Amblyopia is defined as unilateral or bilateral decrease of visual acuity caused by vision deprivation or abnormal binocular interaction for which no organic causes can be detected by the physical examination of the eye and which in appropriate cases is reversible by therapeutic measures1,2,3.

For detection purposes, on routine examination, amblyopia is defined as a minimum of two Snellen lines difference in visual acuity between either eyes, but amblyopia is truly a spectrum of visual loss ranging from missing a few letters on the 20/20 line to hand movement. Anisometropia is a very common cause of amblyopia. Refractive condition of the two eyes is usually not the same. Anisometropia is the condition in which the refractive status of the two eyes shows a considerable difference. The vision in anisometropia may be binocular, alternating or it may be entirely uniocular. Each 0.25 D difference between the refraction of the two eyes causes 0.5% difference in size between the two retinal images and a difference of 5% is probably the limit, which can be tolerated. If the defect in one eye is high and more especially if the visual acuity is not good, it may be excluded altogether from vision at an early stage in life, the better eye is alone relied upon and if it is not so already, the more ametropic eye tends to become amblyopic, the image from it being suppressed.

Aims and Objectives
To determine the relationship between anisometropia and depth of amblyopia.

Material and Methods
The present study was carried out on patients attending the OPDs and IPD clinics of Gandhi Eye Hospital Aligarh, U.P. from June 2002 to July 2003. Both male and female patients in the age group of 6-40 years presenting with anisometropia of 1.0D and more of spherical and or 1.0D or more of cylinder were included in the study. Patients with decreased visual acuity due to any ocular or systemic pathology were excluded from the study and so with history of trauma and patients with manifest strabismus.

After obtaining a proper history regarding diminution of vision, its duration, use of glasses or contact lens, a complete ocular examination was done. This included visual acuity (unaided visual acuity, visual acuity with pinholes using Snellen chart for literates and E-charts for illiterates and children), torch light examination, cover test, slit lamp examination, retinoscopy under mydriatic followed by post mydriatic test (PMT) to get best corrected visual acuity. The difference in refraction between the two eyes was documented. Fundus examination (using direct/indirect ophthalmoscope) was done. Ocular movements were checked in all 9 gazes. Worth 4 dot test and synoptophore examination was done to check for binocular vision. All types of Anisometropia (spherical hypermetropic and spherical myopic, mixed, simple, compound and mixed astigmatic) were taken into the study.

To correlate the degree of anisometropia with the depth of amblyopia, all the cases were divided into 5 groups in the increasing degree of anisometropia in the following manner: -

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<tr>
<th>Group</th>
<th>Degree of Anisometropia</th>
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<tr>
<td>1</td>
<td>1 Dioptre-2 Dioptre</td>
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<tr>
<td>2</td>
<td>2.25 Dioptre-3 Dioptre</td>
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<td>3</td>
<td>3.25 Dioptre-4 Dioptre</td>
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<td>4</td>
<td>4.25 Dioptre-5 Dioptre</td>
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<td>5</td>
<td>5.25 Dioptre and above</td>
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Amblyopia was defined as a difference of vision of two Snellen lines or greater with the acuity of the amblyopic eye being less than 6/12. Depth of amblyopia was graded into mild moderate and severe depending upon the visual acuity in terms of Snellen lines 6/12-6/18, 6/24-6/36 and 6/60 or less respectively for mild, moderate and severe amblyopia.

Results
A total of 102 anisometropic patients were included in the study group, majority of them were males (69.6%), the male to female ratio being 2.28:1 (Table No.1). It was observed that out of 102 cases, incidence among 16-20 years group was higher (25.50%) followed by 17.64% in the age group of 11-15 years (Table No. 1).

Most common type of anisometropia reported in the study is spherical anisometropia (simple + compound) (42.15%) followed by compound astigmatic type i.e. 34.31%. A total of 74 patients, out of 102 patients were found having Amblyopia (Table No.2).

It has been observed that in smaller degrees of anisometropia as in group 1 (1-2D) and 2 (2.25-3D), there was a higher percentage of patients having mild amblyopia.
while only small percentage (7-9%) had severe Amblyopia (vision 6/60 or less) and about 35-36% had moderate depth of amblyopia, but in higher degrees (Group 5) of anisometropia, a large percentage (68%) of patients had severe amblyopia and only 13% had mild Amblyopia (Table Nos. 3 & 4).

It was observed clearly as depicted in table no 4 that, as the degree of anisometropia increased from 1 Dioptre to 5 Dioptre or above, there was a proportional increase in the depth of amblyopia.

Discussion

Early detection of anisometropia is essential to prevent the development of amblyopia in more ametropic eye.

In the present study it was observed that anisometropia was more prevalent in the age group of 16-20 years (25-50%). It could be explained on the basis of the fact that patients in this age group are more involved in studies, are more aware of their problems related to vision and eye strain.

Rustein (1999)7 in his study presented a data from a patient group comprising of 32 males and 28 females out of 60 anisometropes. The present study showed that in all the age groups, anisometropia was more amongst the males as compared to their female counterparts. The male and female ratio was found to be 2.3:1. Higher prevalence in males could be because of an easy and independent access to hospital and clinics.

Attebo et al. (1998)1 in his study of 118 persons classified as having amblyopia, 109 (92%) gave a history of a diagnosis of “lazy eye” or said that they were aware that one eye had always been weaker and nine persons gave no such history. In the present study, it was observed that out of 102 patients, 44 (43.13%) noticed decreased vision in the eye of closing the other eye while 23 (22.54%) gave the history of a diagnosis of “lazy eye” or long standing poor visual acuity in one or both eyes and only 7.84% complained of asthenopic symptoms.

Anisometropia has been historically considered to be a significant amblyopiogenic factor. The term amblyopia denoted unilateral or bilateral reduction of vision for which no cause could be detected by physical examination of the eye and which in appropriate cases is correctable by therapeutic measures. For detection purposes, on routine examination, amblyopia is defined as a minimum of two Snellen lines difference in visual acuity. The term

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<th>Table 1: Age &amp; Sex wise distribution of Anisometropic patients (n = 102)</th>
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<td><strong>Percentage</strong></td>
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<th>Table 2: Distribution of Amblyopia among Anisometric Patients (n= 74)</th>
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<td><strong>Age groups (years)</strong></td>
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<th>Table 3: Amblyopia in various group (Degrees) of Anisometropia (n= 74)</th>
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<td>Group I 1 - 2D</td>
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<td>Group II 3.25 – 4.0D</td>
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<td>Group IV 4.25 – 5D</td>
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<td>Group V 5.25 D &amp; above</td>
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<td><strong>Total</strong></td>
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(57-58%) while only small percentage (7-9%) had severe Amblyopia (vision 6/60 or less) and about 35-36% had moderate depth of amblyopia, but in higher degrees (Group 5) of anisometropia, a large percentage (68%) of patients had severe amblyopia and only 13% had mild Amblyopia (Table Nos. 3 & 4).
anisometropic “amblyopia: is widely accepted to describe amblyopia presumed to be caused by anisometropia alone.

Copps\(^2\), was the first to attempt to confirm an association between anisometropia and amblyopia in the absence of strabismus which was accepted by several other authors later. Incidence of amblyopia in nonstrabismic anisometropia as reported by many workers is variable: 60% by Ainsworth (1966), 86% by Yuksel et.al.\(^{11}\), 80% by Krazystkona (1967), 53% by Vries (1985)\(^3\), while Attebo et al. (1998)\(^4\) found it to be 50%. In the present study, out of 102 orthoptropic anisometropes, 74 (72.54%) were amblyopic\(^4,5,6,10\).

Amblyopia is found to be more common and severe in anisohypermetropia or anisoastigmatism. Mitchell and Attebo et al. (1998) also supported the fact of Rustein (1998)\(^8\) that amblyopia is more prevalent in patients with hyperopic than myopic anisometropia. Later Rutstein and Corliss (1999)\(^7\) in their study reported that higher degrees of anisometropia generally causes deeper amblyopia for hyperopes, but not for myopes.

Conforming to the findings of various studies done previously, the present study also shows amblyopia to be much more common (40.53%) in spherical anisohypermetropes (simple and compound), closely followed by compound hypermetropic anisoastigmatism (37.84%) while very low prevalence (5.40%) was observed in spherical anisomyopes (simple and compound) and in myopic anisoastigmatics (5.40%).

**Conclusion**

Depth of Amblyopia was determined to vary proportionally with the degree of Anisometropia.

**Bibliography**


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| Table 4: Relationship of Degree of Anisometropia with the Depth of Amblyopia (n = 74) |
|---------------------------------|-------------------------------------------------|-----------------|-----------------|
| **Degree of Anisometropia**     | **Amblyopic patients**                          | **Depth of Amblyopia** |
| 1 – 2 D                         | No.%                                            | Mild 6/12 – 6/18 | Moderate 6/24 – 6/36 | Severe 6/60 or less |
| Group I                         | 14                                              | 857.14          | 535.71           | 17.14             |
| Group II                        | 12                                              | 758.33          | 436.36           | 19.09             |
| 2.25 – 3.0 D                    | No.%                                            | 750.00          | 533.33           | 213.33            |
| Group IID                       | 14                                              | 541.66          | 433.33           | 325.00            |
| 3.25 – 4.0                      | No.%                                            | 313.63          | 418.18           | 1568.18           |
| Group IVD                       | 12                                              |                  |                  |                  |
| 4.25 – 5.0                      | No.%                                            |                  |                  |                  |
| Group V                         | 22                                              |                  |                  |                  |
| 5.25 D & above                  | No.%                                            |                  |                  |                  |
| **Total**                       | 74                                              | 30              | 22              | 22               |
| **Percentage**                  | 100                                             | 40.54           | 29.72           | 29.72             |

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Etiopathogenesis, clinical features and investigations were discussed in the previous issue, now we will discuss the treatment.

