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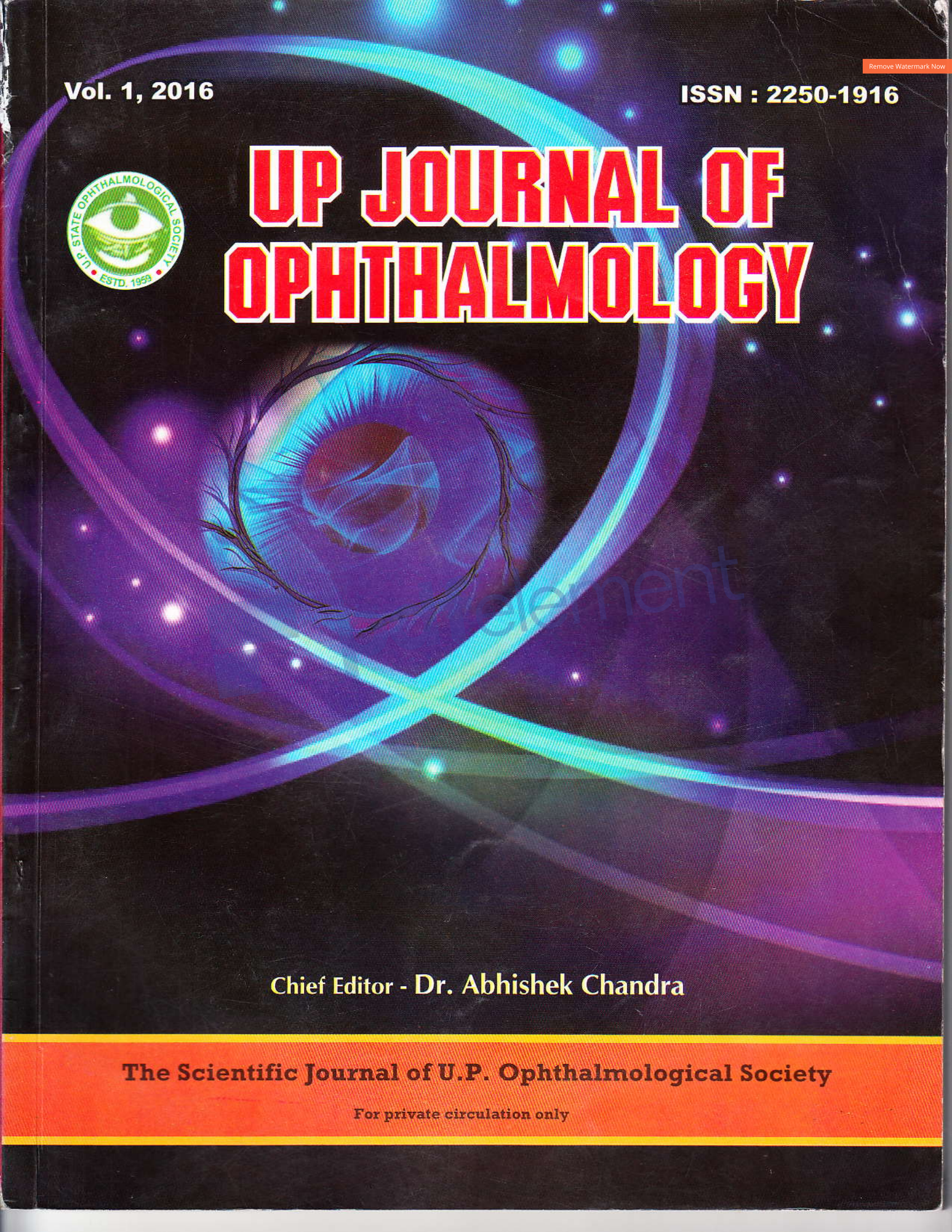
UP JOURNAL OF OPHTHALMOLOGY



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The Scientific Journal of U.P. Ophthalmological Society

Contents

Message from the President

Dear Friends,

The UP Journal of Ophthalmology is consistently making quality contribution to research in the field of Ophthalmology. This has been made possible by the efforts and the contributions of all of you, our friends, colleagues, all the editors of different volumes, members of editorial board, and contributors.

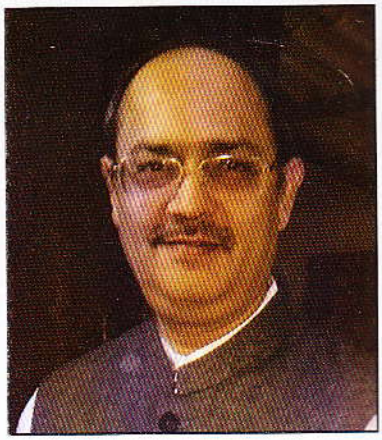
The responsibility of editing this issue was given to Dr. Abhishek Chandra, who has been a very dedicated researcher himself, besides being versatile in talents. I am sure the present issue will add to the knowledge in Ophthalmology, be able to raise new questions while answering some older ones; as well as chart a new direction for furthering research in Ophthalmology. Most importantly, it would be able to keep our minds stimulated and oriented towards research.

The present issue covers diverse issues and I congratulate Dr. Chandra and the entire editorial team for the timely publication.

With best wishes,

Prof. S. P. Singh
President, UPSOS
Principal, MLN Medical College
Allahabad

Welcome Message



Dear Dr Abhishek Chandra

When you strive for excellence, your efforts become part of "The history in making".

The passion, with which you have indulged yourself in bringing this issue of the journal of UPSOS(NOS), would surely be an example.

It is indeed a pleasure to have you in our team, and I am sure we would be able to initiate "The resurgence" of Ophthalmology in Uttar Pradesh, our Alma.

In good faith,

Dr. Malay Chaturvedi
(Secretary General)

From the Editor's Desk...

Dear Friends,

I am indeed happy to bring forth the present issue of the UP Journal of Ophthalmology. Being given the responsibility of editing the Journal for the first time unopposed, the role of bringing forth a volume of research papers is particularly challenging.

I have tried to stand up to the challenge, and 'add' meaningfully to the disciplinary trajectory by including articles covering a range of issues, and also ensuring originality of research published. I wish to express my thanks to our friends and colleagues, who have shown keen interest in furthering research in Ophthalmology, and contributed to the Journal.

We have not been able to publish all the articles that we have received. As Milton writes in his poem, "On His Blindness"; "...They also serve who only stand and waite." With these lines, may I acknowledge the contribution of those whose articles we have not been able to publish this time.I have also tried to get articles from across the state so as to have full representation. In this edition we have different subsections such as Original article, review article, diagnostic procedures, case reports and articles on newer techniques such as articles on nanoparticles which would give newer insight to the readers.

May I also express my thanks to the entire editorial team who have worked hard to bring this issue in time.I would also like to thank various pharma companies who have contributed for this journal and without whose support this issue would not have been possible. My effort would be to deliver this journal to each & every member of UPSOS.

Thanks and with hopes that the Journal will continue to grow with respect to quality of research publication, contributions, as well as spread in terms of readership.

Abhishek Chandra

Editor, UP Journal of Ophthalmology
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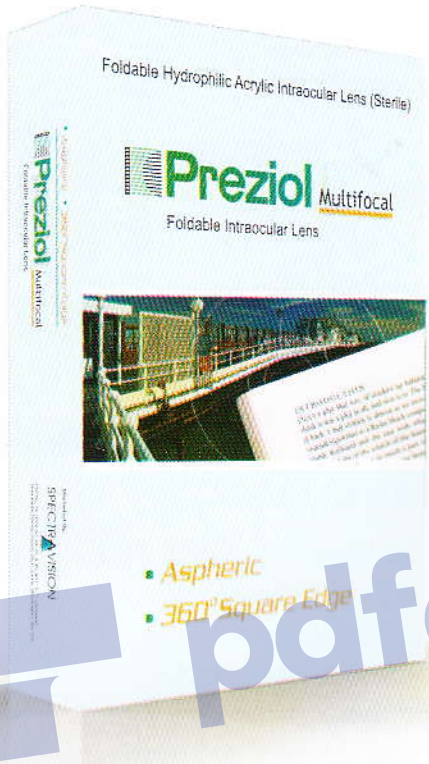

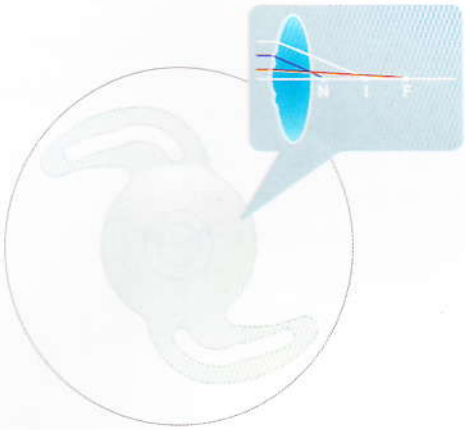

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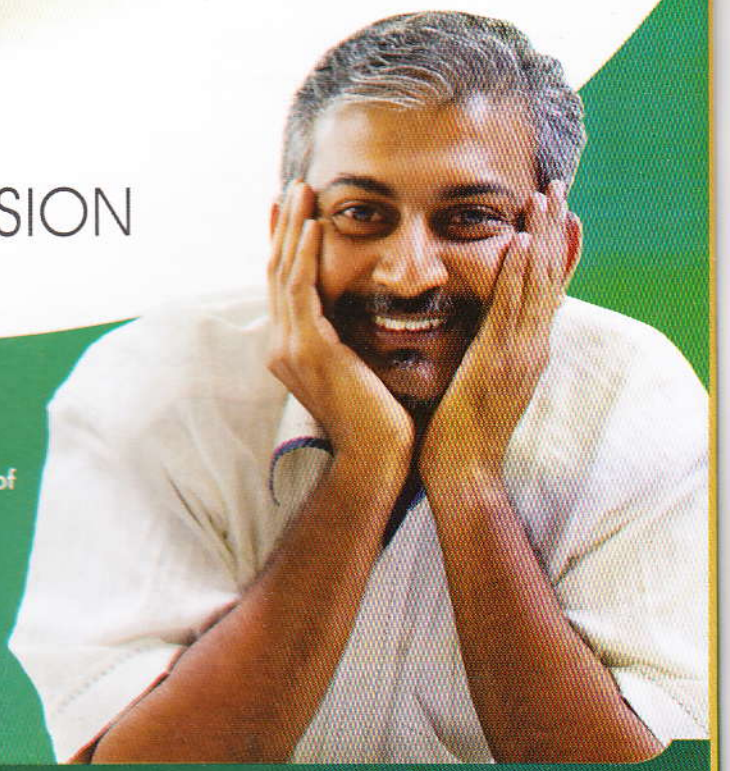

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References

1. Wojtowicz JC, Butovich I, Uchiyama E, et al. Pilot, prospective, randomized double-masked, placebo-controlled clinical trial of an omega-3 supplement for dry eye. Cornea. 2011;30(3):308–314. 2. Macsai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis). Trans Am Ophthalmol Soc. 2008;106:336–356. 3. He J, Bazan HE. Omega-3 fatty acids in dry eye and corneal nerve regeneration after refractive surgery. Prostaglandins Leukot Essent Fatty Acids. 2010;82(4–6):319–325.

