalkonium chloride (BAK), chlorobutanol, sodium perborate, and stabilized oxychloro complex (SOC)-were reviewed. Compared with other preservatives, SOC caused the least amount of damage to rabbit corneal epithelial cells. BAK has demonstrated cytotoxic effects in cell culture, as well as in animal and human studies. Physicians should consider treatment with new-generation preparations containing low-risk preservatives such as SOC, especially in patients receiving multiple ophthalmic medications.

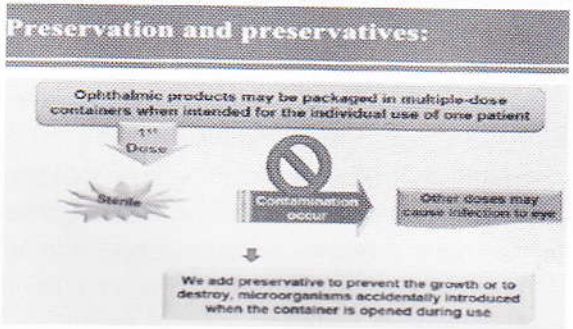

Fig. 1 Role of preservative

Modes of action of preservatives

Preservatives generally offer limited protection against viral contamination. Bactericides and fungicides may evince their effects on a variety of microbial cellular targets, for example; the cell wall, the cytoplasmic membrane or the cytoplasm. It is often difficult to assign a precise target for a specific class of preservative; the target can and does change with preservative concentration. As a consequence, preservatives can often interfere with several different microbial cellular mechanisms (Table 1).

Cell Wall	Cytoplasmic membrane	Cytoplasm
Phenols	2-Phenoxyethanol	2-Phenoxyethanol and other organic alcohols
Aryl and alkyl acids	Parabens	Aryl and alkyl acids
Organo mercurials	Organo mercurials	Halogenated preservatives
EDTA (edetic acid)	EDTA	
Chlorhexidine, cetrimide	Chlorhexidine, hexachlorophene	Chlorhexidine (high concentrations)
Glutaraldehyde	Formaldehyde donators e.g. bronopol, imidurea	Formaldehyde donators e.g. bronopol, imidurea
Anionic surfactants	Benzalkonium chloride (BKC)	

Table 1 - Site of preservative activity in microbial cell

Such cytotoxicity may also affect mammalian cells. Hence inclusion levels should be minimal, consistent with adequate preservation. There is a regulatory expectation that the reason for preservative inclusion, proof of efficacy, safety information, control methods in finished product and details of labelling in the finished product should all be addressed by the applicant [11]. Mechanisms for activity at the locations listed in Table 1.

S.N.Medical College, Agra

Performance Requirements for Preservatives	
Property	**Performance Requirement**
Antimicrobial activity	Active against bacteria (Gram +ve/Gram –ve), molds, yeasts and fungi at low inclusion levels
Aqueous solubility	Solubility exceeds minimum inhibitory concentrations (MIC) over anticipated product pH range
Partitioning Behavior	Remains essentially in the continuous aqueous phase in multi-phase products
Stability properties	Chemically and physically stable during manufacture and at end of product shelf-life.
Non-irritant properties	Non-irritant at concentration used in product, especially germane for treatment of sensitive mucosal membranes, e.g. nose, eye, etc
Organoleptic properties	Odor and taste acceptable where product is administered orally, intranasally or by inhalation (the latter two routes of administration still have a significant 'swallowed' fraction)
Compatibility properties	Does not react or reacts minimally with other product components, including the proposed container closure.

Table 3 Performance required for preservatives

Classification of Preservatives

Historically, preservatives have been classified into two categories: detergent and oxidizing preservatives. More recently, a newer system of preservation, ionic-buffered preservatives (acting as oxidizing preservatives), has been introduced; their methods of action and examples of each different type are described later.

Detergent Preservatives

Detergents are compounds that cause bacterial cell death by way of interrupting the lipid component of cell membranes. The contents of the microbial cell are extruded from the cell due to membrane instability. As described earlier, detergents have the longest running history in ophthalmic medicine. Examples of detergent-type preservatives include benzalkonium chloride (BAK) and cetrimonium.[3]

Oxidizing Preservatives

Oxidative preservatives alter the lipid membrane of microbes in a different fashion to detergent preservatives, by penetrating the membrane and altering the DNA, protein and lipid components of bacterial cells.[4] Oxidizing preservatives are considered second-generation ophthalmic preservatives and were developed because of their reduced toxicity to human ocular surface cells in comparison with detergent preservatives. Although ocular surface cells may still be injured by oxidative preservatives, the low concentrations contained in ophthalmic preparations deem these effects insignificant.[4]Noecker *et al.* reported that medications preserved with Purite® induce less corneal toxicity than those preserved with BAK.[5]Examples of oxidizing preservatives include sodium perborate and stabilized oxychloro complex (SOC).

Recently Introduced Ionic-buffered Preservatives

Ionic-buffering systems are the latest class of ophthalmic preservatives to be incorporated into topical medicines and act in a similar manner to oxidizing preservatives within multidose bottles. SofZia (Alcon, TX, USA), the most recent preservative of this kind, is a combination of boric acid, zinc, sorbitol and propylene glycol. This ionic-buffered system has been shown to have both antibacterial and antifungal qualities.[6] When exposed to cations, such as those that are normally encountered in the tear film of the eye, the substance is deemed inactive. This is thought to induce less cytotoxicity to the ocular surface compared with more conventional preservatives.

Historical & Practical Review of Benzalkonium Chloride

Benzalkonium chloride is a detergent and quaternary ammonium compound with a broad range of antimicrobial activity. It was first introduced as a germicide in the 1910s and became more widely used in the 1940s.[7] In the ophthalmic industry, BAK was first used in the 1940s as a means to preserve hard contact lens solutions. Since then, BAK has been used in nearly all classes of ophthalmic solutions, from antiglaucoma medicines to over-the-counter artificial tear solutions.

Benzalkonium chloride is the most frequently used preservative in ophthalmic solutions today, [8] and its concentration in glaucoma formulations ranges from 0.004 to 0.02%. The reasons for the frequent use of BAK as a preservative includes its extreme efficacy in combating microbial contamination of bottles, its ability to break cell–cell junctions in the corneal epithelium, thus allowing for antimicrobial and antihypertensive drops to enter the anterior chamber, as well as familiarity among those formulating ophthalmic preparations in industry. While the efficacy of BAK is well known, there is a multitude of published studies that document the detrimental effects of BAK. [913] Benzalkonium is known to induce necrosis (at concentrations of 0.05–0.1%) and cellular apoptosis (at concentrations of 0.01%) by way of disturbing the cellular membrane in bacterial cells.[10] However, human ocular surface cells can also absorb this detergent, and effects on ocular surface cells are similar to those seen in bacterial cells. The effects of the detergent are cumulative and become more severe with more concentrated and frequent exposures.[10] Breakdown of the corneal epithelium and increased permeability of the cornea as a result of BAK toxicity is well documented.[11] Higher concentrations of BAK (as can be induced through repeated exposure and subsequent accumulation of BAK in ocular surface tissues) can reduce tear break-up time by causing disruption of the lipid component of the tear film and hence causes tear-film instability.[12] This is especially problematic in glaucoma patients, as they inherently have a decreased rate of basal tear turnover.[14] In one study, it has been shown that ocular cells repeatedly exposed to BAK can overexpress the cell marker Apo 2.7, which has been implicated in apoptosis.[13]

Evolution of Preservatives sinceBenzalkonium Chloride

Cetrimonium is a detergent-type preservative. Its ophthalmic uses have included preservation of artificial tear preparations such as Civigel (Ciba Vision Ophthalmics, GA, USA) .Cetrimonium causes keratinisation and inflammatory infiltrates at the limbus and within the conjunctivalstroma and epithelium.[3] Its corneo–conjunctival cell toxicity has been deemed similar to BAK. Owing to its antiseptic and cationic surfactant qualities, cetrimonium is used mostly as a softening agent in hair treatments. It is also used as a fermentation aid, a dispersant and in preservation of antifungal creams.

Chlorobutanol

Chlorobutanol is a detergent preservative that was formerly used as an active ingredient in hypnotic and sedative agents.[9] Chlorobutanol has been used as a preservative agent in artificial tears, where it has been documented to cause significant keratitis and irritation to the ocular surface.[15] While it damages the ocular surface cells, the toxic effects take longer to manifest in human corneas than do the effects of BAK.[16] Human corneal epithelial cells exposed to chlorobutanol display a decreased amount of mitoses and deterioration of overall cell integrity.[16] Chlorobutanol does not, however, affect the stability of the lipid component of the tear film.[17]

Although the antimicrobial activity of chlorobutanol is extensive, [18] its use has been limited due to the fact that it becomes unstable when stored at room temperature for extended periods of time. Unlike BAK, chlorobutanol does not act like a surfactant.[17] The method of action of chlorobutanol is cell lysis by way of disruption of microbial cell membrane lipid configuration.[17]

Edetate Disodium

Edetate disodium (EDTA) is a chelating agent used in a variety of nonophthalmic products, including hair conditioner, facial cleansers, aftershaves and deodorants. In the recycling industry, it has been used to recover lead from used lead-acid batteries. In the medical field, uses include the treatment of acute mercury poisoning, lead poisoning and hypercalcemia. EDTA has gained use in ophthalmic solutions owing to its ability to bind metals. Therapeutically, EDTA has been used to remove calcified plaques that occur in the superficial cornea in band keratopathy.[19] EDTA has also been used in eye washes to aid in neutralization of calcium hydroxide or lime burns to the cornea.

Edetate disodium also has preservative effects based on its ability to chelate. When added to topical medicines in low concentrations, EDTA has been shown to inactivate trace amounts of heavy metals, which aids in the preservation of the solution.[18] Ophthalmic solutions that have employed EDTA include Acular® (ketorolac tromethamine ophthalmic solution) (figure 2) and Betagan® (levobunolol hydrochloride ophthalmic solution USP).

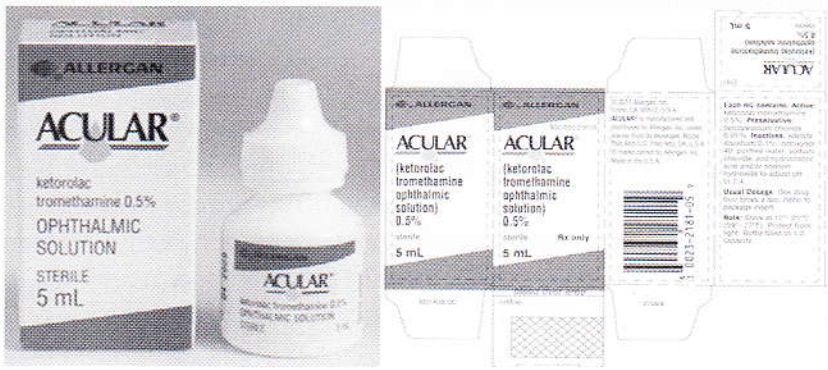

Fig. 2Acular® (ketorolac tromethamine ophthalmic solution)

Polyquaternium-1 (Polyquad®)

Polyquad® is a detergent-type preservative derived from BAK. Polyquad was formulated in the mid 1980s by Alcon as a preservative for contact lens storage solutions. It was developed because other preservatives (e.g., BAK) were known to become concentrated in contact lenses that had been stored in conventional lens solutions. When placed in an aqueous ocular environment, the contaminated contact lens can act as a reservoir of preservative that can later be released. Polyquad does not become concentrated in contact lenses.

Although it is a detergent, Polyquad has unique properties distinguishing it from BAK. Bacterial cells attract Polyquad, yet human corneal epithelial cells tend to repel the compound.[20] Polyquad is the main ingredient in Tears Naturale II (Alcon) (fig. 3) and Opti-Free Express MultiPurpose Disinfecting Solution (Alcon), as well as other storage solutions for contact lenses.

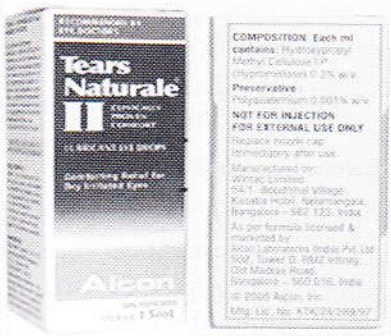

Fig. 3Tears Naturale II (Alcon)

While Polyquad has been shown to be much less toxic to the corneo–conjunctival surface than BAK, [21]it has been shown to cause superficial epithelial damage to the cornea.[22] The main detriment associated with polyquaternium-1 is its tendency to reduce the density of conjunctival goblet cells, thereby decreasing aqueous tear film production.[21]

PolyhexamethyleneBiguanide

Polyhexamethylenebiguanide (PHMB) has been used in contact lens solutions such as ReNu® (Bausch & Lomb, NY, USA) (Fig.4). The benefits of PHMB against *Acanthamoeba* and bacteria are well known.[23] PHMB has been shown to be nonirritating to human corneal cells; however, its antifungal activity is limited.[18] PHMB employs its microbial activity by integrating into bacterial cell walls, thereby disrupting its membrane and has been shown to lethally alter the transcription of bacterial DNA.[24]

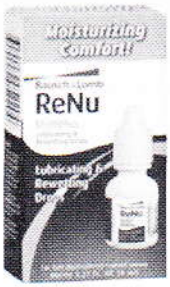

Fig. 4ReNu® (Bausch & Lomb, NY, USA)

Stabilized Oxychloro Complex

Stabilized oxychloro complex (Purite, Bio-Cide International Inc., OK, USA) is an oxidative-type preservative and was introduced into ophthalmic medicines in the mid 1990s under the trade name Purite. One of its derivatives, sodium chlorite, has been used in water purification systems since the 1940s.[25] Purite has become a component of several different types of artificial tear and antiglaucomapreparations, including brimonidine tartrate ophthalmic solution (Brimodin-P, Cipla) (fig. 5) and Refresh Tears (Allergan).

Fig. 5Brimodin-P

Stabilized oxychloro complex has been shown to be well tolerated by the ocular surface.[25] Even at very low concentrations of SOC (0.005%), the antimicrobial activity is broad.[4] This was substantiated during a trial in which SOC was administered to patients up to eight-times daily.[25] SOC has been shown to lack cytotoxicity *in vivo*; however, more studies are needed to assess ocular side effects independent of active ingredients.[26] The antimicrobial effects are broad and include antibacterial, antifungal and antiviral

effects. Chemically, SOC is a mixture of chlorine dioxide, chlorite and chlorate.[4] When exposed to light, SOC dissociates into water, oxygen, sodium and chlorine free radicals.[27] The chlorine free radicals are thought to inhibit microorganism protein synthesis within cells by way of glutathione oxidation, which causes microbe cell death.[101]

Sodium Perborate (GenAqua™)

GenAqua™ is a preservative composed of sodium perborate and is contained in Genteal lubricant eye drops (Novartis Ophthalmics, NJ, USA) (fig. 6).

Sodium perborate is an oxidative preservative that has been used in dental hygiene solutions since the 1950s. When it was introduced in ophthalmic solutions, it was one of the first of the oxidative-type preservatives used. Sodium perborate alters protein synthesis within bacterial cells by oxidizing cell membranes and altering membrane-bound enzymes, causing enzymatic inhibition. Upon exposure to an aqueous environment, it is catalyzed into hydrogen peroxide, water and oxygen. This is a property exclusive to this compound. The hydrogen peroxide formed by this reaction effectively kills microbes.[26] Furthermore, the efficacy of GenAqua has been demonstrated onAspergillusniger.[26] There are few studies documenting the ocular tolerability and side-effect profile of GenAqua.