**Treatment Medical treatment**

**Laser photocoagulation**

The Macular Photocoagulation Study Group showed that laser photocoagulation was effective in the treatment of well-defined extrafoveal or juxtafoveal choroidal neovascularization secondary to AMD. In patients with subfoveal choroidal neovascularization, however, laser photocoagulation was not beneficial in eyes that had large lesions and moderate-to-good initial visual acuity.

**Procedure**
- Angiogram <96 hrs old
- Locate centre of FAZ on pretreatment FFA
- Outline CNVM on FFA using landmarks
- 200 - 500 u spot size confluent burns
- 0.2 -0.5s duration, uniform white burn
- Extrafoveal lesions treatment to be extended 100u beyond the margin of lesion
- Juxtafoveal lesions avoid extension on the foveal side
- Post treatment photograph has to be taken to ensure complete treatment.

**Follow-up**
- Patient after laser treatment needs to be followed up at 2, 4 and 6 weeks
- Repeat FFA on follow-up visits

**Macular Photocoagulation Study (MPS)**

In Patients with well-defined extrafoveal CNVM after a follow-up of 5 years, 64% of eyes assigned to no treatment compared with 46% of eyes randomized to argon laser experienced severe visual loss (six or more lines of visual acuity loss using Bailey-Lovie visual acuity charts). The difference was statistically significant. Although the risk of severe visual loss was reduced in treated patients, a high rate of persistent and recurrent CNVM was observed. The recurrence rate observed in treated eyes at 12, 24, and 60 months were of 41%, 51%, and 54%, respectively.

Patients with well-defined juxtafoveal CNV were treated with krypton red laser. At 3 years after randomization, 49% of laser-treated eyes experienced severe visual loss compared with 58% of untreated eyes.

**Laser to drusen**

There have been attempts for drusen reduction by laser to decrease the risk of geographic atrophy and CNVM. No significant difference in the development of CNVM was noted in the treated and untreated groups. To date, however, prophylactic laser photocoagulation in patients with high-risk ARM remains an experimental treatment and should not be performed outside randomized clinical trials.

**Feeder-Vessel Laser Photocoagulation**

Feeder vessels are defined as vessels that are seen in the earliest phases of the indocyanine angiogram, and appear to originate from a definite spot in the choroid and branch into a CNV with distinct blood vessels. Feeder vessels are identified in only a small percentage of patients examined with subfoveal CNV, so the treatment can be used in only a small number of cases. The first series published on the use of indocyanine green-guided feeder-vessel photocoagulation to treat subfoveal CNV in patients with ARMD was published by Shiraga and colleagues. To date, there are not enough data to support the use of feeder-vessel photocoagulation as a routine treatment for patients with CNV and ARMD.

**Photodynamic therapy**

Photodynamic therapy (PDT) involves the intravenous infusion of a drug (photosensitizer) and the application of a continuous nonthermal laser light directed at the CNVM. The wavelength of the laser light used corresponds to the absorption peak of the drug, but it is not strong enough to produce any thermal (photocoagulation) damage.

**Mechanism of action:** The drug gets concentrated in the immature endothelium of CNVM, and light-activation induces a photochemical reaction in the target area that causes immunologic and cellular damage, including endothelial damage of new vessels. Endothelial damage and the resulting platelet adhesion, degranulation, and subsequent thrombosis and occlusion of the vasculature might be the predominant mechanism by which light-activated drugs work. Since the photosensitizer...
accumulates predominantly in the CNV, a fairly selective damage to the CNV is expected.

To date, only PDT with the photosensitizer Verteporfin has been proven to decrease the risk of visual loss in patients with neovascular ARMD. Verteporfin (a benzoporphyrin derivative monoacid, BPD-MA; Visudyne, Novartis AG) is a light-activated drug. The application of photodynamic therapy with verteporfin involves two main steps: intravenous infusion of the drug and activation of the drug by light at a specific wavelength (689 nm) with a low-power, nonthermal laser. The therapy includes retreatment as often as every 3 months if leakage from choroidal neovascularization is detected on follow-up fluorescein angiograms.

Procedure

The intravenous infusion of verteporfin is given throughout a 10-minute period.

Then, 15 minutes after the start of the infusion the laser light is applied for 83 seconds.

Guidelines for the treatment of patients with ARMD and subfoveal CNV with PDT have been recently published. In these guidelines, treatment with PDT is recommended for patients with predominantly classic CNV and for those with occult and no classic CNV with recent disease progression (e.g., presence of blood associated with the CNV, growth of the CNV, or deterioration of the visual acuity within the past 12 weeks) and a lesion size of four or fewer disk areas or a lesion size greater than four disk areas associated with low levels of vision (i.e., approximately in the level of 20/50 Snellen vision). In these guidelines, it is also recommended to treat juxtafoveal lesions that are so close to the fovea that conventional laser photocoagulation almost certainly would extend under the center of the FAZ, and extrafoveal lesions that are contiguous to the optic nerve provided that treatment spots do not overlie the optic nerve. The recommendations included a 3-month interval follow-up for at least 2 years from the time of initial treatment in all patients, except in those in whom no treatment was recommended for two consecutive visits (6-month period). Patients should receive retreatments as often as every 3 months if there is any fluorescein leakage from CNV noted. Although no data are currently available on the treatment of pregnant or
nursing women and patients with moderate or severe liver disease, the guidelines suggest to carefully consider PDT in these patients. Photodynamic therapy is contraindicated in patients with porphyria. Patients must be warned, however, that they will be sensitive to direct sunlight or bright indoor lights for 24 to 48 hours after drug infusion and that they should avoid direct sunlight for about 2 to 5 days after treatment.

New PDT drug: SnET2 a new PDT drug is undergoing phase 3 trial of neovascularization of AMD. Initial results have not proven the efficacy convincingly. New study will likely be necessary to prove efficacy in a convincing manner.

**Transpupillary Thermotherapy**

Transpupillary thermotherapy (TTT) was first described by Oosterhuis and colleagues and used in the management of choroidal melanoma. For this treatment a modified infrared diode laser (810 nm) attached to the slit-lamp is used. Reichel and associates published the first report on the use of this form of therapy to treat patients with subfoveal occult CNV.

In a retrospective, non-randomized study of 28 eyes of 28 patients with subfoveal CNVM (classic, occult or mixed). Fifteen patients (53.57%) maintained their pre-treatment vision, 2 (7.14%) patients showed improvement of more than 2 lines and 11 (39.28%) patients showed deterioration of vision by >2 lines. Angiographic and clinical regression of CNVM was noted in 19 patients (67.8%).

Recent interim results presented from Transpupillary Thermotherapy Trial for neovascularization in AMD did not meet the primary end points and resulted in a 5% vision loss at 1 month.

**Therapies Under Investigation**

**Anti-Vascular Endothelium Growth Factor**

Pegaptanib sodium injection (MacugenTM, EyeTech Pharmaceuticals, New York, NY) an anti-VEGF aptamer is a polyethylene glycol (PEG)-conjugated oligonucleotide that binds to the major soluble human VEGF isoform. This drug is to be given as intravitreal injection once every 6 weeks. Trials have shown beneficial effect of MacugenTM preventing visual loss in patients with predominantly classic, minimally classic, or occult subfoveal CNV and hence has been approved by the US, FDA for use in wet AMD.

A clinical trial using rhuFab V2 (ranibizumab, LucentisTM, Genentech) fragment of a recombinant humanized monoclonal antibody directed toward VEGF has also started. In experimental models of CNV, ranibizumab injections prevented formation of clinically significant CNV and decreased leakage of already formed CNV with no significant side effects other than acute anterior chamber inflammation. For the first time in trials of AMD a drug has shown improvement in visual acuity. The data has been submitted to the FDA & approval is awaited.

The off-label use of intravitreal Bevacizumab (Avastin) is new becoming popular to treat all types of CNV and has shown excellent results.

**Steroids:** Many corticosteroids, including triaminolone acetonide (TAAC) and anecortave acetate, are potent antiangiogenic agents. The mechanism of action of steroids may be due to their effect on vascular endothelial cell turnover, inhibition of the inflammatory response, or another means.

In a study by Danis et al using TAAC, visual acuity was statistically significantly better in the treated group than in the control group at 6 months’ follow-up. No patients in the control group had increased intraocular pressure, whereas 25% in the treatment group developed this complication. In the control group 22% of all phakic patients developed increased lens opacities compared with 57% in the treated group. Intravitreal injections of TAAC have been used also in the management of subfoveal recurrences following laser photoagulation of extrafoveal CNV.

Use of combined intravitreal injection of TAAC and PDT with verteporfin. Although there seemed to be a possible benefit of this combined therapy, the number of patients treated was small and there was no control group.