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Clinico-microbiological profile of ocular mycosis with special reference to filamentous fungi

- Annapurna Parida*, Ragini Tilak*, Diksha Prakash**, Samir Kumar***, OPS Maurya***

Introduction

Mycotic keratitis presents as a suppurative, usually ulcerative, corneal infection. This entity may account for more than 50% of all cases of culture-proven microbial keratitis and of ophthalmic mycoses, especially in tropical and subtropical areas.

Filamentous fungi are the principal causes of mycotic keratitis in most parts of the world. In studies done around the world, either *Fusarium* spp. or *Aspergillus* spp. were the most common isolates. Dematiaceous fungi, such as *Curvularia* spp. and *Bipolaris* spp. are the third most important cause of keratitis in a number of studies, while the coelomycete *L. theobromane* has been reported to cause keratitis in India and the southern United States.

Most of the causes of blinding corneal pathology are preventable. Proper diagnosis of pathological organism in time can help reduce the unnecessary use of antibacterial or antifungal drugs that might lead to resistance. Corneal trauma is the most frequent and major risk factor for fungal keratitis. In fact, the physician should have a high level of suspicion in a patient with a history of corneal trauma, particularly with plant or soil matter. A history of corneal trauma with vegetable matter or organic matter is reported in 55% to 65% of fungal keratitis, as corneal epithelial layer prevents entry of organism inside the cornea. Fungi gain access into the corneal stroma through a defect in the epithelium, then multiply and cause tissue necrosis and an inflammatory reaction. The epithelial defect usually results from trauma (contact lens wear, foreign material, prior corneal surgery). The fungi can now penetrate an intact descemet membrane and gain access into the anterior chamber or the posterior segment. Mycotoxins and proteolytic enzymes augment the tissue damage. Apart from trauma, decreased host immunity is one of the important causes of fungal infection in cases of diabetic patients, steroid intake topically or orally and intake of any immunosuppressant drugs. Topical steroids as the principal risk factor enhance ocular fungal growth. Steroid use as initial therapy was reported in 1 to 30% of patients having microbial keratitis.

In India, as fungi are the leading causative organism, therefore, rather than following the empirical treatment protocol, it is better to go for identification of the pathogen. It is of utmost importance for the Microbiologists that they try to recognize fungal elements early to expedite the treatment procedure. In India many factors contribute towards the higher incidence of fungal keratitis. India being an agricultural country, most of the corneal trauma is agricultural. The Indian population lacks access to proper eye care, either due to ignorance or lack of facilities to handle eye injury. This leads to rampant use of traditional medicine which are again dried plant material in liquid preparation or animal origin like milk, urine etc., all of which might compound the injury.

* Department of Microbiology, Institute of Medical Sciences, BHU, Varanasi
** Fellow, L.V. Prasad Eye Institute, Bhuvaneshwar
*** Department of Ophthalmology, Institute of Medical Sciences, BHU, Varanasi

In this study, we have tried to find the risk factors behind development of mycotic keratitis and expedite treatment by giving an early conclusive diagnosis. We tried to find out the demography pattern and occupational susceptibility of the patients. The identification of causative organism and it's susceptibility to commonly used antifungal agents were also studied to see the pattern of resistance based on genus.

Aim

To study clinico-microbiological profile of ocular mycosis with special reference to filamentous fungi.

Material and Method

Processing of slides:

1. **KOH wet mount preparation:** Potassium hydroxide mounting fluid

Distilled water	80 ml
Potassium hydroxide	20gm
Glycerol	20ml

2. **Gram's staining**

3. **Lactophenol Cotton Blue mount preparation:**

Lactophenol cotton blue (LCB) stain:

Phenol	20gm
Lactic acid	20ml
Glycerin	40gm
Cotton blue	0.05gm
Distilled water	20ml

Culture Methods

SDA and blood agar media in petri-dish was used for fungal pathogens isolation. SDA agar supports growth of nearly all fungal pathogens including yeast and filamentous fungi. BA helps growth of bacterial pathogens in the bacterial corneal ulcer.

Antibiotic Sensitivity Testing:

- **Disk diffusion testing for filamentous fungi**

  Commercially prepared paper discs for Fluconazole (25µg/disc), Amphotericin-B (100 units/disc), Itraconazole (10µg/disc) and Voriconazole (1µg/disc), Ketoconazole (10µg/disc) from HiMedia Lab were used.

- **Minimum inhibitory concentration method for filamentous fungi**

  Itraconazole, Voriconazole, Amphotericin B, Fluconazole Ketoconazole were dissolved in DMSO. Drug dilution were prepared following the additive two fold drug dilution scheme to the final concentration for Itraconazole, Voriconazole, Ketoconazole and Amphotericin B, 0.038 to 16µg/ml, for Fluconazole 0.25 to 128µg/ml.

Observation and results

The proposed study was carried out in the Departments of Microbiology and Ophthalmology, Sir Sunder Lal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi.

We took corneal scrapes from 51 patients excluding obvious bacterial or viral corneal ulcer cases over a period of one year from February 2014 to January 2015. These patients have shown large ulcers with elevated margins, covering more than 2/3rd of cornea with satellite lesions (Fig. 1).

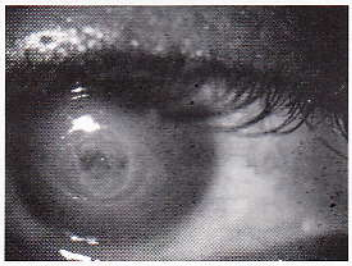

Fig 1. Corneal ulcer

Epidemiological profile of mycotic keratitis:

Demographic profile

Out of 23 positive cases, maximum 48% belonged to age group 41-50. 1 patient belonged to the 11-20 age group and 1 to the >60 age group. 4 patients each belonged to the 31-40 and 51-60 age groups. Rest 2 patients belonged to the 21- 30 age group. Overall male and female numbers were nearly equal (male-12 and female 11).

Residential status

In the culture proven cases 60% patients reside in rural areas. These patients have occupation related to farming and animal handling mainly.

Predisposing risk factors

Right eye (RE) was involved in 57% cases. A history of recent injury was present in 91% cases. In one patient, fungal corneal ulcer had developed after cataract surgery which was performed in a camp. In another case, the patient was suffering from Grave's Ophthalmopathy and the ulcer developed due to exposure. 18 patients (78%) admitted that they have put steroid containing eye drops without consulting any physician. There was no case of contact lens user in our study.

Diagnostic methods and their sensitivity

All corneal scrape material was processed through 20% KOH, gram stain and 1% methylene blue and observed microscopically. Out of 51 cases, in 23 cases fungal hyphae were observed in 10% KOH wet mount preparation after 12 hours (Fig 2).

Fig 2, Fungal hyphae in 10% KOH mount

Gram staining was unable to elucidate fungal hyphae in corneal sample satisfactorily. It gave positive result in 10 (46%) cases only. Methylene blue stained fungal hyphae in 12(52%) cases(Fig 3).

Fig 3, Fungal hyphae in methylene blue stain

The number increased after KOH. But scrape material was not always sufficient in amount to carry out many smear preparations; hence Methylene blue + 10%KOH method was not performed in all cases. Table below is showing sensitivity of all the above methods taking the number of culture positive cases as 100%.

Diagnostic Method	Positive	Negative	%
KOH wet mount	23	0	100
Gram stain	10	13	46
Methylene blue wet mount	12	11	52

Out of these 51 cases, 23(45.1%) were culture positive for filamentous fungi where growth was observed on Sabouraud Dextrose Agar at the point of inoculation. Rest of the cases showed no growth even after 28 days of incubation.

Distribution of fungal isolate

In most of the culture positive cases, growth appeared within 24-48 hours of incubation and confluent growth was observed in 4-5 days. Table below shows the type of isolate and number of each type of isolate found in the study.

Filamentous fungi	No of isolate	%
Aspergillus flavus	7	30
Fusarium spp.	8	35
Curvularia sp	3	14
Bipolaris sp	2	9
Alternaria sp	1	4
Paecilomyces lilacinous	1	4
Unknown	1	4

Colonies of *Aspergillus spp* appeared white at first with small aerial mycelium which turns yellowish green due to pigmentation production. The finding was confirmed by preparation of LCB wet mount where

dichotomously branched hyaline hyphae with characteristic conidiophores were observed. Conidiophores with flask shaped biseriate phialides covering entire vesicle and pointing in all directions belonged to the species *Aspergillus flavus*. Total 7(30%) isolate were *Aspergillus spp.* Further identification through slide culture gave the same result.

In another 8 (34%) cases the isolates were identified as *Fusarium spp.*, they were identified by white cottony growth with purple, orange or brown centre. Dust injury associated with half (50%) of the cases of Fusarium causing mycotic keratitis. In one case, Grave's Ophthalmopathy leading to exposure keratitis by *Fusarium* species was observed.

Antifungal susceptibility testing

Disc Diffusion (DD) Method

In disc diffusion testing, the zone sizes were measured after 48 and 72 hours. *Aspergillus spp.* isolate was highly susceptible to Voriconazole, Itraconazole, Ketoconazole with no resistance at all. Towards Fluconazole 4(57%) isolate were found to be resistant. Amphotericin B was completely unable to prevent the growth of *Aspergillus spp.* isolates except in one case. Voriconazole was the most effective drug with not a single resistant isolate. Fluconazole, Itraconazole and Ketoconazole were ineffective against *Fusarium spp.*

Curvularia species was uniformly sensitive against Voriconazole and Ketoconazole and Itraconazole in DD assay. The Bipolaris *spp.* isolated were sensitive to all the tested antifungals in disk diffusion assay.

Minimum inhibitory concentration method

- Among the *Aspergillus flavus* isolated *Itraconazole* have better action in inhibiting growth with MIC ranging from 0.5-1 in 85.7% isolates. All other antifungals had high MIC values.
- *Bipolaris spp* isolate were resistant to *Amphotericin B, Voriconazole* and *Fluconazole*. Only *Itraconazole* and Ketoconazole were able to inhibit the growth within susceptibility range of MIC <1µg/ml.
- With *Curvularia spp.* isolate no growth was obtained in any of the isolates even after repeating the test twice with modification.
- *Paecilomyces lilacinous* identified in the study was found to be susceptible to *Itraconazole* only with MIC 1µg/ml. All other antifungals were ineffective against this isolate.
- *Itraconazole*, Ketoconazole were sensitive against the *Alternaria spp* isolate with MIC values 1 & 1µg/ml. *Voriconazole* and fluconazole had shown very high MIC of 16 and 32µg/ml.
- Amphotericin B, *Voriconazole* were ineffective in inhibiting growth of *Fusarium spp* with MIC>16 and >16µg/ml respectively in 7 of the cases. *Itraconazole* had MIC ≤1µg/ml against isolates and in one 25% cases ≤8µg/ml. Ketoconazole had MIC of≥8µg/ml against 5 isolates.