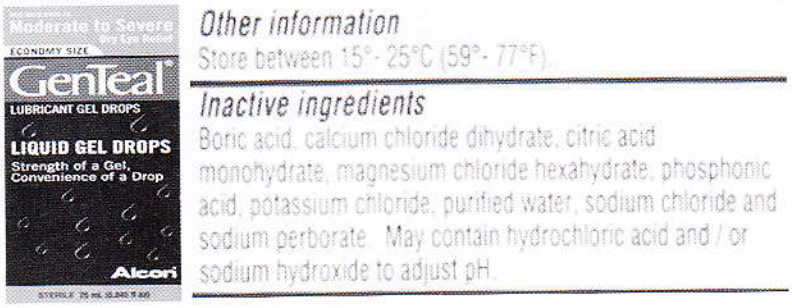

Fig. 6Genteal lubricant eye drops

SofZia™

SofZia™ is the most recent advancement in the field of ophthalmic preservatives and is the preservative system contained in one preparation of travoprost (Travatan Z®, Alcon, Texas). When exposed to cations, such as those that are normally encountered in the tear film of the eye, sofZia is deemed inactive. This is thought to induce less cytotoxicity to the ocular surface compared with more conventional preservatives.

Travatan Z (fig. 7) was introduced as the first prostaglandin analogue to be preserved with a substance other than BAK. The sofZia system effectively preserves the medicine while it is being stored; however, when the drug is introduced into the eye, it is modified into harmless elements that are gentle on the ocular surface.[6] It has been demonstrated that sofZia-preserved travoprost induces corneal and conjunctival changes similar to preservative-free artificial tears. Furthermore, travoprost with sofZia also induced reduced amounts of conjunctival inflammation and corneal changes when compared with travoprost treated with BAK.[28]

Fig. 7Travatan Z

Preservative	Class	Advantages	Disadvantages	Medication examples
SofZia®	Oxidative	Modified into harmless elements upon instillation; smaller amounts of conjunctivo–corneal inflammation compared with BAK	Newer agent requiring more studies to understand ocular safety profile of the preservative independent of active ingredients	Travatan Z®
Sodium perborate (GenAqua®)	Oxidative	Catalyzed into hydrogen peroxide, water and oxygen upon instillation; activity against *Aspergillus*; less toxicity than BAK	Few studies documenting ocular tolerability and side-effect profile	Genteal®
Stabilized oxychloro complex (SOC/Purite®)	Oxidative	Dissociates into water, oxygen, sodium and chlorine free radicals	As with sofZia, more studies are needed to assess ocular side effects independent of active ingredients	Alphagan-P®, Refresh Tears®
Polyquaternium-1 (Polyquad®)	Detergent	Less toxicity to corneo–conjunctival surface than BAK	Superficial corneal epithelial damage reduces density of conjunctival goblet cells	Tears Naturale II®, Opti-Free® Express Disinfecting Solution
Chlorobutanol	Detergent	Toxic effects take longer to manifest than BAK; doesn't affect stability of lipid component of tear film; extensive antimicrobial activity	Causes keratitis and irritation to ocular surface; decreased amount of mitoses to corneal epithelial cells; unstable when stored at room temperature	TobraDex® Ointment
Cetrimonium chloride	Detergent	Excellent antiseptic qualities	Causes keratinization and inflammatory infiltrates at the limbus and within the conjunctival stroma and epithelium	Civigel®
Benzalkonium chloride	Detergent	Excellent antimicrobial efficacy; disruption of corneal cell–cell junctions allow medicinal entry to anterior chamber; well-established familiarity in industry	Breakdown of corneal epithelium; apoptosis of ocular surface cells; accumulation in surface tissues; tear-film instability	Timoptic®, Azopt, Lumigan®, Xalatan
Edetate disodium	Chelating agent	Inactivates trace amounts of heavy metals	Few studies documenting chronic side effects	Acular®, Betagan®

BAK: Benzalkonium chloride.

Table 3 Details of different kind of preservatives

Effect of preservatives on ocular surface

Ocular surface disease, OSD, (which includes dry eye syndrome) can cause redness, tearing, irritation, burning, foreign body sensation, light sensitivity and intermittent blurred vision. Although 15% of elderly patients describe some degree of OSD, up to 60% of patients with glaucoma suffer from it.

The symptoms mentioned above affect the quality of life and even the adherence to the prescribed medications to help preserve existing vision. The active ingredient of a medication, the component that is used to lower the eye pressure, can cause OSD. It is also known that inactive ingredients, such as preservatives, can contribute to OSD. Ocular surface changes, causing ocular discomfort, tear film instability, conjunctival inflammation, subconjunctival fibrosis, epithelial apoptosis, corneal surface impairment, and the potential risk of failure for further glaucoma surgery. Subclinical inflammation has also been described in patients receiving antiglaucoma treatments for long periods of time. However, the mechanisms involved, i.e., allergic, toxic, or inflammatory, as well as the respective roles of the active compound and the preservative in inducing the toxic and/or proinflammatory effects of ophthalmic solutions, is still under study.

Furthermore, the negative effects of preservatives seem to be additive. The more medications a patient takes the more likely symptoms. Preservatives were initially used to kill bacteria in the bottle and it was thought they helped the active ingredient have its desired effect. Since the active ingredient is the component of the medication that lowers the eye pressure, any negative effect it may have is thought to be a necessary evil. For patients with OSD, difficulties tolerating eye medications can possibly be improved by minimizing the effect of preservatives on the ocular surface.

Fig. 8Lissamine green (LG) staining of the conjunctiva in a patient with mild dry eye. LG is a valuable vital dye to use because it is very sensitive and highlights even early devitalisation of conjunctival epithelium

Fig. 9Fluorescein staining of a cornea in a patient with moderate dry eye. Broken tear film over the central cornea (decreased tear film break-up time) and fluorescein staining of the inferior cornea. Fluorescein stains epithelial cells in more advanced disease, as well as absent areas(erosions) on the corneal surface

Fig. 10Fibrosed bleb as result of preservatives in antiglaucoma medications as it lead to increased levels of extracellular matrix (ECM), the transforming growth factor β (TGF-β) signaling pathway-related molecules, and cyclooxygenase-2 (COX-2) in bulbar conjunctivaltissuesand results in failed filtration surgery

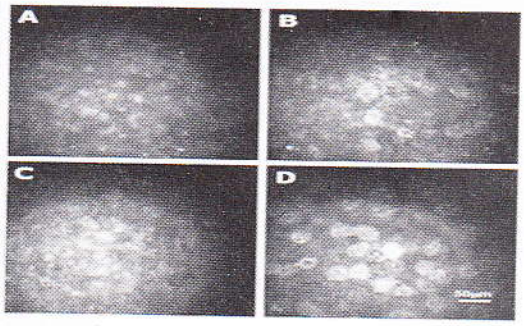

Fig. 11 Toxic effect of BAC on corneal epithelial superficial cells.Representative in vivo confocal images of the corneal epithelium in different groups. (A) Untreated control. (B) 0.01% BAC. (C) 0.05% BAC. (D) 0.1% BAC. Mean cell size at the epithelial surface was shown in (E). Note that the size of surface cells in the corneal epithelium of eyes treated with 0.1% BAC was significantly larger than that of control eyes

CONCLUSION

The most frequently used preservative, benzalkonium chloride (BAK), has consistently demonstrated its toxic effects in laboratory, experimental, and clinical studies. As a quaternary ammonium, this compound has been shown to cause tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, and damage to deeper ocular tissues. The mechanisms causing these effects have not been fully elucidated, although the involvement of immunoinflammatory reactions with the release of proinflammatory cytokines, apoptosis, oxidative stress, as well as direct interactions with the lipid components of the tear film and cell membranes have been well established. Preservative-induced adverse effects are therefore far from being restricted to only allergic reactions, and side effects are often very difficult to identify because they mostly occur in a delayed or poorly specific manner. Care should therefore be taken to avoid the long-term use of preservatives; otherwise a less toxic alternative to BAK should be developed, as this weakly allergenic but highly toxic compound exerts dose- and time-dependent effects. On the basis of all these experimental and clinical reports, it would be advisable to use benzalkonium-free solutions whenever possible, especially in patients with the greatest exposure to high doses or prolonged treatments, in those suffering from preexisting or concomitant ocular surface diseases, and those experiencing side effects related to the ocular surface. Indeed, mild symptoms should not be underestimated, neglected, or denied, because they may very well be the apparent manifestations of more severe, potentially threatening subclinical reactions that may later cause major concerns.

Preservative-free approaches are still in their infancy and much more research is required before they can be considered on an equal footing with preserved approaches. However, several preservative-free ophthalmic devices are available and do offer some promise.

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Limbal Stem Cell Deficiency :Presentation, Diagnosis and Management

- *Prof. R.K.Jaiswal,

The human corneal surface epithelium is continuously repopulated by the limbal stem cells (LSCs). The stem cells in the limbusthat are vital for re-population of the corneal epithelium and to the barrier function of the limbus. . Limbal stem cell deficiency (LSCD) is characterized by a loss or deficiency of the stem cells in the limbus. When these stem cells are lost, the corneal epithelium is unable to repair and renew itself. This results in epithelial breakdown and persistent epithelial defects, corneal conjunctivalization and neovascularization, corneal scarring, and chronic inflammation. All of these contribute to loss of corneal clarity, potential vision loss, chronic pain, photophobia, and keratoplasty failure.There are many causes of limbal stem cell deficiency and it is important to know how to recognize them and how to intervene. Although LSCD can be detected clinically, laboratory tests are necessary to confirm the diagnosis and monitor the disease progression. This article concisely reviews the clinical presentation, techniques for diagnosis and management of limbal stem cell deficiency disorders.

Etiology

The etiologies can be genetic, acquired, or idiopathic.

Genetic:

Limbal stem cell deficiency has been associated with PAX6 gene mutations, which are also implicated in aniridia and Peter's Anomaly.

Acquired:

Inflammatory

Steven-Johnsons Syndrome (SJS), ocular cicatricialpemphigoid, and graft versus host disease.Chronic ocular allergy such as VKC and Neurotrophickeratopathy.

Infectious:

Herpes keratitis and trachoma.

Traumatic/Iatrogenic:

Acquired causes also include trauma from chemical or thermal burns, and prior ocular surgeries or cryotherapies at the limbus. Radiation and chemotherapy are other potential causes, and systemic as well as topical chemotherapeutic medications may be sufficient to cause deficiency. LSCD has also been seen with benzalkonium chloride toxicity with glaucoma medications and Inappropriate contact lens use.

Tumors/Overgrowth of Other Tissue:

Ocular surface tumors and Pterygium are a known cause of LSCD.

CLINICAL PRESENTATION

History:

Pain resulting from recurrent erosions and decreased vision.

Other symptoms:

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Contact lens intolerance, photophobia, tearing, and blepharospasm. A patient with LSCD from chemical burn or trauma will give a history of such an event.

Physical examination

Recurrent epithelial erosions leads to chronic keratitits, scarring, and calcification if untreated. Delayed wound healing and corneal neovascularization eventually leads to a process called conjunctivalization occurs. The corneal surface will be covered by conjnuctiva-like epithelium that undergoes transformation into a cornea-like epithelium with loss of goblet cells, a process termed conjunctival transdifferentiation. Patients usually suffer from recurrent erosions and decreased vision as a result of an irregular optical interface, weak tensile strength, and an incompetent barrier function.

Signs

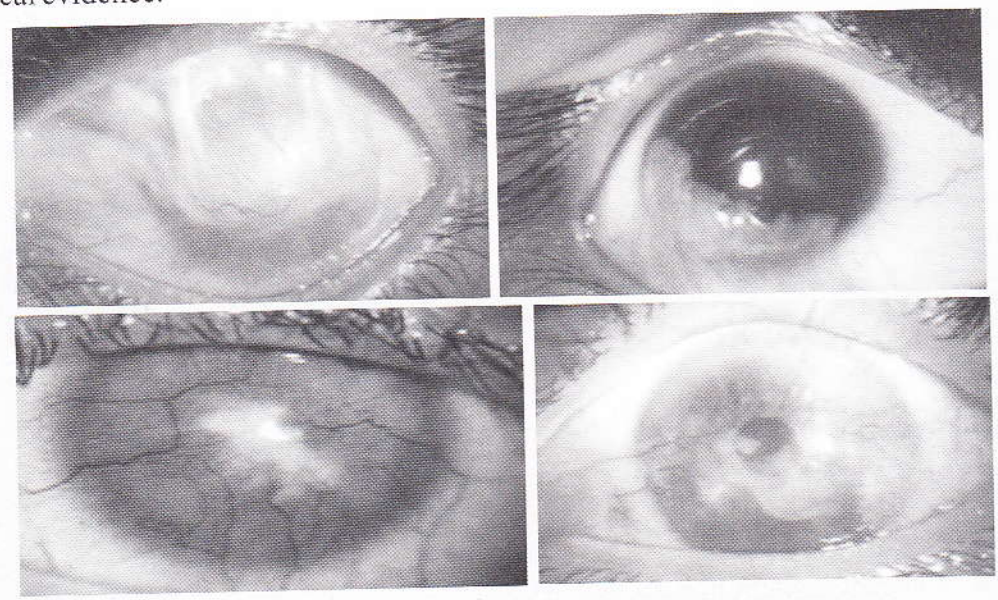
Progressive epitheliopathy with hazy, translucent epithelium extending centrally from the limbus, most commonly from the superior limbus. Epithelial staining, from punctate changes to more confluent staining, is broadest adjacent to the involved limbus and extends centripetally into the cornea to varying degrees in a whorl shape. Patients often have evidence of mild to moderate tear film dysfunction, superficial and deep vascularization, persistent epithelial defects leading to ulceration, melting, and perforation, fibrovascular pannus, and finally scarring, keratinization, and calcification.

Symptoms

Eye pain and blurry vision , Eye irritation, contact lens intolerance, and blurred or decreased vision were the most common symptoms in one study.

Clinical diagnosis

A diagnosis of limbal stem cell deficiency requires both clinical signs and symptoms of the disease along with cytological evidence.

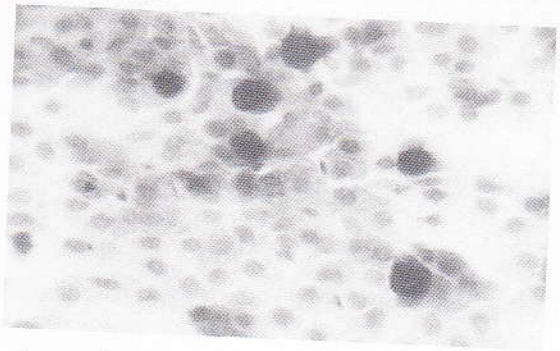


Diagnosis of limbal stem cell deficiency

LSCD can be detected clinically based on the presentation described above. Laboratory tests are necessary to confirm the diagnosis of LSCD and monitor success of surgical interventions. In this section, impression

cytology and in vivo confocal microscopy are discussed.

Impression cytology



Impression cytology has been the gold standard diagnostic test for LSCD.. It is therefore, ideal to study superficial cells, the epithelial morphology and goblet cells.The epithelial morphology alone cannot distinguish conjunctial epithelial cells from corneal epithelial cells.Immunocytochemistry on impression cytology specimens could identify the specific cytokeratin and hence the type of epithelium

In vivo laser scanning confocal microscopy

In vivo laser scanning confocal microscopy (IVCM) provides high-resolution images of the ocular surface at the cellular level. Recently, IVCM has been used to study corneal and limbal microstructures.Thereare significant microstructural changes in LSCD. Vera et al. reported corneal epithelial abnormalities and absence of the subbasal nerve plexus in patients with chronic Stevens-Johnson syndrome, toxic epidermal necrolysis and LSCD. Recently, microstructural changes have been detected in the cornea and limbus in LSCD compared to normal controls.36 In this study, patients are classified into 3 stages of LSCD: early, intermediate, late stage based on clinical presentation and evaluated the corneal and limbal epithelium changes on confocal microscopy. Significant microstructural changes in the corneal and limbal epithelium are seen even in the early stage of LSCD. The corneal epithelial cells in LSCD have less distinct borders and have prominent nuclei. The size of basal epithelial cells increases. Epithelial cells in the deeper layers become affected in more advanced stage of LSCD. In the late stage, epithelial cells show significant metaplasia and there is neovascularization. Compared with the healthy control subjects, eyes with early stage LSCD have an average of 38% reduction in basal epithelial cell density and a 58% reduction in subbasal nerve density. The limbal epithelium also shows similar changes and there is an absence of palisades of Vogt. A combination of morphological changes in the corneal epithelium, and a significant reduction in both basal epithelial cell density and subbasal nerve density might be the early signs of LSCD.