Masked, placebo-controlled randomized clinical trials have been designed and are currently underway to evaluate the effect of anecortave acetate, administered as subtenon juxtascleral injection once every 6 months. Preliminary reports at the end of 12 months failed to meet the primary end point. We may have to wait till the final results for deciding about the efficacy of this drug.

**Surgical Treatments**

**Macular Translocation:** In 1983, Lindsey and colleagues introduced the concept of retinal relocation. However, it gained popularity in the management of patients with subfoveal CNV only after 1993, when the first results were presented. The aim of the surgery is to relocate the central neurosensory retina (fovea) away from the CNV, to an area of healthier RPE, Bruch’s membrane, and choroid. This is still an experimental method of treatment as it lacks randomized prospective clinical trials to support this form of treatment.

**Submacular Surgery:** In 1992, Thomas and colleagues, Berger and Kaplan, and Lambert and associates presented their results after surgical excision of CNV. The technique for CNV removal was as follows: After complete pars plana
vitrectomy CNVM is removed from subretinal space by making retinotomy temporal to fovea (usually) and inducing localized retinal detachment. Fluid-air exchange is performed at the end of surgery and gas tamponade is given.

Recently, the first results of the Submacular Surgery Trial, a randomized clinical trial comparing laser photocoagulation to surgical removal of subfoveal CNV have been published. All patients enrolled in this trial had a subfoveal recurrent CNV following prior laser photocoagulation for extrafoveal or juxtafoveal CNV. No statistically significant differences in visual acuity were observed between patients randomized to laser photocoagulation and surgical excision of CNV in this pilot trial. Similarly, health-related quality of life was not statistically significant different between the two treated groups.

A new trial to evaluate the benefit of CNV removal in cases of newly developed subfoveal CNV is currently underway (Submacular Surgery Trial, Group N). Patients are being randomized to either surgical excision of the CNV or observation. In this study, patients with lesions larger than those eligible for laser photocoagulation following MPS guidelines or with minimally classic lesions in which laser photocoagulation or PDT have not shown any treatment benefit are eligible for the trial. Patients with predominantly classic subfoveal lesions are being enrolled also if after detailed explanation of the benefits of PDT they still prefer to participate in the trial.

Iris/Retinal Pigment Epithelium Transplantation

Several reports on RPE transplantation in patients with neovascular ARMD have been published. Isolated cells and RPE-cell sheets have been used. Fetal or mature RPE have been transplanted. Only rarely have good levels of vision been achieved following RPE transplantation.

Due to possible difficulties in obtaining RPE cells for transplantation and complications related to this procedure, researchers have investigated the possibility of substituting RPE cells for iris pigment epithelial (IPE) cells. Iris pigment epithelial and RPE cells have a common embryonic origin, and some of the RPE functions have been demonstrated in IPE. Few series on IPE transplantation have been reported in the literature. In these series, visual acuity after transplantation remained low, in the level of 20/100.

Prophylactic Treatments

Vitamin and Mineral Supplements

A randomized clinical trial, part of the Age-Related Eye Disease Study (AREDS), was conducted in order to try to evaluate the effect of antioxidants and zinc in patients with ARMD. At 5 years, a statistically significant reduction in the risk of progression to advanced ARMD and a 15-letter decrease in visual acuity score was found in those patients randomized to antioxidants plus zinc in categories three and four. No statistically significant adverse events were found with any of the formulations. However, possible complications of the study medications have been identified. Those with extensive intermediate size drusen (63 μ -124μ), at least 1 large druse (>125 μ), noncentral geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should considered for supplementation of antioxidants plus zinc.

Results from AREDS continue to be gathered and studied. Moreover, a new AREDS is being proposed. A few of the findings from the current AREDS include the following:

- Patients who ate fish more than once per week had a 40% reduction in neovascularization compared with patients who ate fish less than once per month;
- Zeaxanthin and lutein reduced the risk of neovascularization in AMD; and
- Patients taking the zinc regimen appeared to have a lower mortality rate than those patients not taking zinc.

Carotenoids: Lutein and Zeaxanthin:

Lutein and Zeaxanthin are the main constituents of the luteal pigment. This yellow pigment, present at the macula, absorbs blue light. Whereas zeaxanthin is the main pigment present at the fovea, lutein is more abundant in the rest of the macula. Lutein and zeaxanthin are localized mainly in Henle's fiber layer. It is possible that lutein and zeaxanthin may protect the retina from the damage caused by blue light exposure and subsequently decrease the risk for ARMD. In this respect, a case-control study in which plasma levels of lutein and zeaxanthin in patients with ARMD were compared to those in an age-matched control group showed an inverse relationship between plasma levels of these two carotenoids and the risk for ARMD. However, to date, no well controlled intervention trials with lutein and zeaxanthin have been performed. Thus, it is not clear to what degree these pigments may decrease the risk of neovascular complications in ARMD.

Conclusion

Increasing knowledge about the pathogenesis of this disease has led to new therapeutic strategies. As on today the treatment modalities have developed to arrest the disease process to some extent. Future treatments should likely concentrate in preventing the development of CNV in patients at risk, rather than in treating it once established.
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Meibomian Gland Dysfunction

Monica Gandhi MS, Umang Mathur MS

Meibomian gland dysfunction (MGD) is more common an entity than we diagnose it. Many a times our patients complain of irritation, foreign body sensation and are given nonspecific medications. A careful examination will diagnose MGD and a simple treatment can have a more comfortable patient.

Meibomian Gland dysfunction was first noted by Casserius in 1609 and was described by Heinrich Meibom in 1666. Posterior blepharitis is associated with various disorders of the meibomian glands, which are known collectively as meibomian gland dysfunction. There are various classifications of the meibomian gland disease, but none widely adopted.

Anatomy

There are 30-40 glands in the upper lid and about 30 in the lower lid. The glands open at the inner free margin of the lid at the junction of the skin and conjunctiva. The secretions of the meibomian glands serve to lubricate the surface of the lids and contribute to the lipid layer of the tear film.

The role of the lipid layer

- Retards evaporation
- Prevents contamination by providing a barrier to cutaneous sebum
- Lowers surface tension
- Seal between lid margins during sleep
- Smooth optical surface

Pathophysiology

The normal lid flora constitutes of S. epidermidis, P.acne, Corynebacterium, S aureus. These bacteria produce lipase, which can alter composition of the meibomian lipids. This in turn enhances growth of other bacteria. Cholesterol esters encourage the growth of bacteria like S. aureus and may have a role in the pathophysiology. This is evidenced by the fact that MGD responds to local antibiotics.

Histopathology

Obstruction of the orifice with hyperkeratinization and desquamation of epithelium is probably the most important cause of the dysfunction. This leads to increased pressure on the cuboidal lining of the acini and flattening of cells. The stagnated secretion may lead to chalazia.

Symptoms

- Burning
- Irritation
- Itching
- Red eyes
- Decreased or fluctuating vision
- Recurrent chalazia

Signs

- Pouting gland orifices

Fig. 1: The layout of the meibomian glands

Fig. 2: Histopathology of meibomian glands

Fig. 3: The opening of the gland orifices
- Change in the number
- Orifices displaced posteriorly
- Foam in tear meniscus
- Capping with solidified excreta
- Toothpaste like secretion
- Lid margin rounded
- Thickening
- Erythema
- Hyperkeratinization
- Vascularization-"brush marks"
- Telangiectasia
- Notching
- Bulbar and tarsal conjunctival injection
- Papillary reaction on inferior tarsus
- Corneal and conjunctival staining
- Corneal pannus
- Ulceration

**Associated sequelae**
- Contact lens intolerance
- GPC
- Chalazia

**Treatment**

Lid hygiene is currently the mainstay of treatment for meibomian gland dysfunction. This involves warm compress followed by massage and expression of the meibum. Lid scrubs are effective also. This can be tedious and messy task but if the requirement and logic of the treatment is explained to the patient they would be more compliant with the recommended regimen.

There is a need for tear substitutes to stabilize the tear film till the normal secretions are regularized.

Other proven therapies for meibomian gland dysfunction include oral Tetracycline, Doxycycline or Minocycline, topical Erythromycin or Bacitracin, and topical steroids. For refractory cases, topical cyclosporine can be used. The doses recommended are as follows:
- Tetracycline 250mg QID
- Doxycycline 50-100 mg BD
- Minocycline 50-100 mg BD

**Role of Tetracyclines**
- Not as antibiotics
- Decrease bacterial lipase
- Alter the fatty acid composition of the meibomian gland secretions
- Improve their solubility
- Inhibit collagenase
- Effective in protecting the cornea from impending perforation secondary to inflammatory responses

**Adverse effects of Tetracyclines**
- Gastrointestinal--diarrhea, pancreatitis and pseudomembranous colitis
- Benign intracranial hypertension
- Renal tubular damage
- Cross the placenta
  - Permanent discoloration of teeth
  - Retardation of fetal bone growth

**Doxycycline**
- Twice a day
- Not affected by dairy products
- Pregnant females need to be cautioned

**Associated conditions**

Meibomian gland dysfunction has been associated with lacrimal insufficiency, Rosacea and seborrheic dermatitis.