Discussion

Corneal infection of fungal etiology *(keratomycoses)* is very common and represents 30-40% of all cases of culture-positive infectious keratitis (Dunlop *et al.*, 1994, Hagan *et al.*,1995, Thomas *et al.*, 2003).[1,2,3] Moreover, fungi have replaced bacteria as the predominant cause of infectious keratitis in developing countries.

Thomas *et al*(2003) had shown that males were affected more commonly with 2.5:1 ratio in comparison to females. In Sharmeen *et al* (2010), 64.63% males were affected. In our study, the male to female ratio is 1.1: 1 with 52% males affected in comparison to 48% of females.

In our study 48% of the patients belong to the 41 to 50 age group. But taking active age group 21-30 and 31-40 into account, we can say roughly 73% of the population belongs to 21 to50 age group. Farming being the primary occupation, this 73% coincides with the productive age of the population of Uttar Pradesh. M Jayhar *et al,*[4] had found that maximum 66.85% of the affected population belong to the 21-50 years age group.

The rural urban population divide is more or less showing the demography of the patient population. Rural population is dependent on farming and animal handling, hence prone to injury to the eye with vegetative matter. In our study, 60% of the affected patients belong to rural areas. Out of this 45% are farmers or belong to farming households. Sharmeen *et al.* (2010), and AK Narsani *et al.* (2012), reported 37.41% and 44.80% of the affected persons were farmers or agricultural workers.

About 65% of the patients were admitted of having taken corticosteroid eye drops before consulting proper physician. Adding another 15% patients with antibiotic eye drop use history it can be said that trauma might have deposited the fungal matter into non-intact cornea but it is the lowering of usual cell mediated immunity that increases the incidence of fungal corneal ulcer. Corticosteroid instillation is seen as the predisposing factor both in developed and developing countries with studies showing 8% (Srinivasan *et al.* 1997)[5] association.

Filamentous fungi are more common causes of corneal ulcer in tropical and subtropical climates. In our study 100% of the cases were caused by filamentous fungi. All of the culture positive cases had shown fungal hyphae in 10% KOH wet mount test in our study. Comparing other microscopy methods like 1% methylene blue mount, Gram staining with 52% and 35% positivity rates we have concluded that 10% KOH is the best and least cumbersome method. PA Thomas 2003 had given the sensitivity of KOH to be 75-90%.

Positivity of KOH mount method increases with time. Before declaring the scrape material negative for fungal element it should be kept in wet chamber for a minimum of 8-12 hours. This will also increase specificity as tissue and other debris will be digested by 10% KOH. Freshly prepared KOH solution is always more helpful as it lacks any debris. Increasing the concentration of KOH is not always helpful but may reduce the waiting time. KOH is an irritant so protective glove should be worn while handling.

Most commonly used Gram stain had a sensitivity of only 46%. In the review done by PA Thomas in 2003 Gram stain had shown to have a sensitivity of 45-73%. It is more helpful for bacterial causes than fungal.

Culture had been the gold standard of diagnosis of fungal corneal ulcer. But there are some drawbacks to

culture diagnostic methods. Fungi being ubiquitous in presence; a single colony can be considered as contamination. To make culture more specific inoculating more than one media plates or inoculating in a specific pattern would be more useful.

Fusarium spp (34%) has been the most isolated filamentous fungi in our study. Together with *Aspergillus flavus* they constitute nearly 64% of the case population. Most of the studies on fungal keratitis across the globe have identified and reported both *Fusaria* and *Aspergilli*, or one of these two genera as the predominant fungal taxa causing human keratitis (Chowdhary et al. 2005,[6] Gopinathan et al. 2009).[7] Without using molecular technology identification of the filamentous fungi to the species level is not always possible. *A. flavus* is also an important cause of keratitis and is reported in some studies to be the most frequent *Aspergillus* species causing keratitis (Thomas *et al.,* 1986).[8] We isolated *Curvularia species* in 3(13%) cases as the causative filamentous fungi. Mascarenhas J *et al.*(2013) of India also had shown occurrence of *Curvularia species* in 11% cases.

In our study we took the commonly used antifungals for susceptibility testing. Discussing the uncommon first in DD testing Voriconazole, Fluconazole and Ketoconazole were active against *Alternaria* and *Paecilomyces species*. *Amphotericin B* was ineffective against *Paecilomyces* but was able to prevent *Alternaria species*. *Itraconazole* gave intermediate action against *Paecilomyces spp.* whereas it has good activity against *Alternaria spp.*

When MIC was done for this species *Paecilomyces lilacinous* identified in the study was found to be susceptible to *Itraconazole* with MIC 1µg/ml but was found to be resistant to all other antifungals tested. Studies done previously with *Paeilomycesspecies* has given MIC for *Itraconazole* 8µg/ml and for *AmphotericinB* as >16µg/ml (Manuel Cuenca-Estrella, *et al.,* 2006).[9] In our study we also found MIC for Amphotericin B >16µg/ml.

With DD sensitivity testing we found Fluconazole sensitive against 10(43%) and resistant against 10(43%) and intermediately active against 14% cases. Nearly 57.1% of *Aspergillus spp.* and 75% *Fusariumspp.* were resistant to *Fluconazole*. One isolate of *Curvularia* was resistant to *Fluconazole*.

Aspergillus spp. is ubiquitously present in the environment. It penetrates already injured cornea (mostly injury due to vegetative matter) and establishes infection when the host immunity is further lowered (corticosteroid eye drops). All the *Aspergillus spp.* isolates of our study were associated with vegetative matter injury. All these isolates were highly susceptible to *Voriconazole* and *Itraconazole*. So the first line of treatment should be *Voriconazole* eye drops for *Aspergillusspp.* causing keratitis.

Conclusion

Fungal corneal ulcer is more common in rural areas with people involved in farming. Topical steroid along with trauma is most common risk factor. Filamentous fungi are most common aetiology. Azoles are commonly used drugs to treat fungal keratitis, however resistance to these drugs are now emerging. Identification of the fungus and its susceptibility pattern is the key to success in the management of fungal keratitis.

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Role of Oral Citicoline in Treatment of Adolescent Amblyopia

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ABSTRACT

Aim- To compare efficacy of Citicoline to occlusion and near activity exercise in amblyopia management in adolescent age group.

Material and Methods- We included 79 eligible patients of age group 10-19 years for study. Consent was taken from each of patients. All candidates underwent full ophthalmological examination and were prescribed the best corrected spectacles. They were divided in three groups(A, B, C) using randomization chart. Group A received full time occlusion, Group B received full time occlusion and near activity exercises and Group C received full time occlusion and oral Citicoline 500 mg BD for three months. They were followed up four weekly up to 24 weeks.

Results: During follow up 9 patients were lost to follow up. Out of 70 patients who completed study, 36 (51.43%) showed improvement in their vision for distance. We measured this improvement in lines on Snellen's Chart. No improvement was found in 14 patients (58%) in Group A, 15 patients (60%) in Group B and 5 patients (23.81%) in Group C. Of the respondents, groups A, B and C constituted 41.67%, 40% and 76.2% respectively. The difference among the three groups was statistically significant (p value-0.024 chi-square test).

Conclusion-Oral Citicoline is a new and effective modality for amblyopia management and chance of improvement in visual acuity is better than other treatment modalities.

Keywords- strabismus, amblyopia, occlusion.

INTRODUCTION

Occlusion still remains the gold standard for the treatment of amblyopia. It was first advocated by Comet de Buffon[1] in 1743. It was abandoned and rejected for many years; but later on regained its popularity as the most effective treatment modality for amblyopia. Although the success rate of occlusion therapy is estimated somewhere between 30% to 92%, one of the major problems with it is compliance. This problem becomes specially evident in the case of children as their cooperation level is less than needed.

In spite of best efforts, like counselling and discussing the advantages of the apparently simple occlusion therapy, compliance rate could never improve and reach a satisfactory level. Even parents of patients with an urban background, besides those of rural patients, were found to be doubtful about the effectiveness of occlusion therapy. Most of the patients, specially children find it socially embarrassing to wear the patch owing to the cosmetic blemish associated with it for longer period of the day.

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Various studies have revealed that there is no demonstrable advantage to prescribing greater number of hours of patching, in either the rate or magnitude of improvement after fixed months of therapy. Thus, it is most logical to appreciate that pharmacological enhancement to occlusion therapy may overcome certain shortcomings such as problem of compliance and cosmetic blemish of the established occlusion therapy. However, the role of occlusion in older children and teenagers is still debatable. Thus, addition of some pharmacological agent potentiates the effect of occlusion in older children, and fear of compliance and cosmetic blemish is avoided in young children. It is well known to every Ophthalmologist that Levodopa and Carbidopa were instituted in amblyopia with significant visual improvement but were withdrawn due to their toxic effects. It is an established fact that Citicoline increases dopamine concentration.

Studies on rats have provided evidence that Citicoline potentiates dopamine release in the brain, presumably by stimulating release of acetylcholine. It is postulated that dopaminergic stimulation is a major mechanism for citicoline's effect on the retina.[2] This hypothesis is bolstered by a recent animal study showing citicoline raises the retinal dopamine concentration in rabbit.[3] Citicoline has demonstrated retinal ganglionic cell regeneration in tissueculture.[4] Citicoline (1,000 mg I.M. daily) was found to significantly improve visual acuity in patients with amblyopia

Citicoline is routinely used by Neurologists in cases of stroke, Alzeihmer's disease and bipolar disorders in much higher doses and for longer duration as compared to Ophthalmologists. Severe toxic effects are not reported in patients with neurological disorders being given Citicoline. However, very few studies are available in India to evaluate the effect of Citicoline in amblyopia as an adjuvant to occlusion therapy.

MATERIAL AND METHODS

This prospective comparative study was conducted in patients with amblyopia in age group 10-19 years, presenting in outpatient department and/or squint and orthoptic clinic at Regional Institute of Ophthalmology, M.D. Eye Hospital, MLN Medical College, Allahabad, India during July 2013 to June 2014 after taking permission from the ethical committee of the institute.

Total 79 eligible amblyopes of age group 10-19 years were included in the study. Consent was taken from each patient's parents. Then they were randomly divided into three groups.

Group A (28) received only occlusion therapy along with full refractive correction.