Detection of goblet cells in the corneal epithelium of patients with LSCD has been reported.However, there is inconsistency regarding the morphological features of goblet cells on the confocal images

MANAGEMENT

Medical management of limbal stem cell deficiency-Optimization of ocular surface health is the first step in the management of LSCD. Often, there are constant insults to the corneal epithelium from multiple concurrent external disorders such as dry eyes, ocular surface inflammation, soft contact lens, and drug toxicity from multiple eye medications the transplanted limbalgraft.Dry eyes can be treated with frequent preservative-free artificial tears, punctual occlusion, and topical cyclosporine. Long term preservative free topical cortical steroids might be necessary to control ocular surface inflammation as in chemical burns and Stevens-Johnson syndrome. In the case of LSCD due to contact lens wear, complete cessation of the wear is necessary and topical corticosteroids may facilitate the recovery.Fluid-ventilated, gas-permeable scleral contact lenses are valuable in the management of severe ocular surface disease. Scleral lenses also promote healing of PED refractory to other treatments and prevent PED recurrence.

Surgical management of limbal stem cell deficiency-Unilateral or bilateral partial LSCD may only require observation if the patient is asymptomatic. Repeated mechanical debridement known as the sequential sector conjunctival epitheliectomy, amniotic membrane transplantation, and ipsilateral limbal translocation to an area of LSCD are suggested as an early therapeutic option. Amniotic membrane promotes epithelialization and reduces angiogenesis and inflammation. It preserves and maintains the epithelial progenitor cells and thus can be used instead of limbal transplantation in the management of partial LSCD. Total unilateral LSCD requires a conjunctival limbal autograft which may be harvested from the healthy fellow eye. Recently, a technique called "simple limbal epithelial transplantation" was described. Direct transplantation of the 2 × 2 mm piece of healthy limbal donor is cut into pieces and secured on amniotic membrane using fibrin glue without ex vivo cultivation can successfully reconstruct the ocular surface after pannus excision. In total bilateral LSCD, limbal stem cell transplantation from allogeneic tissue is necessary. Allogeneic tissues may be obtained from a cadaveric or a living-related donor and transplanted to the ocular surface directly. Alternatively, transplantation of the cell sheet after cultivation can also achieve success. Allografts require prolonged systemic immunosuppression and the long-term survival of allograft is worse than that of autologous transplantation. Keratoprosthesis can be used as an alternative to allograft transplantation to avoid immunosuppression. The Boston type 1 keratoprosthesis can achieve an excellent visual outcome in eyes with LSCD secondary to non-immnumological disorders if there is adequate tear function. Bandage contact lens, conjunctival graft or oral mucosal graft might be necessary to stabilize the ocular surface. The osteo-odontokeratoprosthesis and the Boston type 2 keratoprosthesis are reserved for total LSCD with minimal or no tear function.

Amniotic Membrane Transplantation-Amniotic membrane transplantation (AMT) was first used by Kim and Tseng for corneal surface reconstruction in a rabbit model of total limbal deficiency. Tsubota et al later described use of amniotic membrane with limbal allograft transplantation in patients with ocular cicatricialpemphigoid and Stevensen-Johnson Syndrome. The procedure has been used to create a limbal barrier in pterygium surgery and for conjunctival surface reconstruction following excision of tumours, scars and symblepharon.The amniotic membrane is a thick basement membrane and avascular stromal matrix. Lee and Tseng theorise that these features are crucial to successful transplantation.

Tseng et al demonstrated that in eyes with chemical burns (n=14); Stevensen Johnson Syndrome, toxic epidermal necrolysis or pseudopem-phigoid (n=5); contact lens induced keratopathy (n=3); aniridia (n=3); multiple surgical procedures (n=2); atopy (n=2); and unknown cause (n=2), all amniotic membrane covered eyes (except for two eyes with atopy) showed rapid epithelialisation (2-4 weeks) and reduced inflammation, vascularisation and scarring. For the mean follow up of 15.4 months, 25 of 30 eyes showed visual improvement ranging from 1 to 6 lines. Coneal graft rejection occurred in 9 of 14 eyes and reversible early limbal allograft rejection in 3 of 21 eyes. They concluded that AMT alone is sufficient for partial limbal deficiency with superficial involvement and is superior to allo-limbal transplantation (ALT) since it is not necessary to administer cyclosporine.

Lee and Tseng performed AMT in 11 eyes for persistent epithelial defects with ulceration and obtained successful recpithelialisation in 10 of 11 eyes. Ongoing research into the regulatory mechanism of limbal stem cells may open up exciting frontiers leading to an enhancement of our therapeutic armamentarium in successfully managing these disorders.

In summary, diagnosis of LSCD is often clinical. Significant advances have been made to develop noninvasive tests to objectively diagnose LSCD in recent years. Diagnostic tests that can quantify the stem cell function may help to develop a classification system for LSCD, and monitor the progress of the disease and treatment outcomes. The management of LSCD remains challenging. Many medical and surgical options are available to rehabilitate the ocular surface. When judiciously used, successful outcomes can be achieved in a majority of cases.

Ocular Surface Disorders and relation to Glaucoma

*Dr Mayank Kumar Shukla

Ocular surface disease is a common comorbidity finding in glaucoma patients. The diagnosisof ocular surface disease in the glaucomapatient is often overlooked because the focusof management is on the evaluation of IOP and on the markers of glaucomatous disease progression[1]. Simon et al noticed prevalence of OSD in 47.6% patients on topical antiglaucoma medication[2] and 60% OSD observed by Leung et al.[3] Topical antiglaucoma medication for duration of three months or more has been found to induce significant degree of subclinical inflammation, which has been detected as increase dexpression of HLA–DR on conjunctival epithelial cells[4]. Pro-inflammatory cytokine secretion by conjunctival cells occurs in response to topical treatment for glaucoma[5].

The major effects of topical anti-glaucoma medication and their preservatives on ocular surface includes ocal allergic reactions, chronic conjunctival inflammation, tear film abnormalities, corneal epitheliopathy, punctuate epitheliopathy, medically resistant herpetic keratitis, disruption of epithelial function, chronic inflammatory infiltration, expression of inflammatory markers, impaired wound healing, squamous metaplasia[6,7]. Adverse effects of antiglaucoma medication on ocular surface have been widely described. Effects could be attributed to the active component as well as to the preservative which further amplify toxicity[8]. Most commonly used antiglaucoma medications – timolol and latanoprost, when on chronic treatment can cause ocular surface changes. Timolol reduces tear production, probably by systemic and/or local effects of beta-adrenergic receptor blockade in the lacrimal and/or accessory palpebral glands. It is also known to inhibit proliferation of corneal epithelial cells[6,7].

Side effects may be related to preservative concentration, duration of use, and number of instillation[9]. However, preservatives are needed to preserve the sterility of ophthalmic formulations after multidose bottles are opened[10-12].

Benzalkonium chloride (BAC), a quaternary ammonium compound, is the most commonly used preservative in topical ophthalmic preparations. Its turnover is very slow and may be retained in the ocular tissues for as long as 168 hours after application[13]. BAC promotes the activation of lipooxygenases, synthesis and secretion of eicosanoids, inflammatory mediators and many cytokines such as interleukin (IL)-1a, tumor necrosis factor and IL-8 and IL-10, resulting in irritation, delayed hypersensibility and allergic reactions[14]. Delayed and prolonged effect of BAC is because of incorporation and persistence of BAC molecules in cell membranes[15]. Preservatives exert a detergent effect on the lipid layer of the tear film. This reduces its stability, causing it to evaporate more rapidly, and results in increased ocular dryness[16]. The impaired protective layer, predisposes the eye to inflammation and conjunctival metaplasia. In addition, preservatives have destructive effects on the mucous gland, reducing the number of goblet cells and production of the protective mucus layer[17]. The three mechanisms of BAC toxicity described include a detergent effect, causing loss oftear film stability, direct damage to the cornea and conjunctival epithelium and immune-allergic reaction[15].

Long-term use of topical antiglaucoma therapy, particularly combination treatment regimens has been associated with failure of glaucoma filtration surgery[9,16]. It has been shown that subconjunctival fibrosis develops because of increased fibroblast density in the subepithelial substantia propria, linked to an increase in inflammatory cells[9,12]. Immunohistochemical study of conjunctival and trabecular specimens from surgical patients treated with antiglaucoma eye drops has revealed significantly greater expression of fibroblastic and inflammatory markers in samples from patients who were receiving preserved

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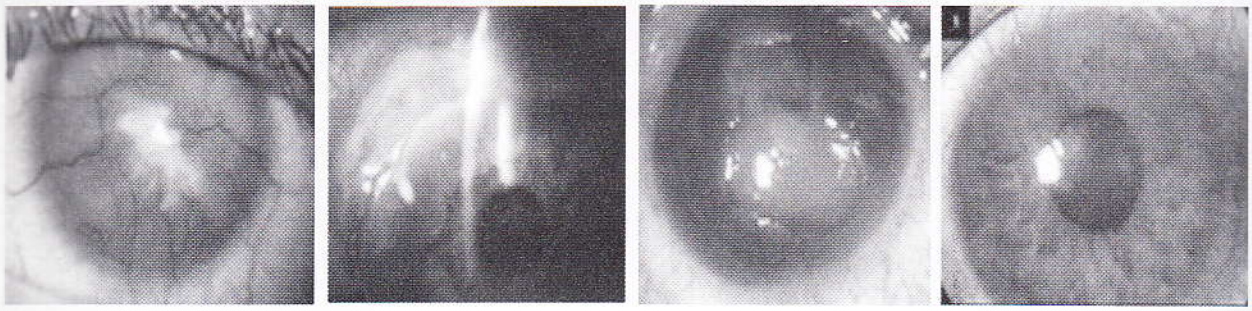
Expression of fibroblastic and inflammatory markers was seen to be higher in patients receiving polytherapy compared with those who were on monotherapy. Intensityof the inflammatory reaction seems related to the number ofpreservative-containing medications used and duration of treatment.

The innervation of the corneal epithelial cells and the stroma has an important influence in the corneal trophism and contributes to the maintenance of a healthy corneal surface1.The sub-basal nerve plexus along with stromal keratocytes secrete a number of neuro-peptides, which facilitate cell mitogenesis and migration, DNA synthesis, neurite extensionand survival, keratocyte proliferation and regulation of epithelialstem cells. Alterations in corneal innervations impairs the wound healing ability of the epithelium and results in dry eye.



The neuropeptides elaborated by corneal nerves influence corneal epithelial cells and these diffusible factors are believed to stimulate the epithelial growth, proliferation, differentiation and the production of collagen type VII16. The epithelial cells, in reciprocation, produce the soluble factors neuronal growthfactor (NGF) and glial cell-derived neurotrophic factor (GDNF)with a neurotrophic effect.

An alternative preservative to BAC is Purite®, a stabilized oxychloro complex (SOC). SOC consists of an equilibrium mixture of 99.5% chlorite, 0.5% chlorate, and trace amounts of chlorine dioxide. This preservative has been shown to have fungicidal, viricidal, and bactericidal activity. Although its exact mechanism of action has not beenfully elucidated, SOC oxidizes unsaturated lipids and glutathione in the cell and has proven antimicrobial efficacy. When SOC is instilled into the eye, it is converted into natural tear components: sodium and chloride ions, oxygen, and water. SofZia, the preservative used, is anoxidising complex containing borate, zinc and sorbitol, has less effect on human cells, which contain copious amounts of oxidases allowing the cells to withstand more oxidative stresses. Thus, ingeneral, oxidising preservatives are safe and effective at low concentrations while having less impact on the ocular surfaceof patients requiring chronic dosing of glaucoma medications.

Labbe A etal. compared toxicologicalprofile of BAC and Polyquaternium inexperimental study, found Compared toPQ-1, BAC consistently and dramatically altered the corneo-conjunctival surface as evaluated by slit-lamp examination, the fluorescein test, impression cytology, in-vivo confocal microscopy, and histology.

Concurrent use of topical cyclosporine to control ocular surface disease has been seen to be helpful in patients with chronic glaucoma who are on long-term usage of topical ocular hypotensive medications. A prospective comparative study done to evaluate changes in ocular surface after topical cyclosporine therapy, in chronic glaucoma patients on long-term topical antiglaucoma therapy has shown significant beneficial effects[16].This study evaluated the ocular surface evaluation of chronic glaucoma patientson long-term topical therapy treated concurrently with a topical cyclosporine 0.05% twice daily for 6 months compared to controls. The ocular surface evaluation tests, ocular surface disease (OSDI) indexscore (OSDI)), central corneal sensation were studied in these at recruitment and at the 6-month followup.

Schirmer's test, ocular surface staining scores, OSDI, corneal sensations, and corneal SBNFLD showed a statistically significant improvement following a 6-month concurrent topical CsA therapy in these patients.

Ocular surface needs to be evaluatedwith care in patients who are on long term anti-glaucoma therapy with consideration of use of concurrent topical cyclosporine to control the dry eye disease.

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ALPHABET PATTERN STRABISMUS

Dr Abhishek Agarwal, Dr Abhishek Chandra, Dr Tirupati Nath, Dr Himanshu Yadav

Duane first described "V" pattern in 1897 in a patient with bilateral superior oblique palsy[1]. But emphasis on importance of performing measurements in straight, upgaze and downgaze in strabismic patients was first given byUrrets-Zavalia in 1948[2,3].He also called attention to the fact that oblique overactions and underactions are associated with increased or decreased convergence or divergence in these positions. Urist[4]introduced this concept to American literature in 1951 and Albert suggested the excellent descriptive terms A and V patterns, which have now found worldwide acceptance.[5]

Definition and Classification

The terms "A" pattern and "V" pattern describe horizontal strabismus that is vertically incomitant. It is characterized by a substantial increase or decrease in the horizontal deviation in the midline position in upgaze as compared to downgaze.

1) **"V" pattern:-**The eyes are more converged in downgaze (more esotropic or less exotropic) than in upgaze.

2) **"A" pattern:-**The eyes are more converged (more esotropic or less exotropic) inupgaze as compared to downgaze.

By convention, the difference between upgaze(25°) and downgaze(35°) must be 15 PD (prism diopters) or greater to diagnose a clinically significant "V" pattern, and 10 PD diopters or more to diagnose an "A" pattern.

3) **"Y" pattern:-**The deviation changes minimally from downgaze to the primaryposition and diverge in upgaze.

4) **"λ"(lambda)pattern:-**The deviation changesminimally from the upgaze position to the primary position, but diverge in downgaze.

5) **"X" pattern:-**The eyes diverge in both upgaze and downgaze as compared to the primary position.

6) **Neutralizing pattern:-**There is orthophoria in the primary position and either divergence in upgaze and convergence in downgaze (neutralizing "V' pattern), or convergence in upgaze and divergence in downgaze (neutralizing "A" pattern).

Due to these variants in the European literature it has therefore become customaryto speak of strabismus with an *alphabetical pattern*.

Prevalence

A or V pattern co exist in about 12.5% to 50% cases of horizontal strabismus[6].According to the 1964 American Academy of Ophthalmology and Otolaryngology panel V esotropia is by far the most common anomaly, followed in order of frequency by Aesotropia, V exotropia, and A exotropia[7].A" and "V" patterns are relatively frequent in patients who have had congenital strabismus.

Etiology

Different mechanisms may be responsible in different patients. The proposed theories are:

Oblique muscle Dysfunction

The most popular theory, suggested by Knapp in 1959[8] attributes most cases of "A" and "V" pattern to the role of oblique muscle dysfunction and the contributing effect of the accompanying torsion. Abduction is a tertiary action of the superior and inferior oblique muscles. Thus, if

A)The superior oblique muscle is overacting, and the antagonist inferior oblique is underacting, there is relative divergence in downgaze and convergence in upgaze; resulting in an "A" pattern

B)The inferior oblique muscle is overacting and the superior oblique muscle is under- acting, there is convergence in downgaze and divergence in upgaze, resulting in a "V" pattern.

The torsion that accompanies oblique muscle dysfunction also contributes to the associated "A"-or "V" pattern[9], V-pattern is associated with excyclotropia due to inferior oblique muscle overaction and A-pattern is associated with incyclotropia due to superior oblique muscle overaction.