Rosacea is a condition that may not be easily diagnosed in people with dark skin. The patient may present with recurrent episodes of meibomitis and chalazia. Borrie found that nearly 100% of rosacea patients had posterior blepharitis, and ocular disease preceded cutaneous manifestation in 20%.

**Pathophysiology**
- The etiology of rosacea is unknown. It is a cutaneous vascular disorder characterized...
by Type 4, cell-mediated hypersensitivity reaction. Certain conditions may trigger an episode like alcohol, hot beverages, tobacco, spicy foods, stress, and sunlight. Demodex mite and H pylori have also been implicated.

Facial symptoms and signs
Recurrent flushing and persistent and/or recurrent midfacial erythema characterize it. The patient may have adult onset acne and telangiectasias. In later stages there may be Papules, Pustules in the midface, with associated rhinophyma.

The ocular symptoms are similar to MGD and there may be inflammatory keratitis, which may result in a sterile perforation.

Treatment
Avoidance of food, beverages and environments, which trigger the episodes along with treatment as of MGD. There is a role of oral isotretinoin and topical tretinoin to suppress sebum production. But there are certain adverse effects like severe erythema blepharoconjunctivitis, worsening of telangiectasia and severe keratitis. And it may be Teratogenic also.

Metronidazole is advocated as the first line therapy due to its antimicrobial, antibacterial, antiparasitic, anti-inflammatory and immunosuppressive properties.

Topical metronidazole 1%cream (not available in India) is effective in treating skin lesions. In a pilot study, Barnhorst et al - found topical compound to be safe and effective in treating eyelid involvement in ocular rosacea.

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Anisocoria means an inequality of the pupils (a – privative; iso – equal; coria – pupil).

Under normal conditions, the pupils remain equal at all times in all levels of light. When pupillary inequality is seen, it usually means that damage has occurred to the iris sphincter, the iris dilator or to their innervation.

Pupil size is determined by the local state of the iris tissue, the chemical events occurring at the myoneural junctions, the tone of the pupillary sphincter (parasympathetic) and the pupillary dilator muscles (sympathetic) in response to nervous stimuli and the general emotional state of the individual.

The retina, optic nerve, chiasm and optic tracts constitute the afferent pathway of the light reflex. Approximately half of the fibers of the optic nerve decussate in the optic chiasm, and the input to each of the parasympathetic nuclei in the brain stem remains equal. Therefore, relative afferent pupillary defects do not cause anisocoria because any changes in light input are distributed equally to both pupils.1

The parasympathetic (pupilloconstrictor) efferent pathway originates in the Edinger-Westphal nucleus in the dorsal midbrain and exits with the motor fibers of the oculomotor nerve to the ciliary ganglion via the cavernous sinus. Postganglionic fibers then travel to the pupilloconstrictor or sphincter muscle of the iris. Most diseases affecting the efferent pathway are unilateral or asymmetric and cause anisocoria.2

The sympathetic (pupillodilator) pathway leaves the spinal column at the eighth cervical level (C8) through the second thoracic level (T2) via the ventral roots to the paravertebral sympathetic chain. These fibers then pass through the stellate ganglion near the apex of the lung; then synapse in the superior cervical ganglion. The postganglionic fibers then travel via the carotid artery to innervate the dilator pupillae.3

Approach to the patient of anisocoria

The first step is to establish which muscle is not working properly. Anisocoria always increases in the direction of action of the paretic iris muscle. If the iris sphincter is paretic, the lighting condition that normally brings that muscle into action (bright light) will accentuate the weakness and increase the anisocoria. Conversely, if the iris dilator were paretic, the anisocoria would be expected to increase in darkness, as reflex dilatation is impaired.4

Pupillary inequality that increases in bright light

There are many causes of anisocoria that increases in bright light.

- Iris abnormalities on slit lamp examination: Sphincter tears, traumatic mydriasis, and iris sphincter atrophy such as by previous herpes zoster uveitis.
- Medications such as atropine
- Oculomotor nerve palsy
- Post ganglionic lesion – tonic pupil
- Angle closure glaucoma
- IOFB – iron mydriasis.
- Adrenergic mydriasis
- Segmental paralysis of the iris sphincter – Adie’s pupil, partial oculomotor nerve palsy
- Fixed pupil after anterior segment surgery

Pupillary inequality that increases in the dark

The two most important causes of anisocoria that increases in the dark are simple or physiological anisocoria and Horner’s syndrome.

Local ophthalmologic conditions: Any condition resulting in an inflammatory response within the anterior chamber may cause spasm within the sphincter muscle, resulting in anisocoria.5

Some medications for glaucoma cause miosis (eg, pilocarpine).

Important conditions causing anisocoria

Pharmacologic mydriasis

An important cause for an isolated dilated pupil is pharmacologic mydriasis. 1% pilocarpine in the affected will reverse the mydriasis caused by atropine and can be used as a diagnostic test in suspicious cases.

Sympathomimetics, which are used to facilitate nasotracheal intubation or ophthalmologic examination, also cause mydriasis.

Inadvertent ocular exposure to anticholinergic agents also has been reported. Patients using scopolamine patches have been noted to have self-limited mydriasis, which has been dubbed “cruise ship anisocoria.”6,7

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Oculomotor palsy: The most worrisome cause of an enlarged pupil is oculomotor nerve dysfunction.

- Anisocoria in the setting of a head injury with decreased level of consciousness may be caused by uncal herniation due to an expanding supratentorial lesion which forces the uncus against the edge of the tentorium, compressing the adjacent mid brain and oculomotor nerve. This results in ipsilateral third-nerve palsy and decreased level of consciousness. In addition, the contralateral cerebral peduncle is compressed against the free edge of the tentorium, resulting in ipsilateral hemiparesis. Such patients require urgent intervention to lower intracranial pressure and have a poor prognosis without rapid surgical intervention.⁸

- When a parasympathetic pupillary defect coexists with ptosis and extraocular muscle palsies in a patient with a normal level of consciousness, the diagnosis is oculomotor palsy with pupillary involvement. In these situations, emergent neuroimaging is indicated to rule out a compressive lesion, such as aneurysm, tumor, etc.⁹

- Oculomotor palsy due to metabolic diseases, such as diabetes, generally spares the pupil, but can be total also.

Acute closed-angle glaucoma

It results in a red painful eye and visual disturbance. In this condition, the pupil tends to be fixed in mid position, with an impaired light reflex.

Adie tonic pupil

Adie tonic pupil predominately occurs in females aged 20-50 years. Patients may complain of photophobia and episodes of blurred near vision or blurred vision when switching from near to far viewing; or they simply may complain of unequal pupils without any other symptoms. Typically, the involved pupil displays a poor response to light, with a relatively preserved response to sustained near fixation but an abnormally slow or tonic contraction. Slit lamp examination often reveals sector palsies of the iris.

The parasympathetic defect in Adie pupil is believed to occur after the fibers leave the ciliary ganglion. As a result of denervation supersensitivity, the affected eye displays an abnormally brisk response to dilute (1/8%) pilocarpine. Normal eyes generally do not respond to such a dilute solution, and this test has been suggested as a way of differentiating preganglionic and postganglionic parasympathetic lesions.⁵

Recent literature reports many patients who have mydriasis due to oculomotor nerve compression and have displayed reactivity to dilute pilocarpine, but these patients should show other signs of CN III dysfunction.

The combination of an idiopathic tonic pupil with decreased deep tendon reflexes and/or orthostatic hypotension is termed Holmes-Adie syndrome. The symptoms of a tonic pupil tend to be self-limited. Aide pupil is believed to be idiopathic or viral in etiology.

Other causes of a tonic pupil include neurosyphilis, diabetes, herpes zoster, giant cell arteritis, and alcoholism.¹¹

Simple anisocoria

Simple anisocoria may be found in up to 20% of the general population and may vary from day to day in the same individual.

In most patients, the degree of anisocoria is less than 1 mm, and no ptosis, dilation lag, or vasomotor dysfunction is present.

In some patients, simple anisocoria may be provoked by oral medications (eg, pseudoephedrine, selective serotonin reuptake inhibitors).

Instillation of 4-10% cocaine solution causes dilation of both eyes.

Old photographs, sometimes from drivers’ licenses, can provide evidence that the anisocoria has been present for some time.¹²

Horner syndrome

Horner syndrome is the result of disruption of the sympathetic innervations to the eye at any place along the pathway.

Dilation lag is a classic finding in Horner syndrome. The affected eye typically has a delayed response to reduced illumination. As a result, the anisocoria of Horner syndrome is greater 5 seconds after entering a dark environment than it is after 15-30 seconds.

In patients with an unestablished diagnosis, instillation of 4-10% cocaine solution is indicated. Cocaine inhibits the reuptake of norepinephrine, causing more norepinephrine to be available at the neuromuscular junction of the iris dilator muscle. Assess the pupils at baseline and at 40-60 minutes. In a positive test, the sympathetically impaired pupil fails to dilate, and the degree of anisocoria increases. If both pupils dilate, physiologic anisocoria is the diagnosis. In some studies, this test has been both sensitive and specific for Horner syndrome.¹⁴

Further delineation of the level of a lesion causing Horner syndrome has proved more problematic. This becomes important, as patients with postganglionic Horner syndrome tend to have a very good prognosis, while preganglionic lesions are often the hallmark of myelopathy or malignancy.¹³
The exception is in patients with carotid dissection, which may result in postganglionic Horner syndrome. However, such lesions also are associated with acute neck pain or other neurologic deficits. Therefore, in cases of painful Horner syndrome, emergent evaluation of the anterior cerebral circulation is indicated.