Group B (28) received occlusion, near activity exercises along with full refractive correction.

Group C (23) received oral Citicoline 500mg BD for three months, occlusion along with full refractive correction.

INCLUSION CRITERIA

- Strabismic amblyopia, anisometropic amblyopia, isometropic amblyopia, meridional amblyopia
- Patients between age 10-19 years,
- Visual acuity in amblyopic eye <6/12, visual acuity in sound eye >6/12, Inter eye acuity difference of 2 or more lines, refractive correction worn for four weeks.

EXCLUSION CRITERIA

- Presence of anterior and posterior segment pathology as corneal opacity, cataract, pathological myopia, any fundal pathology, nystagmus, optic atrophy, any neurological pathology, refractory amblyopia ,previous amblyopia therapy.

A detailed history was taken in each case regarding the chief complaints and reasons for visiting the hospital, whether it being deviation or decreased vision, age of onset of squint, type of deviation and any head posture if noted. History of previous treatment was recorded including any previous management such as occlusion therapy, spectacle correction, and use of miotic, orthoptic therapy or previous eye muscle surgery.

EXAMINATION

- Visual acuity was determined, first for the amblyopic eye and then for better eye. A patch or occluder was used in front of left eye as the acuity of the right eye was checked, and vice-versa.
- Best corrected visual acuity for distance was tested using the Snellen's Chart at 6 metre distance. The same person made all measurements under similar physical conditions.

The visual acuity for near was recorded at 33 cm using near vision chart.

- Refraction under full cycloplegia was done.
- Maximum tolerated refractive correction was given.
- Angle of deviation was measured using the Prism Bar Cover Test (PBCT) at near (33cm) and distance (6 m), both with and without glasses. Whenever PBCT was not possible due to decreased visual acuity or in uncooperative patients, the deviation was measured using the Krimsky's Test (PBRT).
- Anterior segment and fundus assessment under full mydriasis was done to rule out any ocular causes of decrease in vision.
- Fixation pattern was assessed using Heine's Direct Ophthalmoscope by having the patient fixated in star with the eye,closing the other eye. Uniocular fixation pattern was measured and graded as follows as according to Bangerter classification:

a.Foveal
b.Parafoveolar
c.Parafoveal
d.Peripheral / eccentric

- Test for Binocular function
- Sterioacuity with TNO test
- Worth Four Dot test –binocularity.
- Synoptophore examination as required

FOLLOW UP

All the patients were followed up at 1st,4th,8th,12th, and 24th week.

Examination at follow up-

- Visual acuity including distance and near, under similar conditions all the time, as described.
- Refraction under full cycloplegia.
- Stereo acuity, side effects of patching- irritation, diplopia, occlusion amblyopia.
- Fixation pattern, side effects of drug- headache, GI disturbances. Speed of recovery- faster and sustained or non-responding, deterioration if any. Compliance and continuance of counselling.

RESULTS

We conducted this study on 70 patients who completed the study (9 patients were lost to follow up, 4 in Group A, 3 in Group B and 2 in Group C) attending OPD and Squint clinic in Regional Institute Of Ophthalmology M. D. Eye Hospital, Allahabad.

The mean age of our study group was 14.67 years (SD-2.90). Our study population consisted of 60% male (42) and 40% female (28) patients. Most common presenting complaint in our patients was diminution of vision (75.71%), followed by deviation of eye (24.28%). Anisometropia was the most common cause of amblyopia in our study population affecting 74% of population, followed by combined anisometropia and strabismus affecting 17.14% patients, 4.48% isometropia and 4.48% strabismus. Most common type of refractive error found in our study population was hypermetropia (70%of patients) followed by myopia (17.14% of patients) and astigmatism (12.86%).

BASELINE VISUAL ACUITY

Baseline visual acuity was FC-6/60 in 57.12% of total patients, 6/60-6/36 in 25.71%, 6/36-6/24 in 11.42% and 6/24-6/18 in 5.7% of patients in study population.

Table 1: Baseline visual acuity in study groups.

Visual acuity	Group A	Group B	Group C
FC – 6/60	13	15	12
6/60 – 6/36	6	7	5
6/36 – 6/24	3	3	2
6/24 – 6/18	2	0	2

DEPTH/SEVERITY OF AMBLYOPIA

Table:2 Depth of amblyopia in different groups

Depth of Amblyopia	Group A	Group B	Group C
Mild (= 6/18)	2	0	2
Moderate (> 6/18 to = 6/36)	9	10	7
Severe (= 6/60)	13	15	12

VISUAL IMPROVEMENT IN EACH GROUP

Table3: Visual improvement in each groups

Line of improvement	Group A	Group B	Group C
0	14	15	5
1	4	4	6
2	5	4	5
3	1	2	2
>3	0	0	3

RESPONDERS / NONRESPONDERS

Out of total 70 patients who completed the study, 36 patients (51.43%) showed improvement in their vision for distance; remaining 34 patients (48.57%) were non responders.

Among groups, responders were 41.67%, 40% and 76.2% in group A, B and C respectively. The difference among three groups was statistically significant (p value-0.024 chi-square test).

Table 4: Responders/ Non responders

Groups	Responders	Non – Responder
Group A	10	14
Group B	10	15
Group C	16	5

P value – 0.0243

SIDE EFFECTS

Total 4 patients (5.71%) complained of rash due to occlusion given to them. One patient in Group C complained of mild headache which got relieved by medication after two days. Remaining 65 patients had no side effects.

DISCUSSION

Treatment of amblyopia remains a therapeutic challenge for the ophthalmologists. It has perplexed clinicians over the centuries, both with regard to its diagnosis and treatment. This is further highlighted by the vastness and variety of treatment modalities tried and the research done in this field.

Occlusion remains the most popular treatment modality of amblyopia. By means of removing the suppression effect of brain cells driven by the sound eye over the brain cells which are involved in processing vision in the amblyopic eye, patching helps in improving the vision. However, the popularity it commands among the clinicians is not always shared by the patients and their relatives and their parents.

Major failure of the therapy is because of poor compliance due to cosmetic blemish associated with occlusion therapy. The other drawbacks like occlusion amblyopia, problems of fusion disruption and increase in angle of deviation, although rare, are at times disturbing both for the clinician and the child's family.

In our study Group C, we tried to find out the effectiveness of addition of Citicoline to conventional patching therapy for the treatment of amblyopia. Citicoline primarily acts by increasing the synthesis of phosphatidylecholine, the primary neuronal membrane phospholipid, thus enhancing the production of acetylcholine. It is proven that there is dopamine depletion from retinal amacrine cells leading to decreased contrast sensitivity, and dopamine supplemented from outside may reverse this depletion. Citicoline is similar todopamine in action with comparatively very few side effects. Oral Citicoline administration increases the plasma levels of choline and cytidine, the building blocks used to restore neuronal membrane integrity. It is also postulated that Citicoline facilitates the preservation of sphingomyeline, which promotes signal transduction in nerve cells.

Citicoline may significantly impact the brain- remodelling activity. A study in rats has shown that citicoline treatment significantly increases the length and branch point of the dendrites, increasing the overall surface area occupied by neurons, which leads to an increased efficiency of sensory information processing. This mechanism of activity may potentially account for a significant portion of citicoline's neurorestorative functions.

Campos et al[5] have also recorded that citicoline was effective in the treatment of amblyopia. They published the preliminary results of their study and stated that statistically significant improvement in visual acuity was found both for the amblyopic and sound eye in 46 of the 50 patients (92%). The improvement remained stable for at least four months.

Similarly **Porciatti et al**[6] recorded that visual acuity improved 1.4-1.5 lines in the amblyopic eyes and 0.4 in the normal eyes with citicoline. They also reported improvements in the contrast sensitivity and increase in the visually evoked potential. This study was conducted in adult with a mean age of 24.8 years.

Ghosh S and Ghosh R[7] in a study on amblyopic patients, in age group of 10-18 years reported that 71% of the patients had shown visual improvement with adding drug i.e. citicoline to occlusion and near activities. 58.68%overall showed response to therapy of varied level despite of the older age group. 2 line or more than 2 line improvement was seen in 26.76%. Our study is comparable to this study in terms of improvement as we also found 76% patients improved by adding citicoline, which was significantly better than remaining two groups (P value 0.02).

In our study, overall 51.43% patients had shown visual improvement with citicoline. 2 line or more than 2 line improvement was seen in 31.42% patients. Probably this remarkable concurrence of our study with the study of **Ghosh S** and **Ghosh R** is because age group and mode of institution of treatment modality in both the studies are almost similar. More or less amount of visual improvement in most of the patients is also approximately equal in both the studies.

Prachee Vasant Pawar et al[8], also studied effectiveness of addition of citicoline to patching in the treatment of amblyopia in the age group of 4-13 years. They divided the study subjects into two subgroups, one of younger patients (age at start of phases 1 ≤ 7 years) and the other group of older patients (age at start of phase 1 ≥ 7 years). At the end of five months, in phase 2, the mean logMAR of the younger as well as older patients in group 1 was significantly less than that in group 2 showing significantly better improvement in younger and older patients with citicoline along with patching ($p<0.05$).

In contrast to above findings, **Michela Frenisa et al**[9], have reported that addition of citicoline to patching therapy was not found to be more effective than patching alone after a 30 days treatment. In our opinion he should have continued drug for a longer period as most of the studies had used the drug for longer time, realizing that it may take time for full effect of drug to come.

In our study, we found 41.67 % patients to have improved in Group A, 40% in Group B and 76.2% in Group C. Difference among groups was statistically significant (p - 0.02). Total 51.41% patients improved with treatment. This is encouraging that those patients who were older enough should also be given a chance to improve. We cannot comment on stability of vision improvement as this requires a longer follow up which we are doing at our Institute. Most of the patients in Groups A, B and C improved up to 2 line. In Group C, 3 line or more improvement was present in 5 patients (21.7%). It may be concluded that with drug therapy, early and greater visual improvement can be achieved.

Compliance remains the major challenge with occlusion therapy and near exercises and results with these modalities will depend upon compliance of patients. Due to poor compliance and acceptance, your anticipated full time occlusion may actually be part time occlusion only.

So compliance was given extra importance and carefully monitored

- Regular counselling of patients and parents.
- Regular maintenance of a diary by patients/ parents and its regular check up.
- All efforts were made to build up confidence towards otherwise simple looking occlusion method of therapy, thus making compliance and acceptance to achieve a much higher level.

Contrary to this, compliance was much better with the drug therapy. Patient /parents think they will be benefitted by medication. Along with this, the side effects associated with the drug are less, as seen in various studies. Therefore this drug is safe to use. So it may be concluded that use of citicoline can give better results in amblyopic patients, even in adolescent age group.

Limitations of our study were lesser number of patients and a need of longer follow up period to see whether the gain in vision remains stable or deteriorates in longer follow up period.