Horizontal rectus muscle dysfunction

Urist(1958) believed that horizontal rectus muscles were responsible for this incomitance[6,10], in V esotropiaoveraction of the medial rectus muscles caused the increased convergence in downward gaze and overaction of the lateral rectus muscles was responsible for the increased divergence in upward gaze. Conversely, increased divergence in downward gaze in Aexotropia was thought to be caused by underacting medial rectus muscles and in A esotropia by underacting lateral rectus muscles.

Vertical rectus muscle dysfunction

Brown(1953) had the opinion that A or V patterns may be caused by primary anomalies in the function of the vertical rectus muscles in which adduction is the tertiary action. For example, if the superior rectus muscles are primarily underacting, their adductive effect in upward gaze will decrease; in fact, the eyes will diverge in upward gaze because of secondary overaction of the inferior oblique muscles. In downward gaze, secondary underaction of the superior obliques will cause decreased abduction and secondary overaction of the inferior rectus muscles, resulting in increased adduction of the eyes,which, according to Brown, would produce a V pattern.

Anomalies of orbit

Urrets- Zavalia and coworkers,[11] in a study of Bolivian Indian children, found out that in *mongoloid* type of facial development (hyperplasia of the malar bones, upward slanting of the palpebral fissures, and a straight lower lid margin)esotropia was frequently associated with underacting inferior oblique muscles (A esotropia) and exotropia with overacting inferior obliques (V exotropia). In white children with *antimongoloid*features (hypoplasia of the malar bones, downward slanting of the palpebral fissures, and S-shaped contour of the lower lid margin) the opposite was found, esotropia associated with overacting inferior oblique muscles (V esotropia) and exotropia with underacting inferior oblique muscles (A exotropia).

Sagittalization of oblique muscle insertions (figure 4)

In Sagittalization the oblique muscle becoming more parallel to the sagittal (anteroposterior) axis and indesagittalizationoblique muscles become more parallel to the coronal plane concept of which was given

by Gobin[12]. If the superior oblique is desagittalised due to the retroplacement of trochlea (as in plagiocephaly), it becomes a poorer depressor. And relatively the inferior oblique becomes a stronger elevator. Similarly with a more frontally placed trochlea (as in hydrocephalus with frontal bossing), superior oblique becomes more sagittalised in relation to the inferior oblique making it a stronger depressor. This relative action can cause A and V patterns .

Heterotropia of muscle pulley

Demer et al[13] proposed the presence of fibromuscular pulleys of the recti and inferior oblique muscles. Just like the trochlear pulley for superior oblique tendon. If these pulleys are displaced, incomitant deviations can be caused. For example: upward displacement of medial rectus pulleys and downward displacement of lateral rectus pulleys results in A pattern.

Sensory Deprivation

Guyton and coworkers had the view that loss of fusion predisposes the oculomotor system to cyclodeviations of the eyes which, in turn, cause A and V patterns according to the mechanism proposed by Weiss[14]. Guyton and Weingarten showed that formerly fusing patients with intermittent exotropia who lost fusion after surgical overcorrection may develop A or V patterns.

Presentation:

1) **Asthenopia and diplopia:** common complaints in patients with A and V patterns, the increase in a deviation in downward gaze (with A exotropia or V esotropia) may cause acute visual discomfort during reading ,On the other hand, an increase in the deviation in upward gaze (with V exotropia) is best tolerated by most patients since little or no interference with binocular vision.

2) **Anomalous head posture:** The patient with Aesotropia and V exotropia and fusion in downward gaze may hold his or her chin in an elevated position. Conversely, V esotropia and A exotropia may cause chin depression .

   Some adults with an "A" or "V" pattern may not become symptomatic until they become presbyopic; until they need to get their eyes into downgaze to read through their bifocal segment.

Examination

Vision assessment, refraction, detailed orthoptic evaluation with full correction which includes: Abnormal head posture, cover test, examination of ocular movements, Prism bar cover test, sensory evaluation and fundus examination should be done.

Motor Examination:

Alternate prism cover testing is performed with head held in primary gaze using an accommodative target at 20ft (6m). The measurements are made in primary position,upward (25°) and downward gaze (35°) to establish whether an A or V pattern is present and if so whether it is clinically significant. Stuart and Burian established that divergence of the visual lines in upwardgaze and convergence in downward gaze are physiologic variants. Thus V pattern in which the difference in deviation between upward and downward gaze is 15 Δ or more should be considered a significant vertical incomitance. Since an A pattern is never found as a normal variant, a limit of 10 Δ has been set beyond which an A pattern is thought to be significant.

Pseudo A and V Patterns: A pseudo V pattern may be seen in patients with accommodative esotropia. This occurs if the patient having a small amount of hyperopia is tested without using hyperopic correction.

Uncorrected hyperopia gives rise to accommodation in primary and downgaze, as opposed to upgaze, simulating a V pattern. Similarly V- Pattern strabismus may also be seen in cases of intermittent exotropia. Hence full optical correction must be given prior to motor examination.

It is also important to recognize that a "V" pattern may simulate a high AC/A ratio if care is not taken to keep the fixation target in the primary position at near.

Sensory Examination:

Patients with "Y" patterns, or "λ" patterns may be well aligned in the primary position and may have surprisingly good fusion.

If a patient is tropic in all fields of gaze, suppression and varying depths of anomalous retinal correspondence (ARC) may be found.

Ciancia and Helveston et al. found that in patients with "A" or "V" pattern and ARC, the angle of anomaly varies with the angle of deviation, thus resulting in the ARC being harmonious in all fields of gaze.[15]

Treatment:

Goals:

1) To maintain,improve or regain binocular single vision.
2) To restore patients normal facial configuration i.e to eliminate chin elevation or depression.
3) To establish binocular fusion in functional position of gaze.(primary and reading position)

General Principles

- Both sensory and motor components should be addressed.
- Full refractive correction should be prescribed.
- Remove suppression and treat amblyopia before surgery.
- Ocular movements should be carefully assessed.
- Surgery done if the deviation causes symptoms, cosmetic defect and/or produces sensory anomalies like suppression/amblyopia.

Surgical methods:

Vertical transposition of horizontal recti: (figure 3)

Basis: The action of a muscle is weakened in the direction in which its insertion is shifted. This procedure should be considered only if the obliques are not overacting.

1/2 width transposition: corrects upto 15 PD of pattern.

Medial rectus is transposed towards the apex of V.

Lateral rectus is transposed towards the base of V.

Slanting muscle recessions:

Basis: Horizontal muscle tensions are different between the upper and lower margins of the muscle with variant amounts of gaze[16], i.e, horizontal muscle tension at the upper margin is stronger than that at the lower margin in upward gaze.

In the slanting surgery, the upper margins of the LR are recessed more than the lower margins to gain a greater effect on horizontal deviation in upward gaze in patients with "V" exotropia. The usual amount of the selective shift of the tendon to slant its insertion is 2-mm backward.

Surgery on oblique muscles

Inferior oblique surgery

It is indicated in presence of inferior oblique over action and V pattern strabismus. The usual resulting correction after any of the procedures is about 20 PD in elevation[17]. Various weakening procedures include myectomy, Inferior oblique recession or anterior transposition. Bilateral IO myectomies has no effect on the horizontal alignment in primary position[18,19]. Inferior oblique anterior transposition gives more effect than IO recession, but it results in limitation of elevation, so is preferred for patients with dissociated vertical deviation (DVD).

Superior oblique surgery

- Superior oblique weakening should be performed very cautiously as it affects the reading gaze of the patient. Therefore, it is indicated only in patients with significant superior oblique overaction.
- Superior oblique tenotomy is the most commonly performed procedure for superior oblique weakening.

Specific Management

A-Pattern Esotropia

(a) *Patients without superior oblique (SO) muscle overaction*- Recession and symmetric supraplacement of the tendons of the MR muscles by one-half tendon width.

(b) *Patients with SO muscle overaction*- Bilateral SO tenotomy/posterior tenectomy and horizontal rectus recessions to correct esotropia in primary gaze.

A-Pattern Exotropia

(a) *Patients without SO muscle overaction* - Recession and symmetric infraplacement of the tendons of the LR muscles by one-half tendon width.

(b) *Patients with SO muscle overaction* - Bilateral SO tenotomy/posterior tenectomy combined with symmetric surgery on the horizontal rectus muscles to correct exotropia.

V- Pattern Esotropia

(a) Patients without inferior oblique (IO) muscle dysfunction-Recession and symmetric infraplacement of the tendons of the MR muscles by one-half tendon width.

(b) Patients with IO muscle dysfunction - Weakening of IO muscles is combined with appropriate MR recession.

V-Pattern Exotropia

(a) Patients without IO muscle dysfunction - Recession of the LR muscles with supraplacement by one-half tendon width.

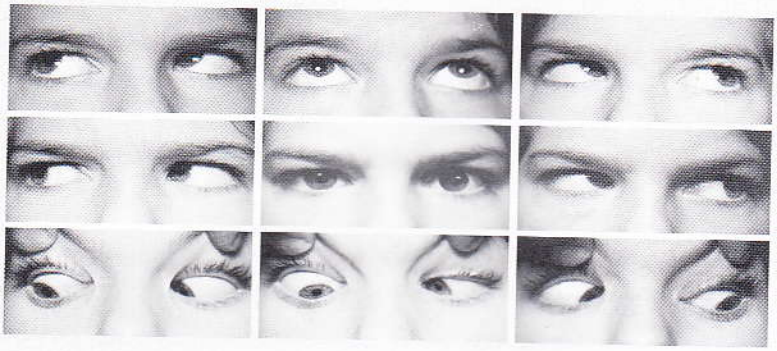
(b) Patients with IO muscle dysfunction- IO muscle should be weakened symmetrically and appropriate recession of the LR muscle performed to correct exodeviation in primary gaze.

Y-Pattern

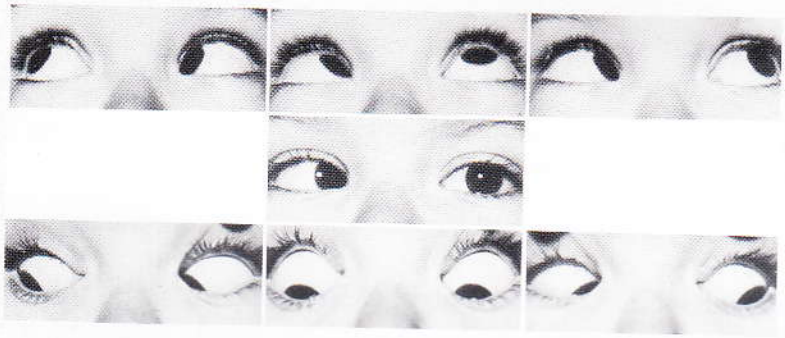
Y esotropia or exotropia usually have IO overaction with evidence of fundus excyclotorsion. Bilateral weakening of IO muscle reduces or eliminates the pattern in upgaze.

Lambda (λ) Pattern

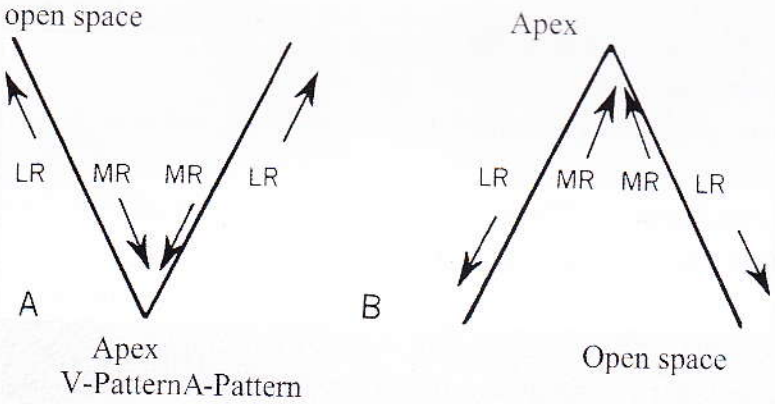
Bilateral weakening of SO will reduce the λpattern if SO overaction is present.



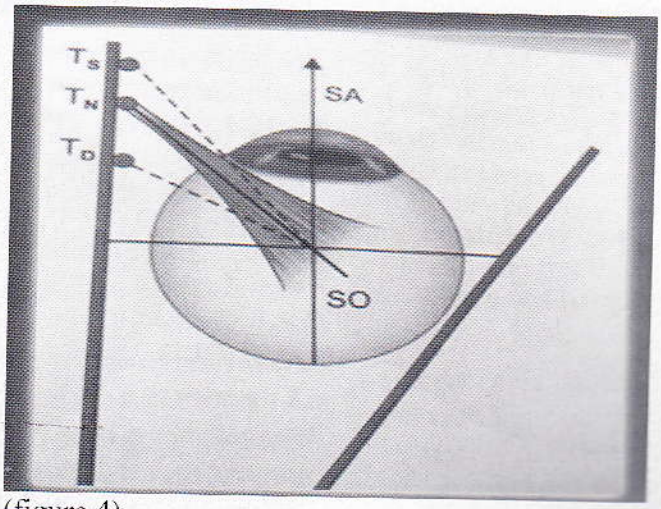
V-Esotropia



A-Esotropia



(Figure 3)



(figure 4)

Conclusion:

Various factors are responsible for pattern strabismus and hence every case is a different case. Special emphasis must be given on measurement of deviation in primary position,upgaze and downgaze, and oblique muscle dysfunction is to be looked carefully as it can significantly alter the surgical management.

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APPLICATIONS OF ANTERIOR SEGMENT OCT IN GLAUCOMA

- KHUSHBOO AGARWAL, TIRUPATI NATH

Optical coherence tomography is a novel,three dimensional technology that allows detailed cross-sectional imaging of the eye based on the principle of low- coherence interferometry.[1] Huang et al[2] first described optical coherence tomography of the eye in 1991,and Izatt et al described anterior segment OCT(ASOCT) imaging using the same wavelength of light as in retinal OCT i.e. 830nm but this wavelength was unsuitable for optimal imaging of the anterior chamber angle so a longer wavelength of 1310nm is now used for better penetration through sclera. The current systems available are-

1.Visante™OCT approved by the US FDA in 2005.

2.Slit lamp OCT (SL-OCT) approved by the US FDA in 2006.

3.Optovue (RTVue) commercially available Fourier domain OCT system with a resolution of 5 microns that received marketing clearance from the FDA in2010.Although indicated for posterior segment imaging, a lens is available to allow imaging of the anterior segment.

APPLICATIONS

1)Angle closure glaucoma

-ASOCT allows detailed imaging of anatomy of cornea, iris and sclera.Structures in the anterior chamber angle can be clearlydelineated, such as the scleral spur and the angle recess. Howeverstructures in the posterior chamber are not well delineated due toattenuation of the light beam of OCT by the pigmented epitheliumof iris.

-Quantitative assessment of angle structures

The scleral spur is used as the landmark for measuring anterior

Chamber angle parameters[3]. Itis seen as a highly reflective structure on AS-OCT images. The parameters formeasurement of the angle are

Angle opening distance at 500μm (AOD 500)[4]: Defined as theperpendicular distance between the iris and trabecularmeshwork (TM) at a point 500μm away from the scleral spur. This parameter was first described by Pavlinand colleagues for Ultrasound Biomicroscopy(UBM)[5].

Angle opening distance at 750μm (AOD750)[4]: Angle openingdistance is measured 750μm away from the scleral spur insteadof 500μm. It was suggested byRadhakrishnan et al.

Angle Recess area at 500,750 μm (ARA 500, ARA 750)[4]: ARAwas first described by Ishikawa[6] and co-workers for UBM. Itis a triangular area, boundaries of which are AOD 500 orAOD 750 (base), angle recess (apex), the iris surface and theinner corneoscleral wall (sides of the triangle). The ARA maytheoretically be a better parameter than AOD as it takes intoaccount the contour of the iris surface rather than a singlepoint on iris as is the case with AOD.

Trabeculo-iris space area at 500, 750μm (TISA 500, TISA 750)[4]: This parameter was proposed by Radhakrishnan et al.It is a trapezoidal area bounded by AOD 500 or AOD 750anteriorly, a line drawn perpendicular from the scleral spurto the opposing iris, the corneoscleral wall superiorly and theiris surface inferiorly .