In patients with Horner syndrome without pain, a chest x-ray to exclude a Pancoast tumor probably is indicated, but further workup may be pursued on an outpatient basis.

Horner syndrome also can occur in incipient transtentorial herniation. Such patients typically experience a rapid deterioration in brainstem function and have a decreased level of consciousness.

**Pharmacologic miosis**

Pharmacologic miosis may be the result of a variety of cholinergic glaucoma medications. A small pupil also may be the result of chance exposure to cholinergic agents. Suspect pharmacologic miosis in otherwise asymptomatic patients who wear contacts and have experienced acute onset of miosis.

Implicated agents include anticholinesterases (eg, flea collar anisocoria) and inhaled anticholinergics (Ipratropium bromide). In such cases, withdrawal of exposure to the agent confirms the diagnosis.

**Bibliography**

Endothelial dysfunction from disease or trauma is one of the leading indications for corneal transplantation. Over the past 100 years, the only solution for endothelial replacement was through full thickness corneal transplantation. While penetrating keratoplasty (PKP) has been shown to yield healthy donor tissue with good endothelial function, this procedure has been plagued by the inherent problems of unpredictable surface topography, retained surface sutures, and poor wound strength.

Problems with PKP

- Long visual recovery time due to the presence of multiple sutures
- Poor quality of vision due to high astigmatism in postoperative period.
- Risk of wound rupture due to a large wound.

PKP can produce anatomically clear corneas, but its refractive results are abysmal. The sutures remain in place for a long time and these can cause suture related problems such as loose sutures, broken sutures, suture infiltrates, and even graft infection. The patients in developing countries such as ours come from remote and rural areas and often do not follow up regularly. Poor quality of vision in these eyes has been associated with high astigmatism. Wound dehiscence is another complication, which can occur in these cases. Patients with bilateral disease often wait for a long time for corneal transplantation in their fellow eye until problems with their first eye resolve.

Advantages of Endothelial Transplantation

This technique of endothelial transplantation offers several advantages, which include the following:

1. **Less postoperative astigmatism**
   
   The technique of endothelial transplant is termed as “sutureless”. At the end of the surgery, only 2-3 sutures are applied on the scleral tunnel. This ensures a quicker post operative visual recovery as compared to a conventional penetrating keratoplasty.

2. **Faster visual recovery**

   The presence of a smooth ocular surface in the absence of corneal sutures ensures a faster visual recovery in the postoperative period.

3. **Stronger wound integrity**

   There are no large wounds or potential areas of wound dehiscence after endothelial keratoplasty.

4. **Less risk of rejection**

   Theoretically, there is less risk of allogenic graft rejection as decreased amount of corneal tissue is transplanted.

**Landmarks in Endothelial Transplantation**

In 1998, Gerrit Melles\(^1\) first described the technique of **Posterior lamellar keratoplasty (PLK)** by which the inner layers of the cornea were replaced using manual dissection. In 2001, Mark A. Terry\(^2\) renamed the technique **Deep lamellar endothelial keratoplasty (DLEK)**. Both options represent improvements over PKP, but they are tedious, highly surgeon-dependent techniques that require extensive manual dissection of the donor tissue and host cornea. Melles developed a technique of stripping the Descemet’s membrane called **Descemet’s stripping lamellar endothelial keratoplasty**, or DSLEK, which does not require manual dissection of a patient’s cornea. The most recent version of endothelial keratoplasty is **Descemet’s stripping automated endothelial keratoplasty**, or DSAEK, which was introduced by Francis Price.

**Advantages of DLEK**

The technique of DLEK involves manual dissection of a posterior lamellar disc using a lamellar dissector and curved corneal scissors (Cindy scissors) or a Terry’s trephine. The posterior dissection of the host provides mechanical support to the graft, and therefore there are less chances of postoperative donor lenticule dislocation\(^3\) as compared to DSAEK where only the Descemet’s layer of the host is removed and no dissection of the posterior stromal layers is done.

**Problems of DLEK**

However, there are problems associated with the DLEK procedure, which include the need for specially designed
blades and trephines for dissection, the creation of an irregular stromal interface and the possible risk of perforation of the host cornea. Further, larger incisions in the host are required and the procedure is technically challenging. Further, there may be interface haze present in between the host and donor corneas.

The need for DSAEK

The new technique of DSAEK eliminates all manual dissections and therefore provides a smooth interface. There are no surface sutures required in DSAEK and hence this shortens the surgical time. The suture related problems such as loose sutures, broken sutures, infiltrates, vascularization and ulceration are obviated. There is less postoperative astigmatism as the corneal surface is smooth and hence this technique provides faster visual rehabilitation. The corneal topography is more predictable and there are minimal chances of wound dehiscence as there are no corneal incisions. The visual rehabilitation after DSAEK is generally one two two months.

Indications of DSAEK

DSAEK is indicated in patients with varying types of endothelial dysfunction. The important pre-requisite before performing DSAEK is the presence of a clear anterior stroma. The presence of any kind of scarring in the stroma rules against performing a DSAEK. The indications of DSAEK in the present surgical scenario are:

- Pseudophakic bullous keratopathy (PBK)
- Aphakic bullous keratopathy (ABK)

Donor Tissue Preparation in DSAEK

The Moria ALTK system (Moria, Antony, France): This machine helps in a clean separation of the corneal stroma from the corneal endothelium. Usually a 350 microns head is used so that the remaining 150-200 microns can be easily transplanted on to the recipient’s cornea. The use of ALTK system facilitates the donor tissue preparation. In addition, the automated system provides faster and better quality of vision than manual technique.

Surgical steps of Descemet's stripping endothelial keratoplasty (DSAEK)

A 5-mm scleral tunnel incision is made temporally into the clear cornea. The area of planned Descemet’s removal is marked with a reverse Siskey’s hook. After scoring Descemet’s membrane, the anterior chamber with irrigated with trypan blue ophthalmic. The central Descemet’s membrane is stripped with a reverse Siskey’s hook.. A continuous infusion system of BSS helps maintain the anterior chamber and minimizes the stress placed on the zonular apparatus in addition to minimizing trauma to the iris, lens, and peripheral cornea. The donor tissue is prepared with the help of ALTK machine. Usually a 350 microns head is used.

Prior to insertion, the posterior donor tissue is folded over on itself like a taco with a 40/60 overfold, with the endothelial side inward. This technique allows a 9-mm
donor button to be inserted through a 5-mm scleral tunnel incision. A small amount of viscoelastic is placed on the endothelial side before folding it to help protect it. The folded tissue is grasped with a special forceps and the tissue is placed into the eye through the scleral tunnel incision. Air injected into the anterior chamber helps unfold the donor tissue, with the endothelial side downward. The air also presses the donor tissue up against the patient's cornea. The air is allowed to stay for 8 minutes, and then BSS wash is given. The scleral incision is sutured with the help of 10-0 monofilament sutures.

Postoperative course

The patient is seen the next morning and the patch is removed. If the graft is in good position on day one, it will heal in good position. The overlying cornea has a variable rate of clearing, but some patients are able to see as well as 20/25 only one week after DSAEK surgery with a clear central cornea.

The interface may clinically appear exceptionally clear, but it remains an interface with at least the donor tissue with a stromal resection. It is this stromal interface of the donor that likely contributes about one line of visual loss to the macular potential.13-14 Extensive work continues to be done to improve the interface in DSAEK surgery. Investigators are working in the areas of femtosecond laser preparation of the donor tissue, but currently, the interface after femtosecond resections in the deep stroma are inferior to that created by a microkeratome.

The endothelial survival after small incision DSAEK surgery is quite remarkable. Even with folding the tissue and other donor manipulations the average endothelial cell count after small incision DLEK surgery is comparable to PK surgery.

The postoperative medical therapy after DSAEK surgery is identical at this time to what is done with PK surgery patients. Topical prednisolone acetate 1% is used four times a day for 3 months, then three times a day until 6 months, then twice a day until 9 months, and then once a day until one year postoperatively. The steroids are then tapered down further until discontinued entirely. Fluoroquinolone antibiotics are used on a four times a day dosage for the first two weeks after DSAEK surgery and then slowly tapered over a period of six weeks.

Visual Recovery Time after various techniques of keratoplasty

The visual recovery time is typically four to six weeks after DSAEK. This is in contrast to the longer recovery times after penetrating keratoplasty. The patient is more comfortable due to the absence of any surface sutures. The amount and duration of topical antibiotics is less after a DSAEK which further shortens the visual recovery period. The approximate visual recovery time after various keratoplasty techniques are:

- **PKP**: 12 months
- **DLEK**: 6 months
- **DSAEK**: 1 month

Our Results

We operated on five eyes of five patients using the technique of DSAEK. All eyes had bullous keratopathy (three pseudophakic bullous keratopathy, two aphakic bullous keratopathy). The DSAEK was performed using the standard surgical technique as described above. The patients were followed up regularly for three months. At three months follow-up period, 60% had BCVA better than 20/40, and 80% had BCVA better than 20/60. The endothelial cell counts were above 2200 cells/square mm in 60% of the eyes, and above 1800 in 80% of the eyes. There were no cases with graft dislocations.