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Electron microscopic changes in Descemet's Membrane(DM) in Pseudophakic bullous keratopathy and Fuchs endothelial dystrophy.

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Abstract:

Purpose: To elucidate ultra-structural changes of the DM and endothelial cells in Fuch's Endothelial Corneal Dystrophy (FECD) and Pseudophakic Bullous Keratoplasty(PKB) by scanning electron microscopy.

Methods: Descemet's membrane from 8 patients were collected following DSEK performed for Fuch's Endothelial Dystrophy in 3 patients and Pseudophakic Bullous Keratopathy in 5 patients. Thin sections were prepared which were then studied by Transmission Electron Microscopy.

Results: In FECD the DM was thickened with excrescence in all 3 cases and composed of 4 layers, though these 4 layers were not present in one FECD specimen. In FECD stripping specimen, we observed that the endothelium was markedly attenuated, especially over the excrescences, to atrophic in our 6 specimens. Excrescences are continuous with the third layer. Endothelial cells were completely degenerated in 2 specimens of PBK. In FECD, HCEC were thinned out, almost unnoticeable over the nodules. No nodules seen in PBK.

Conclusion: Fibroblast like morphological changes occur in endothelial cells in both FECD and PBK with increased rough endoplasmic reticulum, cytoplasmic filaments, lysosomes and increased degenerative changes like swollen mitochondria, however these changes are more marked in FECD than in PBK. DM shows abnormal posterior banded layer consistently in FECD but can also be found in PBK. DM thickening is more marked in FECD than in PBK. Features that are seen in FECD stroma are presence of lipid keratopathy, melanin granules separating it from PBK.

INTRODUCTION

Descemet's membrane is the basement membrane of the corneal endothelium. Unlike Bowman's membrane, it is a true basement and is continuously deposited throughout life by the underlying endothelium, becoming gradually thicker with age.At birth, it is only 2-4μ thick, but by adulthood it grows to 10-12μm. Ultra structurally, it can be divided into 2 zones: an anterior fetal banded zone and a posterior non-banded zone. The anterior banded zone is laid down by the endothelial cells only in embryogenesis and remains unchanged through life. The banded fibres are largely composed of type VIII collagen, a collagen commonly found in fetal tissues, especially around blood vessels. The growth in thickness later in life occurs primarily in the posterior banded zone.[1-4]

Irregularities and excrescences are common in the peripheral aspects of Descemet's membrane and are

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seen frequently with advancing age. These are referred to as Hassal-Henle warts. They do not interfere with vision and are not considered pathologic. When present in the central cornea, they are called guttae. Fuch's Dystrophy is the most common corneal dystrophy causing vision loss.[5,6]

The endothelium is composed of hexagonal endothelial cells.The Endothelial Cell Density (ECD) decreases throughout life. From birth to 14 years, the rate of endothelial cell loss is approximately 3% per year. After age of 14, the rate slows to about 0.6% per year. Specular microscopy in normal young adults corneas reveal an ECD of about 3500[7,8,9] cells/mm^2. The ECD declines to about 2000 cells/mm^2 in older age. As ECD decreases, individual cells enlarge and lose their hexagonal shape.[10,11] The critical ECD below which the cornea decompensates is approximately 300-500[12,13] cells/mm^2.

The endothelium forms the anterior border of the anterior chamber and is therefore susceptible to blunt or penetrating trauma such as cataract extraction or anterior chamber IOL implantation, e.g, endothelial cells damage leading to pseudophakic bullous keratopathy. Endothelial Dysfunction caused by pseudophakic Bullous Keratoplasty (PBK) and Fuch's Endothelial Dystrophy is the leading cause of corneal visual loss and leading indication for corneal transplantation.

Transmission Electron Microscope is recent and advanced tool for the assessment of ultrastructure of Descemet's membrane and endothelial cells.

AIM:

To elucidate ultra-structural changes of the DM and endothelial cells in Fuch's Endothelial Corneal Dystrophy (FECD) and Pseudophakic Bullous Keratoplasty(PKB) by scanning electron microscopy.

METHOD

The study was conducted in the Department of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, in collaboration with the Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University.

In our study, 8 patients, aged 45 to 65, undergoing DSEK (3 FECD cases and 5 PBK cases) consented to the use of their excised DM for evaluation under TEM.

In DSEK, the diseased DM were peeled off, fixed in 2.5% glutaraldehyde and 2% paraformaldehyde in 0.1 M sodium phosphate buffer (pH 7.3) for 12 hours at 4^0 C. After wash in buffer, the samples were postfixed in 1% OsO_4 for 1 hour at 4^0 C. Ultimately, thin sections are prepared which were then elucidated by Transmission Electron Microscopy. The patients included in this study were diagnosed withFuch's Endothelial Dystrophy and PBK.

Fixation of DM and endothelial cells for TEM

Small pieces of tissues were cut and the tissue samples fixed in 2.5% glutaraldehyde and 2% paraformaldehyde in 0.1 M sodium phosphate buffer (pH 7.3) for 12 hours at 4^0 C. After wash in buffer, the samples were postfixed in 1% OsO_4 for 1 hour at 4^0 C. The samples were dehydrated in an ascending grade of acetone, infiltrated and embedded in araldite CY 212 (TAAB, UK). Thick Sections (1 µm) were cut with an ultramicrotome, mounted on to glass slides, stained with aqueous toluidine blue and observed under a

light microscope for gross observation of the area and quality of the tissue fixation. For electron microscope examination, thin sections of grey-silver color interference (70-80 nm) were cut and mounted onto 300 mesh- copper grids. Sections were stained with alcoholic uranyl acetate and alkaline lead citrate, washed gently with distilled water and observed under a Morgagni 268D Transmission Electron Microscope (Fei Company, The Netherlands) at an operating voltage 80 KV. Images were digitally acquired by using a CCD camera (Megaview III, Fei Company) attached to the microscope.

The samples were made free of culture medium by washing/centrifugation (1000X, 5 min) in 0.1 M Phosphate Buffer (PB, pH 7.3). The supernatant was discarded. The pellet (after dispersing the cells) was fixed in a mixture of 2% glutaraldehyde and 2% paraformaldehyde in PB for 2-3 hour at room temperature then centrifuged in PB for 5 min to remove the fixative. The pellet was suspended in PB, again centrifuged and washed. The samples (pellet) were postfixed for 1 hr in 1% osmium tetroxide at 4 Deg C. Samples were then dehydrated in acetone, infiltrated and embedded in araldite CY 212 (TAAB, UK). Thick Sections (1 µm) were cut with an ultramicrotome, mounted on to glass slides, stained with aqueous toluidine blue and observed under a light microscope for gross observation of the area and quality of the tissue fixation. For electron microscope examination, thin sections of grey-silver colour interference (70-80 nm) were cut and mounted onto 300 mesh- copper grids. Sections were stained with alcoholic uranyl acetate and alkaline lead citrate, washed gently with distilled water and observed under a Morgagni 268D Transmission Electron Microscope (Fei Company, The Netherlands) at an operating voltage 80 kV. Images were digitally acquired by using a CCD camera (Megaview III, Fei Company) attached to the microscope.

OBSERVATIONS AND RESULTS:

Among these 8 patients, 3 were diagnosed to have Fuch's Endothelial Corneal Dystrophy and the remaining 5 as having Pseudophakic Bullous Keratopathy.

Slit-lamp examination in FECD patients, preoperatively, revealed the presence of guttatae, Fig 1.

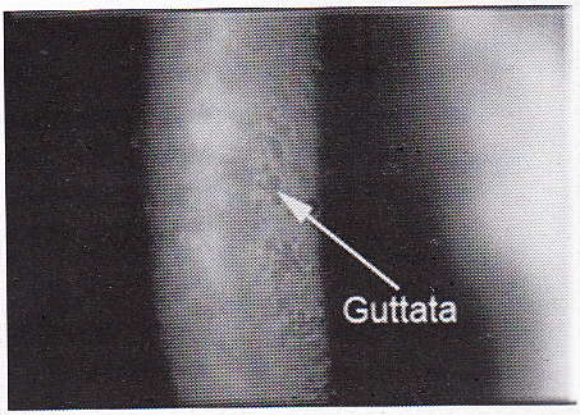
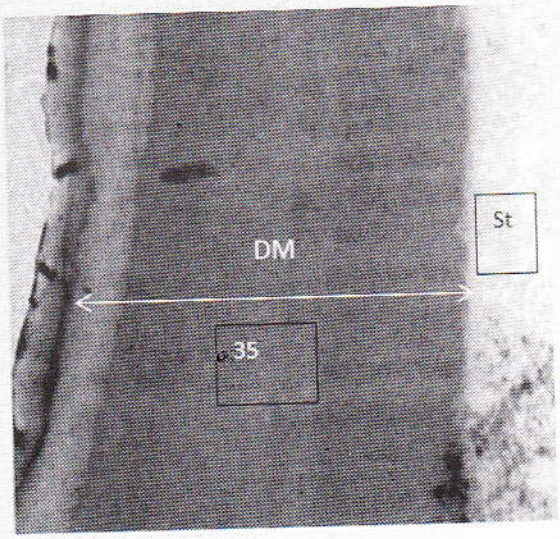


Fig 1. Slit-lamp direct illumination revealing presence of guttata on the posterior cornea in FECD

n slit lamp examination of bullous keratopathy stromal and epithelial edema and bullae were noted few weeks prior to DSEK, Fig 2.

Fig 2. Sclerotic scatter showing the presence of stromal edema and epithelial bullae



Stromal adherence was seen in 1 FECD stripping specimen, Fig 3.

Fig 3. Layers of DM in FECD with markedly attenuated endothelial cells . DM is 35µm thick. Stroma (St) is present in this DSEK stripping specimen X 3000

We observed that in FECD the DM was thickened with excrescences all 3 cases and composed of 4 layers, which are described morphologically, though these 4 layers were not present in one FECD specimen.

The first layer, anterior fetal banded layer, was present and relatively uniform in all FECD cases. Its thickness varied from 3-4µm. It was characterized by wide-spaced collagen. The second layer, posterior non-banded layer, was non-banded, homogeneous, less osmophilic than the first layer. Its thickness was approximately 4-5µm. The third layer, posterior banded layer, was banded and had an osmophilia as the first layer and its thickness was approximately 30µm. It consisted of spaced collagen. The fourth layer, fibrillar layer was approximately 7-9µm thick. It was composed of a loose matrix of collagen. Multiple waves of basal lamina were present in the fibrillar layer, Fig 4.