Trabeculo-iris contact length (TICL) [4]: Defined as the linearlength of contact between the iris and the trabecularmeshwork, beginning at the scleral spur in an anatomicallyapposed or synechially closed angle. It was proposed by Radhakrishnan et al.

All quantitative measurements of the ACA require identificationof scleral spur as the first step. However, according to a recentstudy by Sakata et al, it was not possible to identify the scleral spurin 28% of the eyes on images taken on VisanteOCT[7]. This studyalso found that it is more difficult to identify the scleral spur inpatients with narrow angles than in patients with open angles.

Another study reported that interobserver variability in theidentification of scleral spur can lead to 50% variation inmeasurement of angle area (ARA, TISA) and 10% variation inlinear measurements (AOD).

-Angle assessment can be done in corneal opacity and corneal edemaunlike gonioscopy.

-allows the evaluation of efficacy of various treatmentsuch as laser peripheral iridotomy (LPI)[8], effect of cataract surgery on anterior chamber angle.Memarzadeh et al studied the change in anterior segment morphology by ASOCT and gonioscopy before and after LPI[9]. They noted a significant increase in AOD500,ARA500, TISA 500 and TISA 750 after PI. On OCT images, theconvex iris configuration flattened after LPI.

2.Pachymetry

The ASOCT allows cross-sectional visualization and measurementof central corneal thickness(CCT). It has a direct influence onintraocular pressure (IOP) measurements. Ocular Hypertension Treatment Study (OHTS) for the first time made a critical discovery regarding corneal thickness and its role in intraocular pressure and glaucoma development.

In clinical practice, intraocular pressure is the only modifiable risk factor in the management of glaucoma. According to manometric data from Ehlersand colleagues[10], 44% of patients with normal-tension glaucomawould be reclassified as having primary open angle glaucoma, and35% of patients with ocular hypertension would be reclassified ashaving normal IOP when CCT is taken into account. Herndon etalfound that as many as 65% of patients with ocular hypertensioncould be reclassified as having normal IOP.

Measuring CCT consistently provides additional knowledge regarding IOP accuracy as well as possible prognosis and future treatment effect.

In guidelines established by the American Academy of Ophthalmology (AAO), CCT was recommended as part of the initial examination for POAG and the glaucoma suspect. The relevance of CCT, as stated by the AAO[11]preferred practice pattern for primary open angle glaucoma(POAG), is based on the fact that it "is a risk factor in that it affectsaccuracy of IOP measurements by all applanation techniques. "

3.Imaging of trabeculectomy blebs

Bleb characteristics like bleb structure,location of scleral flap,presence of cystic spaces,bleb height, size of bleb cavity, bleb wall thickness, scleral flap thickness, tangential and radial dimensions of the bleb. Singh et al[12] studiedthe ASOCT characteristics of trabeculectomyblebs and found that conjunctivalepiscleralthickening in the bleb wall was the hallmark of blebs inwhich IOP was successfully controlled.

OCT is particularly helpful in demonstrating level of failure infailed bleb as it can demonstrate ostial closure, flap fibrosis orepiscleral fibrosis as the cause of bleb failure. It can thus help ininitiating appropriate management in rescuing a failing bleb.

4.Glaucoma drainage implants

AS-OCT provides high resolution images of glaucoma drainage implant and help in assessing position, patency, drainage, intra-luminal stent suture,tube-cornea or tube-iris touch.

AS-OCT VS GONIOSCOPY

Closed angle on gonioscopy is defined as non-visibility of posterior TM, whereas angle closure on ASOCT is defined as any contact between

peripheraliris and angle wall anterior to scleral spur[13]. In comparison to gonioscopy, AS-OCT show less interoperator variabilitydoes not require technical expertise. Angle can be viewed in its natural state without distortion of angle structures as AS-OCT is a non-contact technique.Thus, AS-OCT could be used to screen patients for primary angle closure.But it is unlikely that gonioscopy will ever be completely replaced, as several imaging techniques like AS-OCT are dynamic and does not allow complete(360) visualization of angle.

AS-OCT VS UBM

Ultrasound biomicroscopy, a diagnostic method described in the early1990s , uses a high frequency transducer (50-100 MHz),thus permitting an axial and lateral resolution of around20 to 40 micron, even though at the expense of a reductionin ultrasound penetration (approximately 5 millimeters)[14]. The advantages of the method are the possibilityof evaluating retro iris structures and performingquantitative measurements of the camerular sinus.The benefits of UBM include its utility in identifying nonpupillary block mechanisms for angle closure mechanisms that may contribute to angle closure in the majority of Asian patients[15].Both UBM and AS-OCT can identify narrow and

closed angles with reasonable performance. Neither, however, can reliably differentiate between appositional and synechial closure, an essential distinction prior to surgical intervention.Finally, the identification of the scleral spur can be ambiguous for both UBM and AS-OCT. Without the localization of this landmark, diagnostic uncertainty may remain[16].

Main limitations of UBM are: high cost, the dependence of aqualified examiner, the observation of a restricted regionof the camerular sinus, and the need for dipping the ultrasound probe.

CONCLUSION

Widespread use of anterior segment OCT may permit accurate diagnosis of angle closure cases thus help pick up more cases of angle closure, which constitutes 50% of all glaucoma cases worldwide[17,18]. Ease of image acquisition and noncontact nature may make it a desirable tool for large-scale

screening of patients with narrow angles. Furthermore, it's apotentially valuable tool in glaucoma research and may help usunderstand better the natural history and patho-physiologic mechanism behind different types of glaucoma. However, thereare certain limitations of ASOCT such as limited visualization ofstructures posterior to the iris and difficulty in identification of keylandmarks (e.g. scleral spur) in closed angles.

IMAGES OF VISANTE A-OCT

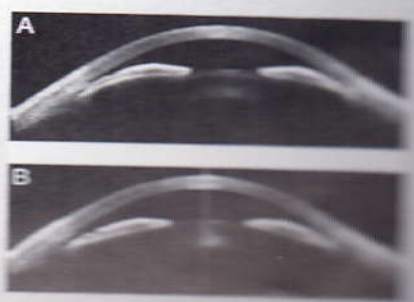


FIGURE 1:-(A) Anterior segment OCT image with relatively lower ACD (1.64 mm) and higher LV (1.3 mm) at pre LPI. This eye showed greater AOD750 change (255.8%) after LPI (B).

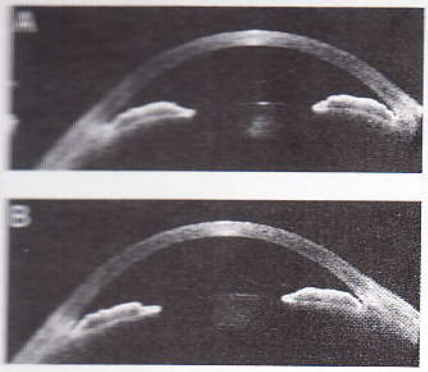


FIGURE 2:-(A) Image of eye with relatively higher ACD (2.20 mm) and lower LV (0.95 mm). (B) A small amount of AOD750 change (64.4%) after LPI

IMAGES OF FOURIER DOMAIN AS-OCT

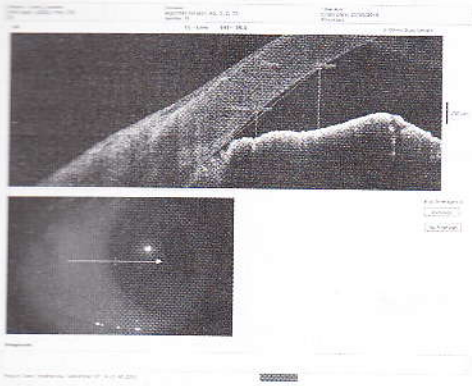
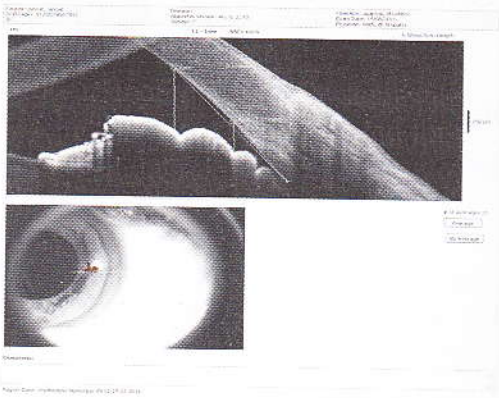


FIGURE 3:-AOD at 1mm and 2mm



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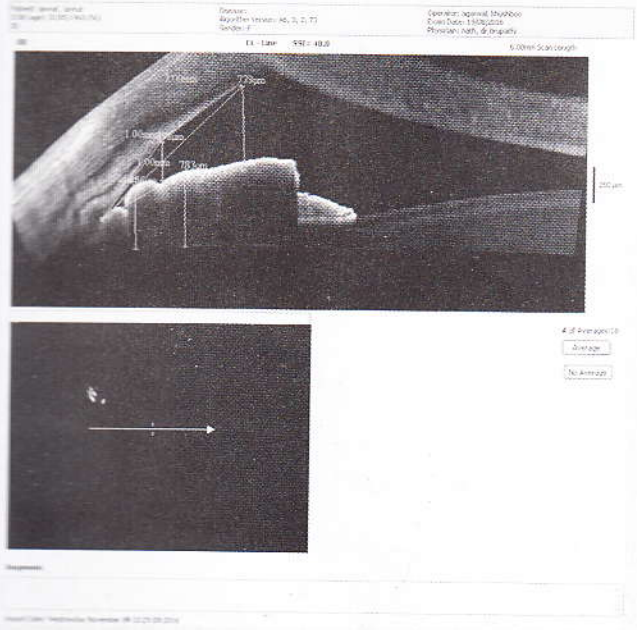


FIGURE 5:- AOD at 1mm and 2mm ; IT at .5mm and 1mm:convex iris curvature

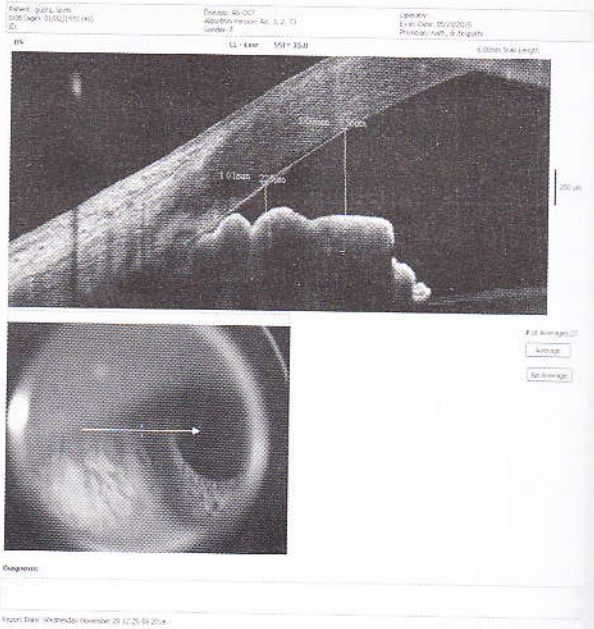


FIGURE 6:-AOD at 1mm and 2mm

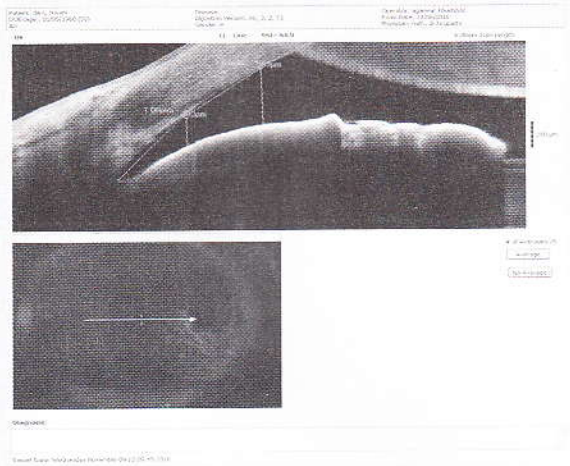


FIGURE 7:-AOD at 1mm and 2mm

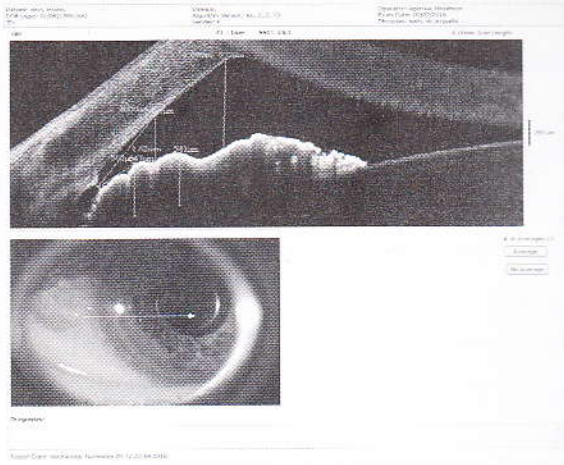
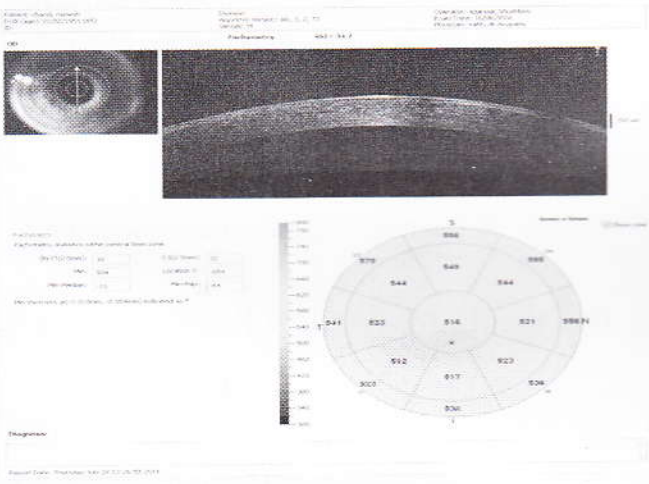
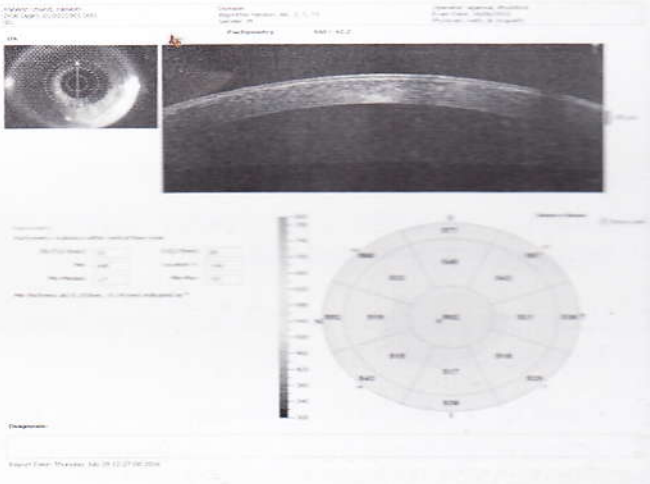


FIGURE 8:- AOD at 1mm and 2mm ; IT at .5mm and 1mm:convex iris curvature

PACHYMETRY





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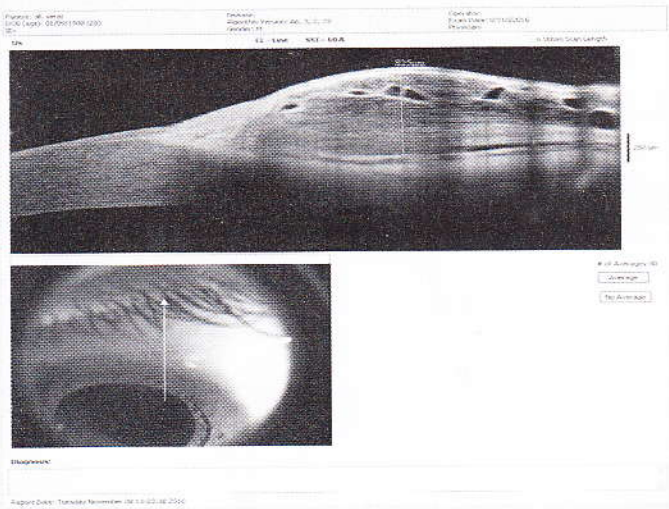

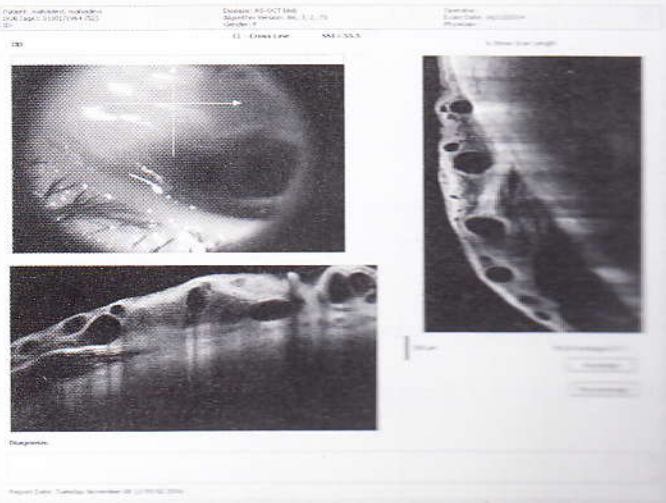

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LASERS & ITS APPLICATIONS IN OPHTHALMOLOGY

Dr. Vinit Kumar S Kamble *

An acronym for LASER , Light Amplification by Stimulation Emission of Radiation was first coined by Gurden Gould. In 1916,Albert Einstein laid the foundation for invention of laser. The first working laser in Ophthalmology was made by Theodore Maiman in 1960. He utilized pulsed ruby laser coupled with monocular direct ophthalmoscopic delivery system.