Challenges of DSAEK

- **Preparation of donor tissue**: The use of ALTK machine is another step towards achieving a smooth interface during lamellar surgeries. Research work is being done in areas of femtosecond laser for preparation of donor tissue.
- **Unfolding of donor lenticule inside the recipient eye**: This is especially important in order to minimize the endothelial cell loss. Various techniques to unfold the tissue have been advocated which include unfolding with air or balanced salt solution.
- **Donor dislocation in early postoperative period**: A repeat air injection can be tried up to three weeks in cases of donor dislocation.

Conclusion

DSAEK patients do not require the same degree of monitoring as standard PK patients and therefore require less post-op clinic time. With no sutures or corneal incisions the wound healing or ulcerations are not an issue. Astigmatism management is also not a problem after DSAEK surgery. With its superior topography, rapid wound healing and long term safety, the endothelial keratoplasty of DSAEK is going to be another milestone in corneal transplant surgery.

References

Microstructural analysis of the ocular structures is gaining increasing importance in ophthalmic diagnosis. Although the inherent transparency of the cornea was exploited initially in instruments such as the slit lamp biomicroscope, detailed invivo high magnification ocular observations still remained a difficulty. Clinical confocal microscopy was developed to overcome the limitations of conventional light and electron microscopy such as the need to fix and process samples before evaluation. This new bio-imaging technique enables non-invasive analysis of corneal structure and function. Minsky described the first confocal microscope in 1957. Since then, several improvements have occurred. The most modern confocal microscopes have light source focused onto a small volume within the specimen tissue and a confocal detector is used to collect the resulting signal to produce an image with enhanced lateral and axial resolution. This new imaging paradigm and its application in vivo provide insight into the understanding of the structure and function of the eye. The tandem scanning confocal microscope was first used to examine a human eye in vitro by Lemp et al in 1985 and invivo by Cavanagh et al in 1990. Bohnke and Masters have detailed the optical techniques for ocular biomicroscopy and theoretical foundations of confocal microscopy.

**Principle of the confocal microscope**

The principle of the confocal microscope was first described by Minsky. He proposed that both the illumination (condenser) and observation (objective) systems be focused on a single point (have common focal points), hence the name "confocal" microscopy. This dramatically improved the axial (z) and lateral (x, y) resolution of microscopy by eliminating out focus information, bringing lateral resolution to an order of 1 - 2 μm and axial resolution to 5 - 10 μm. This allows for possible magnification of upto 600 times, depending on the numerical aperture of the objective lens used. As the field of view of the confocal imaging systems is limited, it is necessary to rapidly scan the focal point across the sample and reconstruct the image to allow a real time on-screen view.

**Types of Confocal Microscope**

Depending on the method of scanning, the tandem scanning confocal microscope (TSCM), the scanning slit confocal microscope (SSCM) and the confocal laser scanning microscope (CLSM) have been described. In the tandem scanning confocal microscope, thousands of light beams are moved over the fixed object, generating a high scan rate. These parallel beams are generated by a Nipkow wheel, a disc with thousands of pinholes spinning at high speed. These apertures are arranged in tandem- i.e. as diametrically opposed pairs. Light passes through one pinhole and is then reflected back through the corresponding pinhole situated opposite. The high speed rotation of the disc enables the light beam to scan the full field of view many times a second, thus producing a real time image. The scanning slit confocal microscope uses a light source with one dimensional slit scanning instead of two dimensional spot scanning. The confocal laser scanning microscope uses a laser beam and this generates
a monochromatic, bright, intense, sharply focused and coherent light. A novel digital confocal laser scanning microscope (CLSM) recently developed, is a combination of the Heidelberg retina tomography (HRT II) and the Rostock cornea module. The LSM has a computer controlled hydraulic linear scanning device and a water contact objective and a diode laser beam of 670nm wavelength is used as the light source. The Rostock scanning laser confocal microscope provides reproducible images of high resolution with uniform illumination and precise depth measurements.

Confocal microscopy of the normal human cornea

Superficial cells are seen with clear visible cell borders, bright cytoplasm and black nuclei. These cells are characteristically polygonal, usually hexagonal in shape. The intermediate layer of wing cells comprises of cells smaller than the superficial cells, with bright cell borders and dark cytoplasm. These cells are fairly uniform in size and shape. The basal epithelial cells (figure 1) are located just above the Bowman’s membrane and are seen as a distinct mosaic, with light cell boundaries. The basal epithelial cells are the smallest cells in the epithelium. The Bowman’s layer appears as a homogenous acellular layer and nerve fibres of the subepithelial nerve plexus (figure 2) are seen as beaded nerve fibers. Keratocyte nuclei are identified as bright reflections in the stroma. The anterior stromal keratocyte nuclei (figure 3) are more abundant and oval compared to the posterior keratocyte nuclei (figure 4) which were less abundant and more oblong in shape. Endothelial cells (figure 5) are visible as bright cell bodies and dark cell boundaries, characteristically hexagonal in shape with fairly uniform appearance in size and shape.

References

Ophthalmology has progressed by leaps and bounds. Refractive surgery has evolved from Radial Keratotomy (RK), to Excimer Laser Vision correction. Refractive surgeons and researchers have refined earlier techniques to further improve quantitative and qualitative results. Hence today Excimer laser manufacturers have adapted Wavefront technology to ophthalmology to treat not only refractive errors but also higher order aberrations (Aberropia) captured by Aberrometers which in turn guide the Excimer laser ablations.

What are aberrations?
A ray of light which is misdirected from its desired image point is an aberrated ray of light. If we compare the real output wavefront to the ideal one, we call the difference wavefront aberration. The more the wavefront aberration differs from zero, the more the real image differs from the ideal image. Hence, the poorer the quality of image formed on the retina.

How to describe aberrations
There are two concepts possible to describe aberrations, namely, ray and wave optics. Like any object, phenomenon or event, wavefront aberration as a physical quantity should be identified by means of decomposition in a conventional system called a basis. A basis wisely chosen can give specific information about the quantity to be examined, and we can identify the aberration types that the optical system suffers from.

The commonly used bases are 1) Orthogonality (locality) basis, 2) Taylor basis and 3) Zernike basis.

There are two types of optical aberrations. Lower order aberrations (LOA) such as defocus (simple myopia & hypermetropia), tilt and astigmatism, can be corrected by glasses, contact lenses and standard laser corrections. Higher order aberrations (HOA) include coma, trefoil, spherical aberration and tetrafoil, and adversely affect vision in most cases. The role of all HOAs in vision is unknown at this time though several theories have been proposed. Typically the more central the HOA is the more effect it has on vision.

Spherical aberration occurs when an optical system does not focus all parallel rays to a single point. The paraxial (central) rays and the peripheral rays have different foci. As a result, instead of a concise focus, they are distributed over a small region of the image. In humans, spherical aberration increases as the fourth power of the pupil size. At night pupil dilation increases spherical aberration. Studies have shown that the young human eye is a system in which the positive spherical aberrations introduced by the cornea are partially compensated by the negative spherical aberrations created by the lens. Changes that occur in the lens with age lead to loss of this compensation leading to an increase of total ocular aberrations and hence a corresponding loss in optical quality.

Coma, one of the more dreaded HOA, occurs when ocular components are not co-axial and in pupil decentration. Here the image of a bright point would have the shape of a comet with a “tailing” effect.

Aberrometry & Wavefront Analysis
The next evolution to come on to the visual science scene in refractive ocular imaging is the aberrometer, and wave front analysis. This technology is based on astro-physical principles, which astronomers use to perfect the images impinging on their telescopes. Dr. Bille, the Director of the Institute of Applied Physics at the University of Heidelberg first began work in this field while developing this specific technology for astronomy applications in the mid-1970s. For perfect imaging, astrophysicists have to be able to measure and correct the imperfect higher order aberrations or wavefront distortions that enter their telescopic lens system from the galaxy. To achieve this purpose, adaptive optics is used wherein a deformable mirrors reform the distorted wavefront to allow clear visualization of celestial objects. Extrapolating these same principles to the human eye, it was thought that removal of the wavefront aberrations of the eye might finally yield the long awaited and much desired ultimate goal of “super vision”.

Wavefront refraction can be conceptualized as spatial refraction i.e. knowing the refraction of the eye at every given point on the cornea. It is analogous to measuring topography of the whole eye as an optical system, in contradistinction to corneal topography that measures topography (aberrations) of the corneal surface.

There are several methods of measuring the aberrations of the eye:
1. Shack-Hartman Aberrometer (outgoing optics) – a thin laser beam enters the eye and is focused on the retina. As the emerging rays reflect off the macula and refracts

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**OPHTHALMIC TECHNIQUES**

Higher Order Abberations and Wavefront Technology
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out of the eye through each part of the optical media, they are captured by a grid and focused onto an array of lenslets which quantifies their deviation, and creates the wavefront pattern from the recorded deviations.

2. Tscherning Device (ingoing optics) – A grid of laser beams is projected into the eye. The deviation of this grid from an ideal pattern is used to quantify and compute a wavefront map.

3. Adaptive optics (ingoing optics) – involves recording the ingoing rays of light which are manually steered by the patient to define the wavefront needed to cancel ocular aberrations.