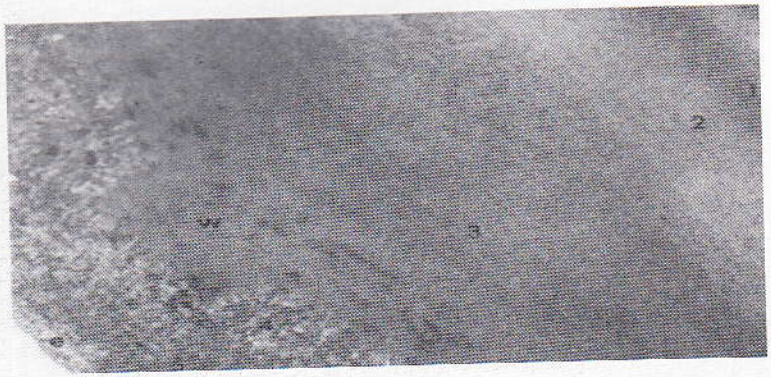


Fig 4. Descemet's membrane in FECD showing 4 layers: 1. Anterior fetal layer, 2. Posterior non-banded layer, 3. Posterior banded layer and 4. Fibrillar layer. W-Wart, E-endothelium X 5000

In FECD stripping specimen, we observed that the endothelium was markedly attenuated, especially over the excrescences, Fig 5.

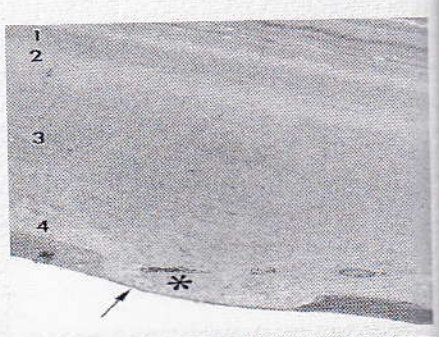
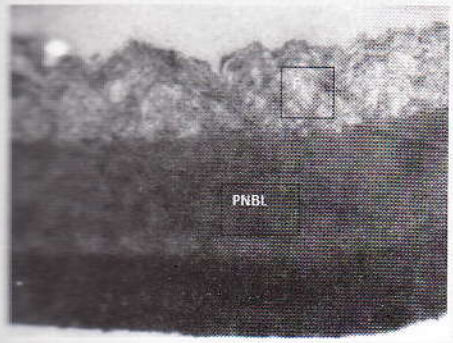


Fig 5. FECD: showing 4 layers, 1. Anterior fetal layer, 2.Posterior non-banded layer, 3. Posteriot banded layer and 4. Fibrillar layer. Asterix showing excrescence and arrow- attenuated endothelium X(×4200) nodule (asterisk) arising from the posterior banded layer is covered by attenuated endothelium (arrow)



In 2 cases of PBK, the DM was composed of 4 layers similar to FECD, Fig. 6.

Fig 6. 4 layers in PBK: thin PNBL and thick fibrillar (F) layer. No excrescence seen X 6000

In the remaining 3 stripping specimens, DM was less in thickness, approximately 8-9µm as compared to DM in FECD specimens. Moreover, no posterior nodules were present, Fig 7.

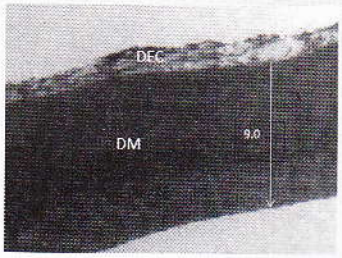
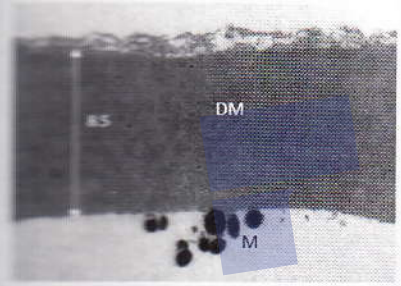


Fig 7. DM 9.0µm thick and Endothelial cells are completely degenerated and almost unremarkable X 4300



The endothelial cells were unremarkable or exhibited variable degree of degeneration, atrophy or loss. Large melanin granules were present on DM, Fig 8.

Fig 8. Transmission Electron microscopy showing degenerated endothelial cells (DEC) and a homogeneous DM 8.5µm thick. Melanin granules (M) are present on stromal side X 4300

Disintegrating endothelial cells left a large intercellular dropped out space containing debris and granular material, Fig 9.

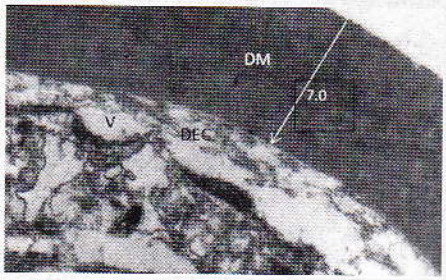


Fig 9. Degenerated endothelial cell (DEC) in PBK with a thinner DM, 7.0µm. Intracellular lacunar spaces (S), pigmented granules (P) X 6000

In addition, most of the intercellular junctions between the endothelial cells were loosened or absent due to the degeneration and loss of adjacent cells. Yet we observed few normal intercellular junction complexes in 2 samples of FECD, Fig10.

Fig 10. Normal intercellular junction (J) with dropped out spaces (S) in one cell X 6000

Higher magnification of TEM revealed the presence of increased number of lysosomes and vacuoles in the endothelium in both FECD and PBK.

This explains the over-production of enzymes which are responsible for the cytolysis on the endothelial cell membrane and eventually leading to the destruction of the architecture of the endothelium.

DISCUSSION

The primary defect of FECD is in the endothelium because HCEC loss, thickened DM and the presence of posterior nodules in the central cornea. In our study, we found that the pattern of DM changes consists of 4 layers in 2 cases of FECD and 2 cases of PBK. These layers were: Anterior banded fetal layer, Posterior non-banded layer (PNBL), Posterior banded layer (PBL) and Fibrillar layer.

The anterior banded layer was relatively constant and represented the fetal portion of DM. It was present in all cases. The banding of this layer is due to the presence of wide-spaced collagen. The PNBL is usually present in an otherwise normal cornea and thickens with age. It has been suggested that this may reflect abnormal endothelial function early in life with the production of the abnormal PBL rather than the normal PNBL. In FECD the corneal endothelium produces excessive amounts of basement membrane material of an abnormal composition resulting in the formation of a posterior collagenous layer. Extreme accumulations of this material created mushroom-like formations, guttatae, projecting into the anterior chamber. The initial manifestation in FECD is central guttatae.

In their study, Takeo Iwamoto and A. Gerard DeVoe(1971)[14] found that Descemet's membrane was markedly thickened in six cases and showed various structuralalterations. Five different regions could regularly be distinguished in the pathologic Descemet's membrane in all cases. From anterior to posterior they were (1) "anterior banded region" with 1,000 A-banded pattern, (2) "nonbanded region," without clear banding (these regions are seen in normal corneas); (3) "posterior banded region" filled with 1,000 A° -banded material ("warts" are formed by its partial backward protrusions); (4) "border region" composed of groups of "thin fibrils," "long-spacing bundles" of 1,000 A° periodicity with two type of banded pattern, and "basement membrane-like material"; and (5) "fibrillar region" which consists of "basement membrane-like material" and collagen fibrils. One case had warts located very posteriorly, and another, withno clear warts, but both could be interpreted as variations of the above structure.

The endothelium was thin, consisting mainly of two types of abnormal cells. Loosening of the functional complexes was common, and partial discontinuity of the endothelial cover was also seen. The Type 1 cell had cytoplasmic filaments, increased rough-surfaced endoplasmic reticulum (RER) and cytoplasmic processes, simulating fibroblasts. The Type 2 cell had elongated RER and lysosomes within a less dense cytoplasm, and was probably a degenerate form of the Type 1 cell.Based on their findings, the following hypothesis was proposed: For unknown reasons, possibly hereditary, the endothelial cell morphology and function become similar to those of fibroblasts and they start producing collagen fibrils and basement membrane-like material, forming the fibrillar region of Descemet's membrane. At the border region, the collagen fibrils disintegrate into thin fibrils and partly further transform into long-spacing bundles. These, together with basement membrane-like material, are finally incorporated into the posterior banded region. Acceleration of this process forms warts. Similar changes can be seen at the extreme periphery of the normal adult cornea as a physiological phenomenon. In our study, DM in FECD comprised of 4 layers,

except the "border layer" which was not seen in our study. In Iwamoto's study and our study both, loosening of intercellular junction complexes and degenerative changes in the endothelial cells were noted.

In 1982, William M. Bourne et al.[15] studied the ultrastructure of DM by TEM in corneal buttons removed from 11 phakic eyes with FECD. Abnormalities in DM consistent with abnormal endothelial function early in life (prior the age of 20) were present in all corneas. An abnormal fibrillar layer was thicker in those corneas with greater stromal and epithelial edema, possibly indicating that this first layer is formed mainly during period of endothelial decompensation. In our study, fibrillar layer is present in 2 FECD and 2 PBK cases, but we cannot comment whether it is the first layer laid out due to endothelial decompensation.

KevineZaniolo et al. (2012), in Montreal, Canada, evaluated HCEC isolated form corneas with FECD. The purpose of the study was to assess the feasibility of initiating primary cultures of corneal endothelial cells from patients suffering from FECD. They also evaluated which conditions yielded the best results for culture.Ultrastructure of DM revealed an abnormal Posterior Banded Layer (PBL) and a fibrillar layer. There were guttatae as well in the posterior banded layer. Details of a DM with large striated bodies of 0.11µm periodicity were present in the edge of the PBL and perpendicular to the surface. Similarly, in our study, the specimens revealed the above-defined layers, except we couldn't culture the endothelial cells for further proliferation.

The ultra-structural changes in FECD, for example, presence of lipid keratopathy, melanin granules in the stroma, increase in the thickness of DM, fibrils in the cytoplasm of the degenerating endothelial cells explain that the process is more chronic than in PBK.

CONCLUSION

With advancing diseases, the endothelial cells in FECD and PBK become increasingly dedifferentiated from their normal morphology as well as function. This alteration or metaplasia makes them appear more fibroblast-like cytologically with increased rough endoplasmic reticulum, cytoplasmic filaments, lysosomes, membrane-bound vacuoles, phagocytosed pigment granules and some desmosomal intercellular junctions. Increasingly degenerate changes occur with swollen mitochondria, widened intercellular spaces, larger vacuoles and pinocytic nuclei and death of many cells.From our study, we deduce that in FECD and PBK, there are ultra-structural changes: DM comprises of 4 layers: anterior banded fetal layer, posterior non-banded layer, posterior collagen layer and fibrillar layer. But the presence of lipid keratopathy, melanin granules, thickened DM, fibrils in the cytoplasm in FECD specimens denotes a more chronic process in FECD as compared to PBK, which appears to be short-termed activity.