Properties :

Monochromatic: having one colour/wavelength.

Coherence: spatial & temporal. The light from a laser is said to be coherent, which means that the wavelengths of laser light are in phase in space & time.

Collimation. Ordinary light can be a mixture of many wavelengths. **Directional**: laser light is emitted as a narrow beam as compared to ordinary light from light bulb is emitted in many directions away from source. Due to all these properties laser light can deposit a lot of energy within a small area.

How LASER works ? : All lasers in use require 3 basic elements:

1) An active medium that emits coherent radiation
2) A means of energy input known as pumping
3) The opportunity for oscillation & amplification through optical feedback.

Principle: Radiation emitted by spontaneous emission (Bohr's model) occurs randomly in time, but radiation emitted by stimulated emission (Einstein) is in phase with the stimulating wave & is therefore coherent.

Effects of Lasers : Laser tissue interactions :

Photothermal	**Photochemical**	**Mechanical**
⇩	⇩	⇩
Photocoagulation / Photovaporization	Photoradiation/ photoablation	Photodisruption
E.g Argon,Krypton,Diode , Nd:YAG crystals	E.g Excimer(193nm)	E.g.Femtosecond(1053nm)

Mode of operation : which depends on :

Laser material used & mode of excitation of material.

Types of Modes :

- Continuous wave operation
- Conventional pulsed operation : Q switched & Mode locked

Continuous wave operation :

Output is relatively constant with respect to time.

*DNB, RIO,IGIMS,Patna

It delivers overall more total energy & less power.

Delivers Energy over a relatively long period (fraction of sec. to a sec.).

e.g Argon, Krypton etc.

Conventional pulsed wave operation :

Mode locking is a technique by which laser can be made to produced pulses of light of extremely short duration,in order of picoseconds $10^{-12 sec}$ or femtoseconds $10^{-15 sec}$

APPLICATIONs :

Lasers in Glaucoma

Angle-closure glaucoma is usually due to pupillary block between the lens and iris. This prevents aqueous from following its normal course through the pupil to the angle & Schlemm's canal & out of the eye. Pupillary block results in the peripheral iris being pushed against the cornea, there by blocking off the angle. Therapy is directed towards creating an internal bypass with an opening in the iris between anterior & posterior chambers. Before lasers, this was achieved by a surgical iridectomy, but now the laser has all but eliminated this procedure. An iridotomy is created by the absorption of irradiated light by the melanin in the iris, resulting in a thermal effect with disruption & hole formation.

Lasers in Diabetes

Diabetic retinopathy is broadly divided into nonproliferative & proliferative types. In the nonproliferative type consist (venous dilation, aneurysms, hemorrhage, edema, exudates). These five stages can then be classified on ETDRS. Proliferative retinopathy includes the production or proliferation of new tissue, supportive or neovascular in nature in the chorio-retinal area secondary to retinal hypoxia. These include neovascularization at the disc &/or retina, glial proliferation & vitreoretinal traction. The basic rationale of laser photocoagulation is to destroy neovascular complexes, to obliterate areas of micro infarction or capillary closure, to destroy leaking vessels in the macular & paramacular region & to produce a chorio-retinal adhesion that will resist the later ravages of increasing vitreoretinal traction. The proliferation of neovascular tissues is probably the result of localized hypoxia in the region of the retinal vessels near the internal limiting membrane. It would seem that these blood vessels are proliferating in response to some biochemical substance. Intravenous fluorescein angiography consists of injecting sodium fluorescein into the antecubital vein & recording the results photographically at intervals of 0.6 to 0.8 seconds. All abnormalities of the retinal circulation can be seen & treated accordingly.

Panretinal photocoagulation appears to successfully obliterate or cause the regression of neovascularization by one of four mechanisms: the reduction or destruction of areas of hypoxic retina that are producing the vasoformative factor that causes neovascularization from healthier areas of the retina; adherence of retina to choreocapillaris (choroid), allowing more oxygen from choroid to retina; destruction of infarcted areas of retina, allowing more blood to the healthier retina; destruction of leaking vessels & abnormal vascular complexes, which normalizes blood flow to the macular area.The panretinal photocoagulation(PRP) is conducted in three to six stages in approximately two to seven days. Coagulation of 100 to 200 microns in diameter with power intensities from 100 to 400 mw & exposures of 0.05 to 0.2 seconds with sites increasing as one treats the more peripheral retina.

Posterior Capsulotomy

One of the most common uses of the Nd-YAG laser is to perform a posterior capsulotomy. There may be less incidence of edema of the macula (cystoids maculopathy) & decreased retinal detachments with the extracapsular method, which also allows for the insertion of a posterior chamber intraocular lens vs.anterior

chamber lens. This again is not clear cut, but it may be more physiological in the posterior chamber & there may be less long-term corneal complications. One of the problems with the extracapsular technique is that the capsule sometimes becomes opaque. Before the YAG laser this had to be dealt with surgically, but now can be done with the ionizing effect of the YAG.

Retinal Tears

The symptoms that may occur with retinal tears are variable & include floaters, sudden showering of spots & opacities, lightning flashes, & blurring of vision. The problem with retinal tears is akin to a tear in the vinyl lining of a swimming pool. Water will eventually seep under the lining & lift the lining off. If the tear is diagnosed early before the retina has lifted, detachment can be prevented by scarring down the retina surrounding the tear. This may be accomplished by using a laser usually the argon laser. If detachment has occurred, then the retina has to be drained & a buckle placed around the sclera. Most floaters are indicators of vitreous degeneration, but a sudden onset probably should be assessed for retinal problems.

Macular Disease

Serous retinal pigment epithelial detachments are round or oval domed elevations of the retinal pigment epithelium. Fluorescein dye will readily collect there. These serous detachments can occur with or without subretinal neovascularization/CNVM . The treatment of the serous detachments without neovascularization is controversial. One prospective study found that argon laser treatment was of no benefit & perhaps harmful. Clinical signs of a subretinal neovascular membrane are a greyish or green pigmentation deep to the retina, subretinal or retinal hemorrhage, hard exudates & subretinal fluid. The membrane is then outlined by fluorescein & its distance from the fovea is measured. There is a foveal avascular zone measuring 400 microns in diameter which cannot be treated with laser as it may obliterate central acuity. Therefore, if the membrane is 200 microns or more from the center of the fovea, the entire membrane should be treated with laser photocoagulation. The most common scenario is that the patient comes to see the ophthalmologist after losing central acuity in one eye & there is no treatment due to scarring following hemorrhage, serous detachment with neovascularization or atrophic degeneration. It is important to advise the patient to monitor the fellow eye daily (by Amsler grid testing) with a view that if subretinal neovascularization should develop, it may be amenable to laser therapy .

Cataract surgery

Cataract surgery has been performed for over two millennia, but advances in technology have transformed the fundamental procedure only over the past 40 years. The use of ultrasound vibration to remove cataracts through a small incision was pioneered by Charles Kelman in the 1960 & the technique has been developed to become the standard procedure for most cataract extractions in developed countries. The Kelman phacoemulsification procedure has also become the main frame work upon which innovations in cataract surgery are built. Such innovations are driven by the need for less trauma during surgery & faster visual recovery after surgery. Surgeons have strived to reduce incision size, heat, intraocular turbulence & fluid level in order to achieve these objectives .Ultrasonic phacoemulsification probe tips tend to create relatively high levels of heat within the eye, resulting in the possibility of injury to the cornea such as corneal burns & endothelial damage. Technological advances over the past decade have reduced the effective energy liberated by the probe, chiefly through using ultrasound energy more efficiently.Perhaps the most promising front in a traumatic phacoemulsification surgery is the application of the yttrium-aluminum-garnet (YAG) laser towards emulsifying the cataract. The first laser procedure for cataract surgery was reported in 1975 by Krasnov, who used a technique called "laser phacopuncture" to make microperforations on the anterior capsule. These pores then allowed the release of lens material into the anterior chamber, which would be theoretically resorbed over time. Krasnov's Q switched ruby laser technique had limited application, since the micropores would only allow the release of very soft cataracts. Furthermore, patients had to be maintained on dilator drops for extended periods to prevent the puncture sites from closing & steroid drops

to reduce anterior uveitis that inevitably occurred from the released cataract in the anterior chamber. Additional experiments with laser cataract surgery occurred with excimer lasers, most notably the 308 nm laser. The xenon chloride 308nm laser was introduced in the late 1980s, but was abandoned for cataract surgery due to concerns over retinal toxicity. The neodymium:yttrium-aluminum garnet (Nd:YAG) laser was used successfully to perform posterior capsulotomy in 1980. The YAG laser gained wide acceptance among surgeons as an excellent method of treating posterior capsular opacification after cataract surgery. The popularity of the Nd:YAG laser in posterior capsulotomies motivated researchers to explore how the YAG laser could be used to treat cataracts. A technique called laser photofragmentation, which uses the Nd:YAG laser to soften the nucleus before phacoemulsification, was explored in the mid-1980s. This procedure did reduce phacoemulsification power & time, but also increased the risk of capsular perforations.

The YAG laser has the potential to dramatically reduce the energy required to perform cataract surgery. Two types of YAG lasers are being developed for cataract surgery: the neodymium:YAG (Nd:YAG) & Erbium:YAG (Er:YAG) laser. The pulsed Q switched Nd:YAG laser, which emits at 1064 nm, does not produce direct laser light at the tip; instead, it generates shock waves through a titanium block at the tip to photolyse the cataract. This technology produces negligible heat at the tip & therefore does not require a cooling sleeve to avoid corneal burns. Consequently, incisions as small as 1.25 mm can be used to perform the procedure. Laser emulsification is relatively short for most cataracts, but can take over 10 minutes for nuclear sclerosis over 3+. Another Nd:YAG laser, which uses photoacoustic ablation under aspiration, delivers energy through a skishaped distal tip to create a "photon trap". This technology is most useful for softer nuclear sclerosis. The Er:YAG laser, which emits at 2940 nm, relies on its infrared spectrum wavelength in cataract surgery. At this wavelength, the laser produces cavitation bubbles that collapse slowly in the cataract & very quickly in water. This leads to propagated energy within the lens, allowing the laser to emulsify the material efficiently without producing thermal energy. The laser can be used with a prechopper to reduce the operating time.

Each of these YAG laser technologies can be coupled with standard I/A pumps to allow a lenticular emulsification with little or no thermal energy. The technologies open up the possibility of performing cataract surgery through very small (<2mm) incision sizes, intraocular lenses to fit through such small openings are being developed rapidly .

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Visual rehabilitation with secondary intra-ocular lens implantation in a case of Hallermann-Streiff syndrome

Dr. Rashmi S. Dr. Praveen S. Alavandi [2]

INTRODUCTION

Hallermann-Streiff syndrome (HSS) is synonymous with Francois dyscephalic syndrome, Aubry syndrome, Ullrich-Fremerey-Dohna syndrome, Oculomandibulo facial syndrome or Oculomandibulo dyscephaly with hypotrichosis.

It is a syndrome with multiple congenital abnormalities which affects face, skull, hair, eyes, teeth and overall growth and development. It affects both males and females in all ethnic groups. Over 150 cases of HSS have been reported worldwide.[1]

The potential causes of this syndrome include an asymmetric second branchial arch defect that arises during 5th or 6th gestational week, maternal viral infection, toxin exposure and paternal age. Most cases are sporadic. An autosomal dominant inheritance with variable expression or a new mutation has been mentioned, but some reports have suggested possibility of autosomal recessive inheritance.[2]

General Features [1,2,3]

Patients generally present with small bird like facies, a beak shaped nose which is pinched and tapering at the tip. The skull is brachycephalic with frontal bossing. They have a small chin, underdeveloped jaw and a small mouth. Hair is usually sparse particularly that of scalp, brows and lashes (hypotrichosis). Skin shows atrophy. They may have natal teeth; and dental anomalies are common. Short stature is seen in about half of the individuals with HSS (proportionate dwarfism). There may be musculoskeletal and cardiac abnormalities. Most individuals have normal intelligence; however 15-30% have some degree of mental retardation. A narrow upper airway, small chin and shape of skull can pose a risk during intubation and general anesthesia. They may suffer sleep apnoea and repeated respiratory infections which can be fatal.

Ophthalmological features [1,2]

Ocular abnormalities are a major problem with the most common ocular features being microphthalmia and cataracts which are present in 90% of HSS patients.[1] Congenital cataracts are one of the most common characteristics of HSS.[1] Cataract may be membranous or may have spontaneous absorption leading to aphakia. Other ophthalmic features include nystagmus, strabismus, blue sclera, and microcornea. Adenexal abnormalities include sparse eyelashes and eyebrows, skin atrophy, hypoplasia of lacrimal puncta, lid abnormalities (entropion, ptosis, lower lid coloboma) and down slanting palpebral fissure. Some other findings which may be present are ocular hypertension, glaucoma, pale optic disc, disc coloboma, choroidal atrophy, macular degeneration, iris atrophy, aniridia and corneal stromal opacities.

The differential diagnoses of this condition include oculodentodigital dysplasia, mandibulofacial dysostosis, cleidocranial dysostosis, progeria and other progeroid syndromes.[2]

THE CASE

A 18-year-old Indian female patient presented with poor vision in both eyes. She was born after an uncomplicated full term pregnancy of a non consanguineous marriage. She was diagnosed to have congenital cataract at the age of one month and lensectomy was done in both eyes. She had been wearing aphakic glasses since childhood. Her general appearance and ophthalmological findings led us to diagnose her with HSS. (Fig.1) There was no notable family history. She had an average height (160 cms), and had mild mental retardation. She had microphthalmos, microcornea, nystagmus and bilateral surgical aphakia. Uncorrected visual acuity in right eye was only counting finger at 3 meters. Even with her very thick and heavy plus 16 Diopters glasses, she could hardly read the 6/60 line in the Snellen's chart. Left eye was totally blind (no perception of light, glaucomatous optic atrophy, exotropia, no fixation).