4. Slit Skiaskopy also called Double-Pass Aberrometry (ingoing & outgoing optics) – a slit of light is scanned into the eye along a given meridian. The timing and scan rate of the reflected light can be determined by photo-detectors to determine the wave aberrations along that meridian. Multiple meridia are scanned to analyze the full area of the entrance pupil.

**Some important terms**

RMS error – an area weighted statistic most commonly used in reading wavefront maps. It is the square root of the sum of the squares of all deviations from the ideal wavefront. Measured in microns, it expresses how distant the wavefront is from the zero function. If the higher order aberrations are less than 0.5 microns, most patients are satisfied with their vision with glasses, contact lenses and standard laser corrections. If the higher order aberrations are less than 0.25 microns, most patients are extremely satisfied with their vision.

Point Spread Function – if the object is a point at infinity, instead of observing a point image on the retina, a bright narrow spot with brutal transition between brightness and opacity (a spread spot) is observed called point spread function. Measured in minutes of arc, it is an indication of the diffraction effects around the margin of the pupil.

The Effective Blur value – is the amount of spherical error in diopters, it would take to create an RMS error equivalent to the RMS error created by all aberrations in a given subject. It is a qualitative assessment of higher order aberrations.

Wavefront aberrometers for measuring optical aberrations are emerging as an important complement to the corneal topographers that have been used in refractive surgery for nearly 30 years. While corneal topography can detect regular and irregular astigmatism and curvature of the anterior surface of the cornea, it does not provide refractive information about the overall visual system, which is one of the most important advantages wavefront testing offers. Additionally, quantitative descriptors of the shapes have been rudimentary, with only single-number descriptors of irregularity, available in most instances. Wavefront offers quantitative and qualitative descriptors of shapes in a much more sophisticated manner.

Wavefront Aberrometery is an interesting and thought provoking...
Wavefront–guided Laser Vision Correction

There are currently two primary applications for wavefront customization. One is the treatment of essentially normal eyes with wavefront aberrations. These include 1) patients who are not happy with best spectacle-corrected visual acuity (BSCVA) of 20/20 or 20/15, 2) those with a poor endpoint on refraction who cannot be corrected to 20/20 and 3) those who have poor night vision or poor contrast sensitivity, despite uncorrected visual acuity (UCVA) of 20/20 or better.

The second application is for abnormal eyes, such as those that result from decentered flattened zones following primary LASIK. These patients are likely to benefit significantly from wavefront-driven treatment of higher-order aberrations. Patients who have an increase in higher-order aberrations following initial treatment may specifically benefit from a wavefront directed treatment.

Results

A study conducted at our centre examined the effectiveness of the VISX Wavescan device for CustomVue™ treatment in terms of uncorrected visual acuity, refractive stability, predictability, intended versus achieved correction, analysis of higher-order aberrations and responses to subjective questionnaire on night vision, glare and contrast sensitivity.

Results have been very stable, with majority of custom-ablated patients showing an improved in HOAs at 12 months. Compared to patients who had conventional treatment, the wavefront group had a less of increase in the higher-order aberrations. 81% showed some improvement in coma, 79.5% showed some improvement in trefoil, and 72% showed some improvement in spherical aberration compared to pre-operatively.

In response to a subjective questionnaire, patients were more satisfied with their vision post-operatively in terms of halo frequency, night vision and glare.
Discussion

Conventional LASIK procedures only reduce lower-order aberrations. Hence the best-corrected visual acuities would be limited by higher-order aberrations. These patients with HOAs, normal corneal topography with no other abnormality, would benefit immensely from customized laser vision correction. Wavefront-guided ablations with lasers, such as the VISX Star S4 Excimer, have the potential to set a new standard for refractive surgery. The WaveScan device, which is part of this system, can be used as a standalone diagnostic tool or in conjunction with the laser, where recent advances in computational power have made its application for custom ablations possible. The VISX Star S4 series with its patented VISX algorithm can ablate virtually any shape and allows for minimum efficient tissue removal during laser ablations. This is important for thinner corneas and higher refractive errors.

One of the keys to treating higher-order aberrations with wavefront technology is the laser’s ability to track the eye to maintain proper centration. The VISX Star S4, in addition to the ActiveTrak real-time eye tracking device, also includes an automatic iris image-registration system for cyclotorsional registration and tracking that links the image to the WaveScan. This appears to have significant advantages over ink-mark-based tracking technology.

Realization of best possible unaided vision may be limited at various levels in the visual system – cortical, retinal, corneal or the spectacle level. Clinical or subclinical amblyopia may make achievement of supervision impossible. But there may be a subgroup of patients that has the potential for an improved BCVA on removal of their HOA. It is important to identify and treat this group so that they are not deprived of the opportunity to gain in their best-corrected vision.

Thus, there may be a large group of patients whose best corrected visual acuity (BCVA) may actually improve significantly on removal of the optical aberrations. These optical aberrations are contributed to by the eye’s entire optical system i.e. the cornea, the lens, the vitreous and the retina. Wavefront (Customized) treatment is tailor-made for these individuals, and is safe, predictable, provides better BCVAs and reduces the incidence of unsatisfactory results. Moving the treatment expectation from “less dependent on glasses or contacts” to a lofty goal of 20/15 or better with no higher-order aberrations is going to make patient counseling paramount. It is too early to know how stable the treatment of higher-order aberrations will remain over time. While the current data evaluating outcomes from wavefront-driven ablations demonstrate extremely high stability, patients need to be aware that their vision may change over time.

Points for Thought

Although wavefront technology is important as a diagnostic and treatment modality the results being
achieved are not to the satisfaction level aimed for. There may be different reasons for this.

1. Let us first look at the precision of our lasers today. Let us assume that it is plus/minus 0.25D at best (although no published study has ever analyzed 0.25D outcomes). With an optical zone of 6 mm it means ±3.5 microns precision. To correct higher order aberrations sub-micron precision is required.

2. With wavefront based treatments we are trying to correct aberrations of the whole optical system by resculpting the corneal surface i.e. we are introducing new irregularities on the corneal surface. These introduced corneal irregularities would again need correction and so on...

3. We think that we can treat all small corneal irregularities (that compensate for the aberrations from the rest of the system) but we are only assuming that they would not be evened out by the epithelium, while the practice teaches us the opposite.

4. Concerning LASIK as a modality how can we expect that a bulky 160 micron flap fit flush with sub-micron precision sculpting on the stroma. Imagine a 1 cm indentation being covered with a 1.6 meters thick rug!

5. There is also a question of whether we really want to correct the intraocular irregularities that are originating from a mostly dynamic system (crystalline lens, pupil), with varies greatly with the accommodative status and the pupil size and age.

6. With wavefront LASIK the microkeratome cut will produce another aberration – the unreliability of the flap.

The achievement of Super Vision is being questioned and debated. It is necessary to remove all the physiological aberrations from the eye? The aberrations have a utility. The theory most accepted about visual perception and particularly on the attention mechanisms, is the one proposed by Francis Crick and Christoff Koch. It points out that one of the most important recognition factors is located in the aberrations of the eye, and that it determines a basic entity called “Multifoco” which is “pre-vision” and “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus”. This is as if retina receives information on whatever is far or close, all around us all the time & “pre-focus".

It is alright to improve the Snellens acuity to Super Vision level but not at the cost of eliminating the optic elements basic to visual perception and requirements. The vision is something more than just seeing objects at a distance as if it were a landscape. We might reduce the present superior vision to the narrow telescopically called Super Vision!

References

17. HC Howland and B Howland, “A subjective method for the measurement of monochromatic aberrations of the human eye, J Opt Soc Am. 67, 1508-1518(1977)

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Bioavailability of topical drugs

Topically applied drugs have to cross the hydrophilic mucin layer to penetrate the lipophilic corneal epithelium and then only can it reach the anterior chamber. All the hydrophilic drugs can cross mucin layer with ease but fail to penetrate the lipophilic corneal epithelium. When lipophilic drugs come in contact with lipid bilayer of corneal epithelium, it gets absorbed easily if it can cross the mucin layer of the tear film.

Mucin layer is highly hydrophilic which does not allow lipophilic drugs to pass through it. Resultant, less than 5% of the lipophilic drug is available to the corneal epithelium for absorption. This can be enhanced by the use of surfactants which also act as preservatives in the eye drop solution. After installation, the drug is present in aqueous layer of tear film in high concentrations. Benzalkonium chloride (preservative) breaches the mucin layer by its surfactant action and opens up the corneal surface for better absorption of the lipophilic drug. However, this method is not safe as BAK is toxic to the corneal epithelium. Resultant frequent instillation of BAK containing drug solution may lead to breach in corneal epithelial surface. Therefore, a better drug delivery desire may end up leaving a bad, infection prone epithelial surface.

Cyclodextrins

Cyclodextrins are a group of structurally related natural products formed during bacterial digestion of cellulose. These cyclic oligosaccharides consist of (α-1, 4) - linked α-D-glucopyranose units with a hydrophilic outer surface and inner lipophilic central cavity. The natural α-, β-, and γ- cyclodextrins consist of six, seven and eight glucopyranose units respectively. The aqueous solubility of these natural cyclodextrins is somewhat limited and thus several different water soluble derivatives have been synthesized. These include hydroxypropyl derivatives of β- and γ- cyclodextrins, randomly methylated and sulfobutylether b-cyclodextrins.