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Spectrum of post-keratoplasty ocular infection with treatment outcome at a tertiary centre in North India

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Abstract:

Aim: To report the microbiological spectrum with their antimicrobial resistance and prognosis in post-keratoplasty [Penetrating Keratoplasty (PK), Deep anterior lamellar Keratoplasty (DALK), and Descemet Stripping Endothelial Keratoplasty (DSEK)] infection at a tertiary care centre in North India.

Material and methods: A retrospective analysis of 106 keratoplasties was performed from 2007 to 2012. 86 eyes underwent PK, 8 eyes DALK and 12 DSEK. A detailed microbiological work up including Gram staining, 10% KOH wet mount, culture on blood agar and Sabouraud's Dextrose Agar, was done in patients with post-keratoplasty infections.

Results: 8 (7.54%) eyes (PK–7, DSEK–1, DALK–0) developed corneal infection. In two eyes (including one that underwent DSEK) *Pseudomonas aeruginosa was isolated.* Both *Pseudomonas* were resistant to all anti-microbial except Polymyxin B. In two patients *Streptococcus pneumoniae* was isolated which were sensitive to commonly used antibiotics. One patient developed *Candida albicans* which showed resistance to all commonly used anti-fungals (CLSI-44A), except Amphoterecin B. One isolate each of *Staphylococcus aureus, Proteus vulgaris and Acinetobacter baumanii* was identified in 3 different patients, which were all susceptible to common antibiotics. All patients except one (*P.aeruginosa*) responded well to susceptible drugs.

Conclusion: High infection rate in post-keratoplasty patients with great diversity of microorganism and increased microbial resistance necessitates detailed microbiological work up in each case.

Key words: Post-keratoplasty, Infection, Candida, Pseudomonas, DSEK, MDR

Introduction:

Post-keratoplasty infection is common but devastating complication associated with ocular morbidity and poor visual outcome.[1,2,3,4] Infection in patients who had undergone keratoplasty can be either due to poor host defense, direct dissemination of microbes from donor to recipient, as MK media can itself act as a good culture media or due to absence of corneal nerves in donor cornea, ocular surface problems, poor epithelialization, limbal stem cell deficiency, suture related problems and post-operative long use of steroids all contribute to poor host defense.[2,5,6,7] Steroid instillation used to prevent graft rejection increases the chances of microbiological invasion especially fungi.

Aim:

The purpose of this study is to report the microbiological spectrum with their antimicrobial resistance and prognosis in post-keratoplasty infection at a tertiary care centre in North India.

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Materials and Methods:

A retrospective analysis of 106 eyes of 102 patients who underwent corneal transplant [Penetrating Keratoplasty (PK), Deep anterior lamellar Keratoplasty (DALK), and Descemet Stripping Endothelial Keratoplasty (DSEK)] from 2007 to 2012 was performed. 86 eyes underwent PK, 8 eyes DALK and 12 eyes underwent DSEK surgery.

Patients who developed corneal infiltrate within 6 months were only included in this study. All such patients were scraped by No. 15 Bard Parker blade. Direct microscopic examination using Gram's stain and 10% KOH wet mount was performed in all patients. The scraped material was further inoculated on blood agar and Sabouraud's dextrose agar. Blood agar and Sabouraud's dextrose agar were incubated at 37°C and 25°C respectively in BOD incubator. Growth was examined by Gram's stain and biochemical tests including oxidase and catalase tests. The growth was confirmed as *Candida* spp. by germ tube formation, ability to growth at 42°C and sugar assimilation with growth on CHROMagar. Antimicrobial susceptibility was performed with Kirby Bauer method for bacteria and antifungal susceptibility testing with CLSI44A. Antibiogram was done against Ampicillin (10µg), Carbenecillin (10µg), Ceftriaxone (30µg), Gentamicin(10µg), Ciprofloxacin(5µg), Levofloxacin(5µg), amikacin(30µg), Imipenem(10µg) and Polymyxin B(300units). For fungi, antibiogram was performed with fluconazole (25µg), itrconazole (10µg), voriconazole (1µg) and amphoterecin B (100units).

RESULTS:

Out of the total 106 keratoplasties that were performed, 8 (7.54%) eyes of 8 patients developed post-keratoplasty infection (PK–7, DSEK–1, DALK–0) .Figure1A,B) Four patients were female and 4 were male. Mean age of affected patients were 44.28yrs. Most common etiology for performing keratoplasty was corneal scarring secondary to corneal infection followed by pseudophakic bullous keratopathy. 4 cases presented with pain and lacrimation in affected eye within 24 hrs of keratoplasty. One patient presented on 3rd day of keratoplasty. Two cases presented at 7th and 15th day and one presented after 1 month following keratoplasty (Table 1).

On Gram's stain, there were pus cell revealed along with yeast cell in one and gram negative cocco-bacilli in another smear. (Figure2A,B) There was growth on blood agar and Sabourauds Dextrose Agar. (Figure3A,B) *Pseudomonas aeruginosa* was the most common organism isolated from affected eye within 24 hours of keratoplasty. Both cases of *Pseudomonas* and one each case of *Acinetobacter baumanii* and *Staphylococcus aureus* were isolated in patients who developed infiltrate within 24 hrs of keratoplasty. *Candida albicans* was isolated from a female patient who complained of gritty sensation after 3 days following corneal transplant. *Streptococcus pneumoniae* was isolated from two patients with pain and discharge after 7th and 10th day of keratoplasty respectively. *Proteus vulgaris* was isolated from a 17 year old girl who presented with pain and discharge after 1 month of keratoplasty (Table 1).

On Kirby Bauer disk diffusion method, both isolated *Pseudomonas aeruginosa* showed susceptibility only to polymyxin B, being resistant to piperacillin, gentamicin, ceftazidime, amikacin, ciprofloxacin, imipenem and meropenem.Figure4 Isolated *Acinetobacter baumanii* and *Proteus vulgaris* were susceptible to piperacillin, gentamicin, ceftazidime, ciprofloxacin, imipenem, meropenem and polymyxin B

Streptococcus pneumoniae was susceptible to penicillin, ciprofloxacin, gentamicin and vancomycin. Isolated *Stapylococcus aureus* showed susceptibility to ciprofloxacin, gentamicin and vancomycin and showed resistant to penicillin. *Candida albicans* was only susceptible to amphoterecin B being resistant to azoles as demonstrated by CLSI44A guidelines (Table 2).

Antimicrobial drops were instilled in affected eye corresponding to their antibiogram. All the patients except one had good response with reduction in corneal infiltrates. One patient infected with *Pseudomonas aeruginosa* who underwent DSEK, failed to have any response and developed endophthalmitis after 24 hours despite continuous topical moxifloxacin instillation. The sensitivity report which was received after 48 hours showed that the organism was only sensitive to Polymyxin B.

Out of 8 cases of infectious keratitis, 3 patients were infected with mulit-drug resistant microorganisms that were resistant to commonly used antimicrobials. In 7 (87.5%) eyes including two eyes infected with multidrug resistant organism, there was complete resolution of infiltrates with good clinical outcome.

Discussion:

Infection after keratoplasty is a setback for patients with poor treatment outcome usually. Meticulous microbiological examination with intense antimicrobial therapy and timely monitoring is necessary to achieve good final visual outcome in graft infection. In this era of multi-drug resistance organism, microbiological profile and sensitivity pattern can only predict the exact nature of infection and the correct treatment required for the particular case. Every micro-organism has a varied spectrum thus should be dealt differently. Gram-positive cocci including *Staphylococcus aureus, Streptococcus pneumoniae, Coagulase negative Staphylococci* are common causative agent whereas among Gram-negative bacteria, *Pseudomonas aeruginosa* is commonly isolated.[8,9]

In our study, incidence of post-keratoplasty infection is higher compared to most studies. Malathi Ambulingam reported that incidence of postoperative endophthalmitis in Tamilnadu was only 0.5% (10/1949) as only ten PK surgeries developed infections[10]. *Enterococcus fecalis* (3) was most commonly isolated microorganism followed by *Pseudomonas aeruginosa* (2) and one case each of Methicillin resistant *Staphylococcus aureus, Alkaligenes fecalis, Kleibsella pneumoniae, Pseudomonas stutzeri* and *Aspergillus flavus*. Low post-keratoplasty infection was also shown by Kattam HM et al (0.11%),[11] Taban M (0.382%)[12] and Thomas M Aaberg (0.178%).[13] In our study, Improper follow-up was the most common cause of high incidence of post-keratoplasty infection as 5 patients developed suture infiltrate after hospital discharge. Long storage of the cornea in MK media was another risk factor. However, a study by Wakimasu et al., reported similar post-keratoplasty infection compared to our study. In his study 27 patients out of 253 developed microbial keratitis (14 bacterial and 13 fungal).[14] Seven eyes were infected with Methicillin resistant *Staphylococcus aureus* & *Methicillin Resistant Staphylococcus Epidermidis.* Candida infection was present in 8 eyes.

Spectrum of the isolated microorganisms varied largely in our study, as Gram-positive bacteria, Gram-negative bacteria and fungus (candida) were isolated. In contrast to the study by RB Vajpayee et al. who reported that Gram positive cocci (*Staphylococcus epidermidis,* 55.8%) being the most common cause of post-keratoplasty infection followed by *Staphylococcus aureus, Acinetobacter* spp., *Pseudomonas*

aeruginosa, Aspergillus fumigatus, *Streptococcus pneumoniae* and *Fusarium solani*[3], our study showed that Gram negative bacilli (two *Pseudomonas aeruginosa* and one each *Proteus vulgaris* & *Acinetobacter bowmanii*) had higher incidence of post-keratoplasty infections. Gram positive cocci (two *Streptococcus pneumniae* and one *Staphylococcus aureus*) were common occurrence in post-keratoplasty infections. One case of *Candida albicans was also identified from suture infiltrate*. Wagoner MD reported *Streptococcus pneumoniae* as the most common cause of post-keratoplasty infections in children.[15]

In our study, both isolated *Pseudomonas aeruginosa* were susceptible only to polymyxin B with resistant to other drugs. Michael S Insler and his team reported a case of post-keratoplasty endophthalmitis caused by *Pseudomonas aeruginosa* showing resistance to gentamicin.[16] Ana Paula *et al.*, reported two cases of MDR *Pseudomonas aeruginosa* infection after cornea transplant. These isolated *Pseudomonas aeruginosa* showed absence of response to intravenous ceftazidime and imipenem eye drop (50 mg/ml).[17] A. Panda reported a case series of 7 eyes infected with multidrug resistant *Pseudomonas aeruginosa*. All isolates were susceptible only to polymyxin B. All the corneo-scleral rims were preserved in MK media. She suggested that although MK media already contains Gentamicin, *Pseudomonas aeruginosa* resistant to Gentamicin, could easily thrive in the media.[18] Insler et al reported that the emergence of more antibiotic resistant micro-organisms in antibiotic supplemented media may result in donor to host contamination following keratoplasty. Increased length of storage is a major cause of transmission.[16] In our study also, both the cases of Pseudomonas were only susceptible to Polymixin B.