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Secondary intra-ocular lens (IOL) implantation was planned in right eye. Biometry showed short axial length (18.76mm) with normal anterior chamber depth (4.34mm). Corneal curvature measured 50 Diopters both horizontally and vertically. IOL power calculated was plus 30 Diopters. There was no posterior capsular support. She underwent glued IOL implantation under peribulbar anaesthesia. Glued IOL implantation is a technique where in posterior chamber IOL is implanted with the use of fibrin glue.[4]

Two partial thickness scleral flaps were constructed exactly 180^0 diagonally apart followed by sclerotomy 1mm from the limbus. Thin sclera should be kept in mind while choosing the positioning of flaps. An anterior chamber maintainer was used. Anterior vitrectomy was done. Sensar 3 piece acrylic foldable IOL was injected through clear corneal incision. First, the leading haptic and subsequently the trailing haptic was externalized using an end gripping 23 G micro rhexis forceps (Micro surgical technology, USA). Both haptic tips were tucked into the intralamellar scleral tunnel made with 26G needle in the bed of scleral flaps. The sclerotomies were sutured and the scleral flaps were glued over using fibrin glue (Tisseel, Baxter, USA). Conjunctiva over sclera flaps were closed with 10-0 monofilament nylon. Corneal wound was hydrated and closed after removing the anterior chamber maintainer. At the end of surgery, well centered sclerally fixed (glued) IOL was achieved.

Post operative course was uneventful. Her vision improved to 6/36 (uncorrected visual acuity) at the end of 6 weeks. At one year follow up, vision remained the same; IOL was well centered, stable with no pseudophacodonesis; haptics were in position with no extrusion.

DISCUSSION

A multidisciplinary approach may be required to tackle the multiple disorders of HSS patients.[3,5,6,7] Ophthalmologists have a major role to play as the patients present with multiple problems related to eyes, majority being congenital cataract or aphakia in later life (either due to spontaneous absorption of lens or surgical removal of cataractous lens).[2,3,8,9] Special attention should be paid during surgical treatment. Careful anesthetic management is needed.[1,6] IOL sizing as well as high plus power IOL could be an issue in small eyes. Shen et al have reported piggyback IOL in a patient with HSS.[2]

The short eye axis and thin sclera need cautious handling during surgery. They pose a risk of post operative hypotony, exudative retinal detachment and choroidal detachment. Cases with exudative retinal detachment after operating cataract in HSS patients have been reported.[10] Surgeon should keep in mind sclerectomy if need arises. A vitreoretinal setting should be available.

Sclerally fixed (glued) IOL is a safe and effective option for providing visual rehabilitation in patients with HSS. Good visual outcome was achieved in our patient which relieved her from aphakic glasses and significantly improved her quality of life. However, careful pre operative planning, meticulous surgery and close post operative follow up are needed.

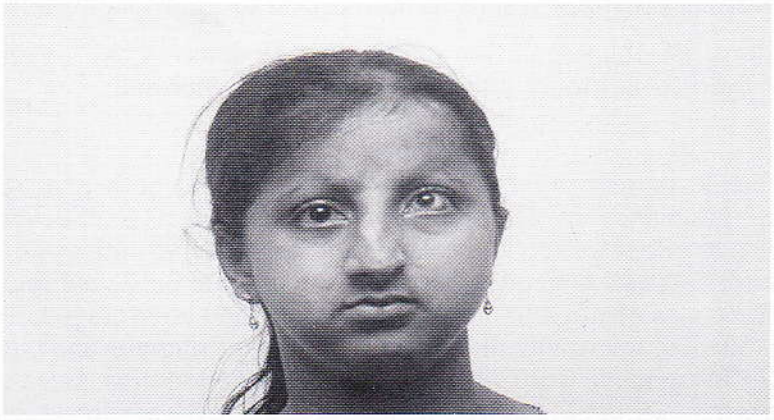

Figure 1: Bird like facies, dermatrophy of face, pinched nose, hyotrichotic patch on scalp, sparse eyebrows, mandibular hypoplasia, blue sclera, microphthalmos.

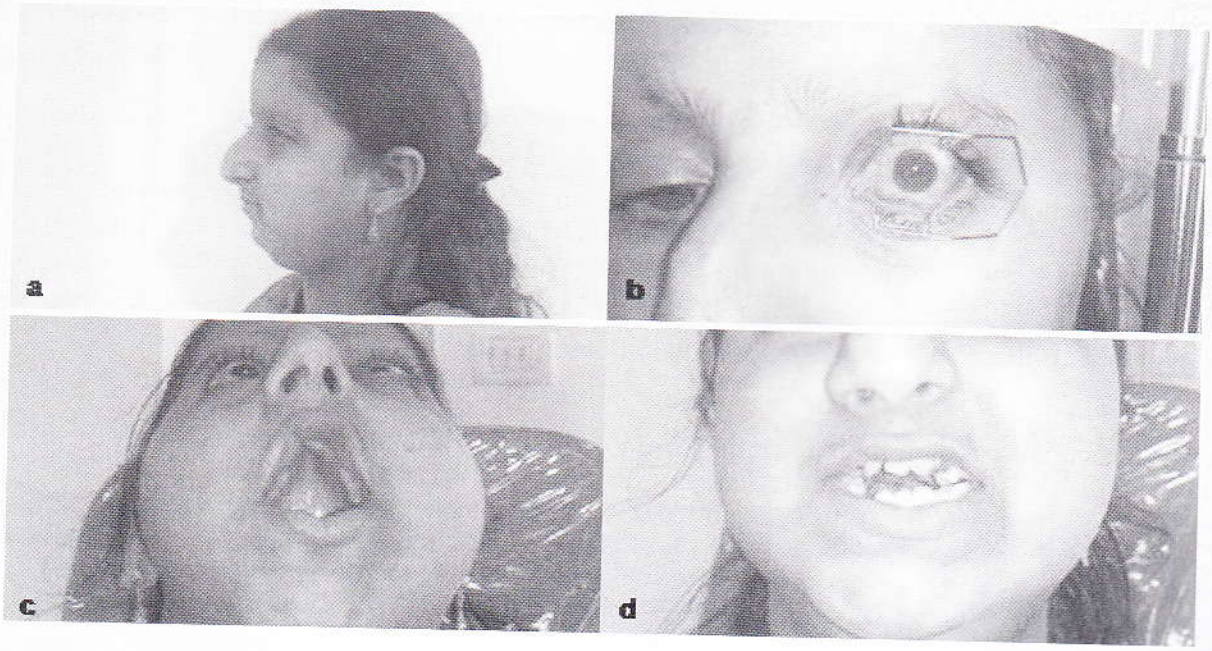

Figure 2: a) Side profile of face; b) Beaked nose, microphthalmos, blue sclera; c) Small mouth; d) Abnormal dentition, micrognathia.

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Surgical management of valsalva retinopathy: a case report

Dr. Manmath Das, Dr. Abhishek Varshney, Dr. Priyanka Chaudhary,

ABSTRACT

We report a case of unilateral valsalva retinopathy caused by severe coughing who presented to us with the complaints of sudden, painless loss of vision in the right eye [RE] for 1 week. Her presenting visual acuity for distance was 20/200 for RE. Fundus examination of RE revealed pre-retinal haemorrhage [PRH]. Left eye [LE] fundus examination was normal. A diagnosis of valsalva retinopathy in RE was made and the patient was subjected to 25 gauge pars planavitrectomy [PPV] with complete visual recovery.

Key-words: Valsalva retinopathy, Nd:YAGhyaloidotomy, MIVS

INTRODUCTION

Valsalva retinopathy is a form of pre-retinal haemorrhage [PRH] that was described by Duane in 1972 as "a particular form of retinopathy, pre-retinal and hemorrhagic in nature, secondary to a sudden increase in intrathoracic pressure".[1] It has been described after activities such as coughing, vomiting, lifting, straining for a bowel movement, strenuous exertion, sexual intercourse, labor, blowing musical instruments, compression injuries, endoscopic procedures (colonoscopy and gastroscopy). Treatment consists of either observation or Nd:YAGhyaloidotomy or pars planavitrectomy [PPV]. With the advent of micro incision vitreous surgery [MIVS], PPV is becoming a viable option for valsalva induced PRH. We report a case of unilateral valsalva retinopathy caused by severe coughing in a young healthy female and its management by PPV.

CASE REPORT

A 20 year old healthy female presented to us with the complaints of sudden onset of decrease in vision in RE for 1 week after severe coughing. There was no history of vomiting, lifting heavyweights, sneezing, straining during micturition or defecation. The patient did not give history any diagnostic or surgical intervention in the recent past. LE examination was unremarkable. RE best corrected visual acuity [BCVA] was 20/200 for distance and N36 for near,anterior segment examination was normal. Fundus examination of the RE showed an attached retina,dome shaped pre-macular hemorrhage with a glistening surface and regular margins suggesting sub internal limiting membrane [ILM] hemorrhage and a dull crescent with irregular margins inferior to it suggesting a sub hyaloid hemorrhage [Fig.1].Optical coherence tomography [OCT] was performed that revealed sub ILM location of blood [Fig.2]. Options of observation, Nd:YAG hyaloidotomy and surgery was given to the patient. The patient was keen for her visual recovery so Nd:YAG hyaloidotomy was tried but was unsuccessful. Following failure of hyaloidotomy, choice of PPV was given to the patient explaining the potential risks of surgery. A 25 gauge PPV was planned. Posterior vitreous detachment was completely achieved, ILM was incised by 25 gauge micro vitreoretinal [MVR] blade and was peeled off using 25 gauge ILM peeling forceps. PRH was then aspiratedusing soft tip aspiration flute [Fig.3]. Post-operative period was uneventful visual acuity showed improvement on day 1 after surgery and was 20/20 for distance by 1st week. At final examination after 6 weeks her BCVA both eyes was 20/20, N6, anterior segment examination was normal and LE fundus examination was also normal. RE fundus examination showed an attached retina [Fig.4]. 6 months post operatively patient was doing well with no visual complaints.

DISCUSSION

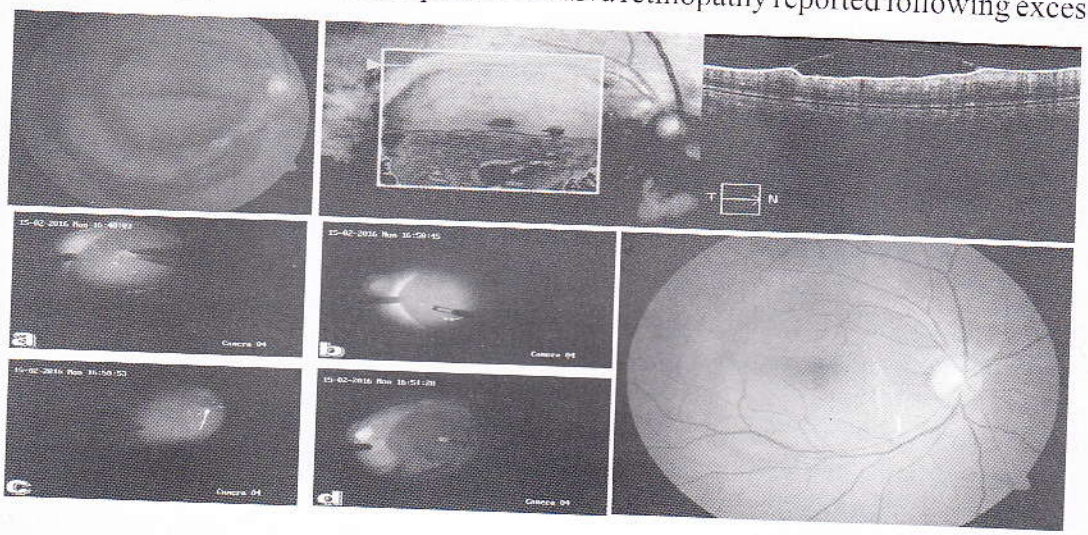
Since its description by Duane in 1972[1] many causes of valsalva retinopathy and its treatment strategies have been described. It has been described secondary to activities like coughing, vomiting, lifting, straining for a bowel movement, strenuous exertion, sexual intercourse, labor, blowing musical instruments, compression injuries, night club dancing, endoscopic procedures (colonoscopy and gastroscopy).

Clinically PRH of valsalva has been described as a well circumscribed, round or dumbbell shaped bright red mound of blood beneath the ILM in or near the central macula with a glistening surface.[2] Sub ILM location of the pre retinal hemorrhage has been confirmed on OCT.[3]It has also been mentioned that if the site of

C L Gupta Eye Institute, Moradabad[1]

hemorrhage is near the fovea, blood can dissect the fovea and can reach sub-foveally.[2] Choroidal hemorrhage in moderate myopia has also been described following valsalva manuver.[2] Complete resolution of PRH usually occurs but it may take months, leaving the serous detachment of ILM which may reattach spontaneously.[2] Nd:YAG hyaloidotomy is usually successful, if the patient presents early. A higher amount of energy is required in this process [4.2mJ to 9.2 mJ]. This can lead to photomechanical injury to the retinal leading to vitreous hemorrhage, intraretinal hemorrhage or subretinal hemorrhage.[4] Apart from that occasional epiretinal membrane formation has also been described.[5] Though PPV has associated risks of surgery like early cataract formation and retinal breaks, but is emerging as an effective and safer technique for the management of dense premacular haemorrhages and insufficient spontaneous reabsorption.[6,7] Other therapeutic modalities described are intravitreal gas injection in conjunction with recombinant tissue plasminogen activator or alone[8] and non-vitrectomising vitreous surgery.[9]

With reference to our case, failure of Nd:YAG hyaloidotomy can be attributed to the relatively late presentation of the patient which lead to the surgical intervention for removal of pre macular hemorrhage. To the best of our knowledge, this is the first report of valsalva retinopathy reported following excessive crying.



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Management of ciliary body staphyloma & complicated cataract with cadaveric scleral patch superimposed amniotic membrane grafting: Case Report

Dr. Sandip D. Patil, Dr. Jignesh J. Jethva, Dr. Neeraj Gohil, Dr. Nilesh V. Parekh

Abstract

Scleral thinning and associated ciliary body staphyloma can be managed with cadaveric scleral patch grafting. Such allogenic scleral grafts are easy to store and use in reconstruction of scleral defects. Here we are going to report how cadaveric scleral patch grafting with superimposed amniotic membrane transplantation is helpful in maintaining structural integrity of globe while avoiding with complications associated with only scleral patch grafting.

Keywords

Ciliary body staphyloma , cadaveric scleral patch grafting , amniotic membrane grafting

Introduction

Sclera is the outer fibrous coat of eye which provides support to the intraocular contents. Scleral thinning is well known complication of pterygium surgery, retinal detachment repair, high myopia and trauma. In some rare cases it may result in staphyloma formation uveal tissue exposure. Scleral reinforcement surgery is necessary when there is associated prolapse of orbital tissues and secondary infection.[1]There are various options of grafts are available for scleral reinforcement surgery. In this communication we would like to report our experience with cadaveric scleral patch graft with superimposed amniotic membrane graft.

Case Report

A 50-year-old female, housewife by occupation, presented to outpatient department of Sir T Hospital Bhavnagar with complaints of gradually progressive painless diminution of vision associated with swelling in upper part right eye since 3 years, following blunt trauma to her right eye by her grandson's hand. Patient had no history of any systemic illness and all the routine investigations like hemogram and chest x-ray were normal. Best corrected visual acuity (BCVA) was hand movement with PL present and PR in all quadrants in the right eye and 6/60 in the left eye. Intraocular pressure was 16 mm of hg in right eye and 18 mm of hg in left eye by noncontact tonometer. The slit lamp examination revealed brown coloured protruded swelling 2 mm above the superior limbus with thinning of surrounding sclera, conjuctival congestion with feeder vessels, shallow anterior chamber superiorly, pupil eccentric reacting to light with complicated cataract [fig.1]. Fundus evaluation was not possible. Ultrasound findings were suggestive of limbal area defect with ciliary staphyloma of right eye [fig. 2]. Left eye fundus was unremarkable due to presence of dense cataract which was otherwise within normal limit.

Then patient was then advised to undergo ciliary body staphyloma excision with scleral patch and amniotic membrane grafting with cataract extraction. Under general anaesthesia first cataract extraction and posterior chamber intraocular lens implantation was performed through temporal section. Then after dissecting conjunctiva, Tenon's capsule staphyloma was excised and the tissue was then sent for histopathological examination. The area of scleral defect carefully exposed. Scleral defect was then reinforced with donor scleral patch grafting after preparing and fashioning it to appropriate size and thickness of scleral defect. Donor sclera was obtained from eye bank preserved in absolute alcohol. To prepare donor sclera for use in surgery, it was soaked in ringer lactate solution for 10 minutes three times, then in Betadine solution for 10 minutes and finally in Gentamycin 20mg/ml solution for 10 minutes.[2]The

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graft was then secured to the edges of scleral defect with 10-0 nylon sutures. The repaired scleral defect then covered with amniotic membrane graft positioned with stromal side down using 10-0 nylon sutures to the surrounding conjunctiva [fig. 3].