If we take the example of topical steroids, being lipophilic they are marketed either as hydrophilic prodrugs (usually acetate or phosphate esters) or in suspension forms. Prodrug fails to achieve high concentration due to low chemical stability and poor in vivo conversion to parent drug. Suspension has again stability problems and requires longer contact time to get absorbed on the surface. Use of cyclodextrin molecule overcomes all these problems by making lipophilic drug soluble in an aqueous vehicle as well enhancing its absorption at the epithelial surface. Topical Steroid preparations with cyclodextrin molecule have shown better bioavailability when used.

β- Cyclodextrin and drug molecule do not interact chemically with each other. Either the whole lipophilic molecule or the lipophilic part of the drug molecule acquires the central core of Cyclodextrin molecule and forms a drug-cyclodextrin complex. This complex formation enhances the solubility of the lipophilic molecule in aqueous solution and increases the shelf life of the aqueous eye drop formulation.

Mechanism of action

When this complex is instilled in the conjunctival sac, because of its water solubility it can cross the mucin barrier very easily and comes in contact with the corneal epithelium without harming the mucin layer. The Lipophilic drug molecule has a high affinity for the corneal surface, so it leaves the Cyclodextrin shell in tear film and gets absorbed in lipid bilayer of corneal epithelium. The cyclodextrin molecule has very low affinity to bind to the lipid membrane so it remains in the tear film.

Since no covalent bonds are formed or broken during this transfer process, the drug-Cyclodextrin complexes are in dynamic equilibrium with free drug and Cyclodextrin molecules. If high concentration of the drug can be maintained for a long time in the conjunctival sac, even a small number of cyclodextrin molecules can deliver a high amount of drug to the epithelial surface. Cyclodextrin molecule act as true carriers by keeping the lipophilic water insoluble drug molecules in solution and delivering them to the membrane surface where they separate from the cyclodextrin cavity into the lipophilic membrane. The empty central core is filled by another drug molecule or by other suitable lipid molecules present in the tear film.

Studies have shown that up till 5% concentration of cyclodextrin molecule increases the drug concentration at the surface. Any further increase in cyclodextrin molecule concentration in drug formulation leads to decrease in bioavailability of the drug. But, on the other hand high levels of cyclodextrin molecules ensure better solubility and longer shelf life of the preparation. To balance this equation small amount of water soluble polymer is being added. The addition of 0.10% hydroxypropyl methylcellulose not only increases the stability of the preparation but also holds the drug-cyclodextrin complex
Polymers enhance the Cyclodextrin complexation of the drug, thereby reducing the amount of Cyclodextrin needed in the formulation. While simultaneously enhancing the absorption of the drug-cyclodextrin complex to the eye surface through the formation of co-complexes. This further increases the drug availability at the eye surface.

**Future trends**

Cyclodextrin makes it possible to formulate lipophilic drugs in aqueous eye drop solutions. This may be useful for the formulation of Cyclosporin, Pilocarpine, Dexamethsone, Diclofenac, Fluorometholone, etc lipophilic drugs. With cyclodextrins, it is possible to increase the drug concentration and bioavailability and create formulations that offer more effective and less frequent treatment schedules for critical patients.

**Suggested reading**

5. Loftsson T, increasing the cyclodextrin complexation of drugs and drug bioavailability through addition of water soluble polymers. Pharmazie 53:733-740.
Over the past decade or so, India has made rapid strides in prevention and control of blindness activities. With its network of world-class eye care services and teaching and training institutes already serving as global and regional resource centers, India is poised to make notable progress on all fronts to achieve the goals of VISION 2020. Indian eye care professionals are well known and respected for their practical application of advanced techniques.

In spite of these achievements, majority of rural people do not have access to comprehensive and quality eye care. In most such areas, the mainstay of eye care service has been through Surgical and screening eye camps. The quality of services provided through such camps had always been questionable but in recent years the initiative taken by NPCB in setting up guidelines for these camps and efforts by Government and NGOs to improve the quality of cataract surgery in these camps, the scenario is changing. As analysis of the profile of patients awaiting of surgical camp services reveals the following:

- Quality eye care services are inaccessible, communication and travel is difficult.
- Cataract occurs relatively early (in the 40's) in many patients when patients are very active and are the sole bread earner for the family.
- They are fairly prone to trauma even in the immediate postoperative period.
- The patients find it difficult to come back for suture removal and an exposed suture can make the eye uncomfortable.
- These patients are less compliant as far as medications are concerned.
- The patients’ demands and expectations have increased over the years irrespective of their location.

All these factors need to be addressed while designing the cataract surgical techniques for these situations. One of the critical factors in the success of eye care programmes that is often overlooked, especially in the third world, is the quality of the visual results after surgery. Everyone keeps talking only of numbers.

Very often financial constraints is referred as the reason for offering lower quality services to the patient. This is neither a good, nor a valid excuse for poor quality surgery and inferior results in remote and rural patients.

Type of Cataract Surgery Ideal for Indian Patients

1. Cataract surgery with secure wound so that patients can resume their earning activities early.
2. Suture less, since many patients will find it difficult to return for suture removal.
3. Surgically Induced astigmatism should be minimal, as many of these patients will not be using glasses for some reasons or the other.
4. Quick Healing, since many patients are noncompliant as far as medications are concerned.
5. Surgery should meet the Needs and Expectations of the patient.

Phacoemulsification is the “state of the art” operation of choice for cataract surgery.

The Phacoemulsification technique offers the following benefits and advantages over planned extra capsular cataract extraction

1) It is performed through an incision 3mm or less in size, which is self-sealing and watertight thereby improving safety during the procedure.
2) It is significantly less invasive thereby leading to much less ocular trauma and consequently less postoperative inflammation which is a significant advantage over other types of cataract surgery in surgical camps as many of the patients are poorly followed up.
3) It results in minimal or no induced astigmatism.
4) It provides much more rapid visual and physical recovery and prompt refractive stability. The visual recovery is immediate if topical anesthesia is used. All these advantages lead to a significant improvement in the patient’s quality of life.
5) In addition, a smaller incision also may reduce the risk of Endophthalmitis.

Limitations of Phaco Surgery in camps

One of the strong limitations of Phaco has been the cost of not only the Phaco equipment but also the supplies related to its use.

Initial investment for Phaco machine

There was a time when the equipment or Phaco machine required a significant investment. At present, most of the companies that manufacture Phaco units are helping physicians and hospitals to acquire the equipment and supplies. The equipment is made available at much
more reasonable prices than their real sales cost, with the understanding that the surgeon would utilize a standard minimum of the Phaco supplies of that particular manufacturer every month.

**Running cost for Phacoemulsification**

Let us analyze, however, the current situation related to costs of performing Phacoemulsification, and compare it with the costs of the supplies needed to perform extra capsular extraction. With the latter, there is the cost of very fine sutures, which are unnecessary in Phaco; there is the cost of local anesthesia involved with either a retro bulbar or a Para ocular injection versus Phaco in which only topical sometimes with intracameral anesthesia is utilized. The cost of the postoperative injection of steroid-antibiotic in the fornix often administered following extra capsular surgery is also unnecessary with Phaco. The cost of even a fairly short stay in the hospital following the extra capsular extraction is higher than in patients with Phacoemulsification.

The significant economical savings to the patient from lost working hours with ECCE vs. almost immediate recovery with Phaco and the improved quality of life with Phaco are other major important contributions. All these are important features to consider when the so-called expenses for both operations are taken into account.

The supplies or tubing needed for each patient was also a heavy expense when performing several cases. The “tubing” which previously had to be discarded after each operation is no longer a problem cost-wise. Now it may be used for as many as 60 cases in the same day. No re-sterilization is needed. The tubing may be used without replacement for a complete day of Phaco surgery.

**Limited human resources**

One of the limitations of large volume Phaco surgery is unavailability of Ophthalmologists trained in Phaco surgery. This is attributed to the fact that there were only few training centres for Phacoemulsification but with passing time more and more centers are coming forward with Phaco training programmes.

In addition, the manufacturer provides advice and hands-on-training by experts to the surgeon so that he/she will be able to enter into the transition period utilizing his/her own personal equipment acquired from that manufacturer.

All of this makes the Phaco technique more accessible to a larger number of surgeons.

Longer learning curve for ophthalmic surgeons and limited applicability in terms of type of cataract.

These limitations have been partly addressed by better understanding of phacodynamics, availability of better Phaco machines and better training facilities.

In high volume surgery, the cost of cataract surgery by Phaco decreases as the numbers of surgeries increase. Over the years, Phaco machines have become cheaper, better, smaller, have multiple capabilities and reusable components, do not need gas to run, are easy to transport, set up and service. The associated procedures (Capsulorrhexis, incision design, lens insertion etc.) have been refined and standardized and made easy to learn and carry out. The consumables such as blades and knives and even foldable lenses made indigenously are available at affordable prices. Quite contrary to what people might suggest, funding is not the single major barrier to Phaco surgery in camps. Rationalization of expenses, saving on non-critical components and above all vision and staff motivation and change in attitude will help a lot in making PHACOEMULSIFICATION the surgery of choice in camps in majority of cataract patients.