The operated eye was bandaged after surgery which was to be opened on next day. Post operatively tablet acetazolamide was given with a view of obtaining soft eye with low intra ocular pressure and thus preventing displacement of the graft during the early stages of union.[3] On the first post-operative day patient had a vision of 1/60 with scleral patch and amniotic membrane graft was in place with sutures. Patient was discharged with moxifloxacin and prednisolone combination eye drops 1 hourly, atropine eye ointment 1 application three times a day and carboxy methyl cellulose eye ointment 2 times a day for lubrication. Patient was then regularly followed for 1 month; steroids were gradually tapered during this period and closely monitored for structural and visual outcomes.

During this period of follow up we observed that that was gradual improvement of visual acuity from 1/60 to 6/60 in right eye. The scleral graft was well tolerated without any signs of undue inflammation. There were no complications associated with scleral patch and amniotic membrane grafting like displacement, thinning, elevations, uveal tissue prolapse, necrosis or sloughing. Amniotic membrane was well in place with signs of re-epithelisation and vascularisation. Tectonic stability of graft then reconfirmed on follow up ultrasound biomicroscopy [fig. 4].

Discussion

There are various options of grafts that are available for scleral reinforcement surgery like sclera patch grafting, lamellar corneal graft, split thickness dermal graft and numerous other tissues like fascia lata, periosteum, and cartilage.[3] Scleral patch grafting can be done by rotational pedicle graft, lamellar scleral autograft and cadaveric scleral patch graft. A rotational pedicle scleral graft can be done if the area of thinning is small and surrounding sclera is healthy.[4] Lamellar scleral autograft is a safe procedure but the limitation of autologous scleral patch graft is the inability to take large grafts to cover large areas of scleral thinning.[5] In cases like high myopes, where the sclera is thin overall, there is a risk of perforation while creating a graft. In our case scleral defect was large and surrounding sclera was not healthy so we found cadaveric donor sclera is good option for scleral reinforcement surgery as it is readily available, strong, flexible, easy to handle and better fit to host defect.[6] Its natural curvature is easy to blend with host sclera. The cadaveric donor sclera is an avascular structure which has advantage of being immunologically inert and good acceptance without undue inflammatory reaction, but this avascular nature and absence of epithelium in scleral grafts may result in lack of vascularisation necrosis and sloughing.[7] The whole survival and tectonic success of the graft is jeopardized owing to this avascularity. Here the superimposition of amniotic membrane on cadaveric scleral patch graft becomes helpful.[8] Amniotic membrane has a thick basement membrane and avascular stroma which can act as an adjunctive to scleral patch graft. Amniotic membrane has anti-inflammatory, antifibrotic and epithelisation promoting properties.[9] It helps in rapid re epithelisation, vascularisation and acceptance of scleral patch grafting. A good amount of structural integrity, tectonic stability and visual rehabilitation obtained in this case with use of scleral patch and amniotic membrane grafting.

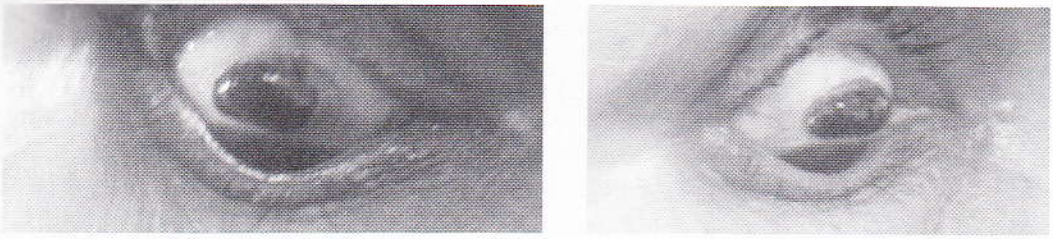

Figure 1- Pre operative photos showing scleral thinning with ciliary body staphyloma

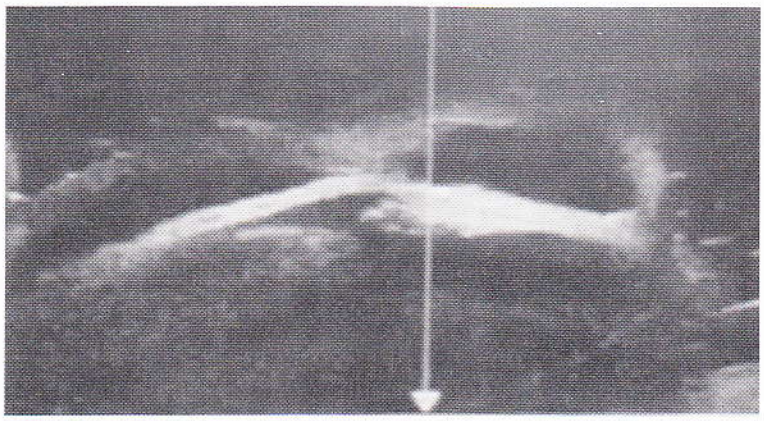

Figure 2- Pre Operative ultrasound showing cystic space in limbal area

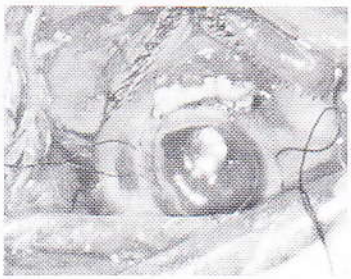

Figure 3- Intra operative photos showing cadaveric scleral patch graft and then superimposed amniotic membrane

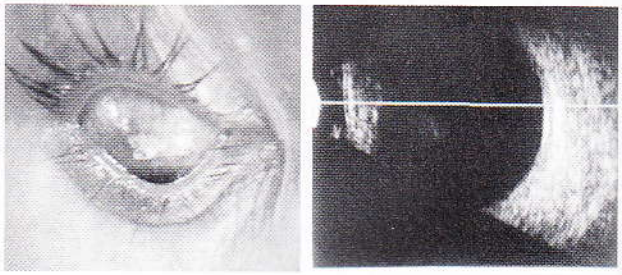

Figure 4- Post operative photo showing preserved globe integrity and post operative ultrasound

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Body Building Protein Supplement Leading to Visual impairment-a case report

- Abdul Waris, Naheed Akhtar

Abstract:

Body building protein and steroid supplements are being rampantly used throughout the world with the craze of six and eight pack abdomen. Here we discuss a case of a young male who fell prey to injudicious use of systemic anabolic steroids and developed chronic Central serous chorioretinopathy leading to marked impairment of vision.

Introduction:

Body mass increasing protein powder supplements use is now quite rampant throughout the world. Most of the supplements contain a mixture of anabolic steroids and multivitamins along with some miscellaneous herbal products. As we know from our previous knowledge that chronic systemic steroid [1,2,3,4] intake in any form whether oral, intranasal, etc. is associated with a myriad of systemic complications like osteoporosis, Cushing's syndrome etc. Central serous chorioretinopathy is an important addition to this list of long term effects of the same.

Brief case report:

A 26 year old male watchmaker came to us with impaired diminution of vision, painless, progressive and associated with distortion of shape of objects (OU) for the past 6 months. After lot of interrogations he admitted to be on a protein powder supplement (Name of the product not exposed) to gain weight and develop his chest and biceps. He was not on any other medications and there was no significant history either. His best corrected visual acuity was 1/60 (OD) and 6/60 (OS). Anterior segment examination and IOP were normal. On fundus examination ring shaped grey elevated areas were seen nasal to fovea. The clinical picture mimicked Central Choroiditis. But FFA and OCT explicitly showed a large neurosensory retinal detachment with thickened retina suggestive of intraretinal edema and multiple leakages in the posterior pole. We ruled out TB choroiditis and VKH syndrome specifically along with other causes related to the case. So a provisional clinical impression of bilateral, chronic multifocal Central serous chorioretinopathy more specifically sick RPE Syndrome due to long usage of steroid was made. The patient was asked to stop all supplements. He was also asked to go to a higher center for possible PDT therapy, which he refused. After 6 months his vision has not improved significantly and he is leading a handicapped life.

Discussion:

By this case we conclude that the diagnosis of CSCR particularly if bilateral and multifocal could be quite challenging as differential diagnosis of VKH syndrome and TB choroditits always come on the way[5].

But if a proper approach and timely intervention is done it could be quite rewarding to the patient. Also there is no report of CSCR resulting from anabolic steroids like Nadrolone etc. It is quite early to invoke it as the

Dept. of Ophthalmology, AMU

cause of CSCR in our patient[6]. But as systemic steroid intake is an established cause of CSCRwith atypical and multifocal presentation the diagnosis is quite clear and attributable to it. Further case control studies are required to further evaluate this association.

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Blepharophimosis syndrome: Case Report

*Dr Ritika[1], *Dr Sanjay Bosak, *Dr Rohit Shahi[1], **Dr Diksha Prakash, ***Prof OPS Maurya

Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) is an uncommondysmorphic syndrome ,which primarily affect the soft tissues of the mid-face.

It comprises of

- narrowing of the eye opening (blepharophimosis)
- droopy eyelids (ptosis)
- an upward fold of the skin of the lower eyelid near the inner corner of the eye (epicanthus inversus)

Also, there is an increased distance between the inner corners of the eyes (telecanthus). Because of these eyelid abnormalities, the patients generally maintain a chin up posture with taut brows in order to see clearly, because they are unable to open eyelids completely.

People with BPES may also have distinctive facial features including a broad nasal bridge, low-set ears, or a shortened distance between the nose and upper lip (a short philtrum), and are at an increased risk of developing visual symptoms related to myopia or hyperopia.

This condition is categorised into two types, Type I being associated with primary ovarian failure along with the facial abnormalities, whereas the Type II having no such systemic associations.

BPES types I and II were each mapped on the long arm of chromosome 3 to the FOXL2 gene. The FOXL2 gene provides instructions for making a protein that is active in the eyelids and ovaries.The mutations probably impair regulation of normal development of muscles in the eyelids, resulting in malformed eyelids that cannot open fully. Mutations that lead to a complete loss of FOXL2 protein function often cause BPES type I and partial loss lead to BPES type 2

This condition is typically inherited in an autosomal dominant pattern, with only one copy of the altered gene sufficient to cause the disorder.

We managed two patients with blepharophimosis syndrome aged 10 and 13 years.

Pre-operative clinical assessment:

Both the patients presented at our institute with complaints of drooping of upper eyelids since birth, as stated by their parents. On examination, we found them to be having bilateral ptosis, epicanthus inversus and telecanthus. The BCVA in case 1 was 6/9 and the case 2 was at 6/12 in both eyes. Tha anterior and posterior segment did not show any abnormalities on slit lamp examination.

Surgical procedure:

Both the cases were operated by the same surgeon and a similar surgical approach after proper informed consent from the parents. General anaesthesia was given in both the cases. The correction was done in two stages, where telecanthus and epicanthus inversus was repaired in the first stage and ptosis repair done in

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** Fellow, LVPEI, Bhubaneshwar
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another stage 6 months later.

Epicanthal fold and telecanthus was repaired using the Mustarde' double Z plasty approach. The site of intended medial canthus was marked using a sterile marking pen as point A. The skin was pulled taut towards midline to obliterate the epicanthal fold and the existing medial canthus was marked as point B. The two marks were joined and their midline was bisected by two short lines at 60^0 from which two more lines directed at 45^0 were drawn towards the intended medial canthus. This Z shaped marking pattern was incised, undermined and retracted with stay sutures. The subcutaneous tissue including the Orbicularis muscle was cut to expose the medial canthal tendon. Thereafter, the periosteum over the nasal bone was exposed and the canthal tendon was tied over the posterior lacrimal crest with the help of 4-0 silk double armed sutures. No transnasal wiring was done in both the cases. The skin was then closed with 5-0 silk sutures, which were removed on day 10 postoperatively.

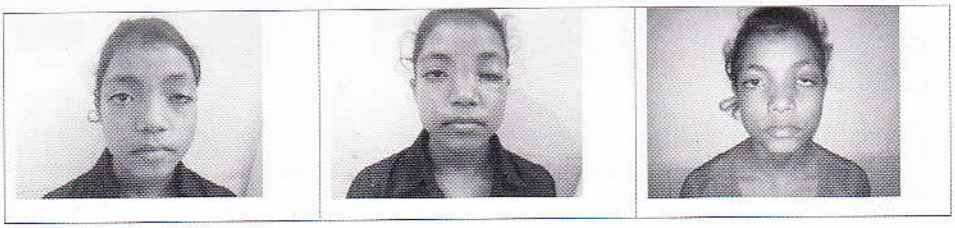
The ptosis repair is scheduled to be repaired in a second stage 6 months later by Frontalis sling surgery. Both the cases were followed postoperatively and the amount of telecanthus and repaired was measured at day 1, day 10 and advised follow up at 3 months thereafter.

Results:

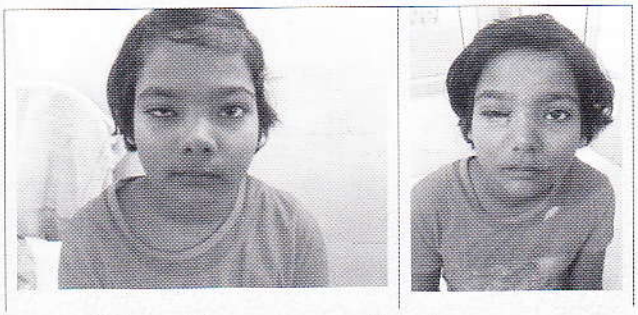
Both the cases showed good correction of the telecanthus, as measured postoperatively.

Discussion:

The treatment of blepharophimosis syndrome requires a combination of proper patient education about the disease entity along with support from pediatric endocrinologists and genetic counselors in the medical management of the disease. The surgical management require a deft oculoplastic approach as this syndrome is associated with varied dysmorphic features. Timely surgical intervention is advised in order to preserve the visual acquity, else delay can lead to the development of amblyopia in severe cases. Many surgeons these days prefer one stage repair of both telecanthus, epicanthus and ptosis. This has also shown equivalent results and thus the choice of repair rests with the clinical judgement and expertise of the operating surgeon.



CASE 1 : At presentation, on day 1 and day 10 postoperatively.



CASE 2: at presentation and Day 10 postoperatively

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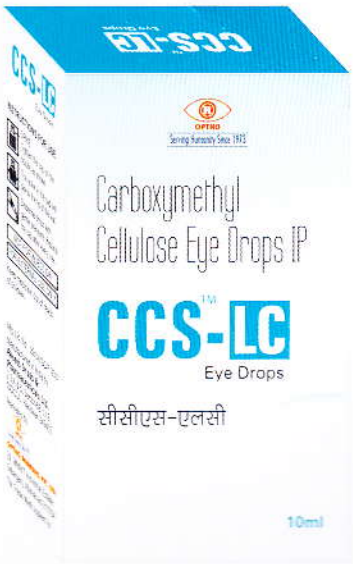

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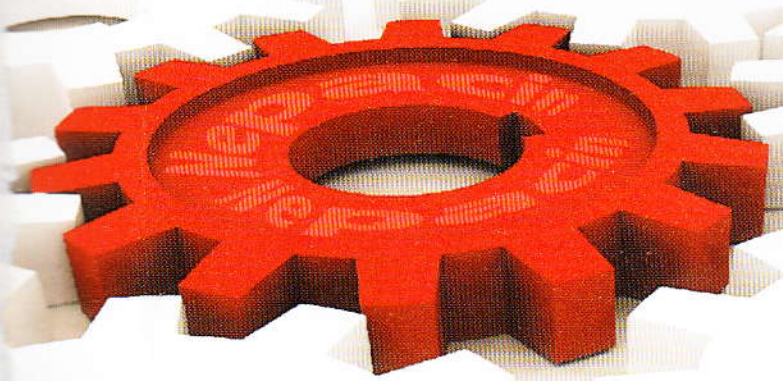

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