Pseudomonas aeruginosa is a potential contaminant of pharmaceutical and cosmetic preparation and is a common hospital acquired (nosocomial) pathogen. The nosocomial microorganism is usually highly resistant to most of the available antibiotics, giving very limited options to the Ophthalmologists for use of antibiotics.[19] *Streptococcus pneumoniae* was another common causative agent of post-keratoplasty corneal infection. This pathogen, being commensal in throat may reach the ocular surface through nasolacrimal duct and cause corneal infection. Moore PJ reported *Streptococcus pneumoniae* endophthalmitis following corneal transplant.[20] In our study there was one case of infectious keratitis following Descemet Stripping Endothelial Keratoplasty (DSEK) surgery. Hannus SB had earlier also reported three cases of infectious keratitis after DSEK surgery. These cases of post-DSEK infections were caused by *Pseudomonas aeruginosa, Streptococcus pneumoniae* and *Enterococcus faecalis*.[21]

Candida albicans, a yeast like fungi may also cause keratitis in patients who have undergone keratoplasty. MR Sedaghat reported a case of *Candida albicans* interface infection after deep anterior lamellar keratoplasty in an 18 year old female presenting with keratoconus. Keratitis was completely resolved after 10 days of continuous interface irrigation with amphoterecin B.[22] Koenig SB reported a case of Candida keratitis after descemet stripping automated endothelial keratoplasty (DSAEK) in a 90 year old male with pseudophakic bullous keratopathy. Despite intensive treatment, patient failed to respond and enucleation was done.[23]

Acinetobacter baumanii is a gram negative bacillus that causes nosocomial infection. Kaun Jen Chen et al (2008) reported a case of post-keratoplasty endophthalmitis caused by *Acinetobacter*.[24] *Proteus vulgaris* was isolated in a 17 year old girl in our case series after one month of the corneal transplant. Lam DS et al (1998) reported a case of post-keratoplasty endhophthalmitis caused by *Proteus mirabilis* in a diabetic patient. Isolated *Proteus mirabilis* was resistant to gentamicin.[25]

Corneo-scleral rim is a major source of microbes. Kehyani K et al. reported that 13% of the corneo-scleral rims had microbes including fungi in 28 eyes. All fungi were *Candida* species on culture. They reported that post-keratoplasty fungal infections occurred only in those cases in which contaminated cornea was transplanted.[26]

Conclusion:

Post-keratoplasty infection is an infrequent complication of corneal transplantation. Reduced corneal sensation with frequent instillation of corticosteroid eye drops enhances the chances of post keratoplasty infections. There is also a great risk of donor to host transmission. Huge diversity of microorganism and emergence of resistance to antimicrobials necessitates the ophthalmologist to scrape the cornea in each patient with corneal infiltrate and subject to antibiotic susceptibility, so that the correct organism along with resistance to drugs be established and the devastating sequel like complete vision loss or painful blind eye can be prevented. This will help in ensuring good clinical outcome.

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Table1: Shows demographic data with isolation of microorganisms

Case no	Age	Sex	Duration	Microorganism isolated
1	35	M	24 hrs	*Pseudomonas aeruginosa*
2	53	F	3 days	*Candida albicans*
3	44	M	24 hours	*Staphylococcus aureus*
4	56	M	7 days	*Streptococcus pneumoniae*
5	17	F	1 month	*Proteus vulgaris*
6	62	F	24hrs	*Pseudomonas aeruginosa*
7	39	F	24 hrs	*Acinetobacter baumanii*
8	48	M	15 days	*Streptococcus pneumoniae*

Table 2: showing isolated microorganism with their antibiogram and treatment response

Case no.	Isolated organism	Susceptibility	Resistant	Treatment given	Response	Surgical treatment
1	*Pseudomonas aeruginosa*	Polymyxin B	Carbenecillin, Gentamycin, Ceftazidime, Amikacin, Imipenem Levofloxacin	Polymyxin B	Cured	No need
2	*Candida albicans*	Amphoterecin B	Azole Resistant	Amphoterecin B	Cured	No need
3	*Staphylococcus aureus*	Ciprofloxacin, Vancomycin, Gentamycin	Penicillin	Vancomycin	cured	No need
4	*Streptococcus pneumoniae*	Penicillin, Gentamycin, Levofloxacin, Vancomycin	No	Vancomycin	cured	No need
5	*Proteus vulgaris*	Ampicillin, Gentamycin, Ceftazidine, Levofloxacin, Imipenem	No	Moxifloxacin	Cured	No need
6	*Pseudomonas aeruginosa*	Polymyxin B Imipenem (Intermediate sensitive)	Carbenecillin, Gentamycin, Ceftazidime, Amikacin, Levofloxacin, Imipenem	Polymyxin B	No response	Evisceration
7	*Acinetobacter baumanii*	Carbenecillin, Ceftazidime, Gentamycin, Levofloxacin, Imipenem, Polymyxin B	No	Moxifloxacin	cured	No need
8	*Streptococcus pneumoniae*	Penicillin, Gentamycin, Levofloxacin, Vancomycin	No	Vancomycin	Cured	No need

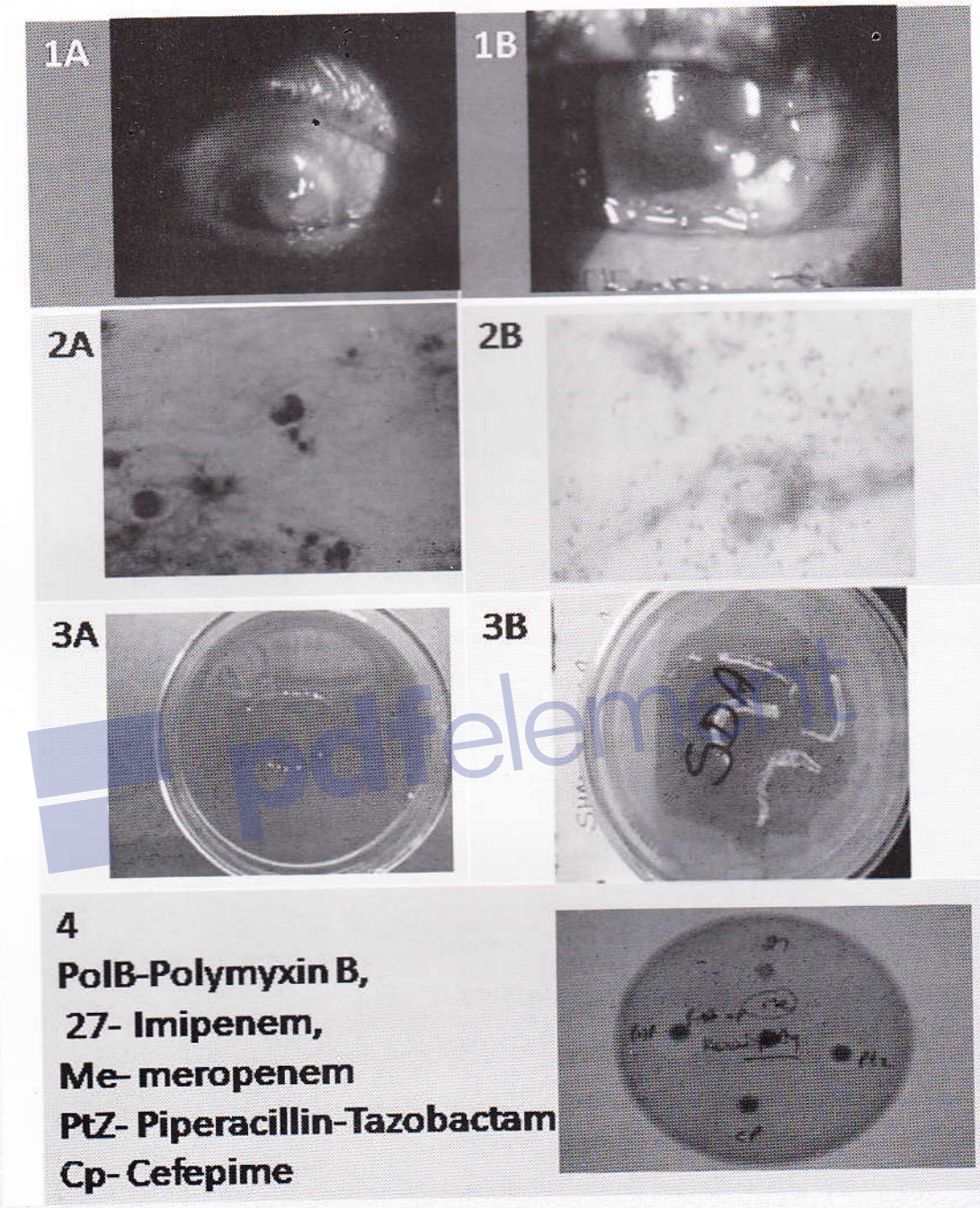

Figure 1A,1B: Clinical photographs showing *Pseudomonas aeruginosa* suppurating lesion and Candida suture infiltrates respectively

Figure 2A,2B: Gram's stain showing yeast cells and gram negative coccobacilli respectively

Figure 3A,3B: Growth on Blood agar and Sabouraud Agar respectively

Figure 4: Susceptibility of *Pseudomonas aeruginosa* to only polymyxin B on Mueller Hinton Agar

COMMUNITY OPHTHALMOLOGY

An Overview of Services Rendered By State Medical Colleges

Dr. R.N Kushwaha , Dr. R.C Gupta , Dr. Jeevan , Dr. Alok , Dr. Avaneesh

Introduction

Visual impairment has immediate and long-term consequences in people of all age groups resulting in lost blind-person years, low educational and employment opportunities, poor economic gain for individual, families and societies and decreased quality of life.

Community Ophthalmology is a system which utilises the full scope of Ophthalmic knowledge and skill, methodology of public health and services of other medical and non-medical agencies to promote ocular health and prevent blindness at the community level with an active, recognised and crucial role of community participation.

***Categories Of Visual Impairment ; WHO(1977)*(1)**

Categories Of Visual Impairment	Level Of Visual Acuity	
Normal vision	(0) 6/6 To 6/18	
Low vision	(1) Less Than 6/18 To 6/60	
	(2) Less Than 6/60 To 3/60	Economic Blindness
Blindness	(3) Less Than 3/60 To 1/60	Social Blindness
	(4) Less Than 1/60 To Light Perception)	Legal Blindness
	(5) No Light Perception	Total Blindness

According to WHO criteria, global estimate predict that there are 314 million people with visual impairment [45 million Blind (visual acuity <3/60) and 269 million due to Low Vision (visual acuity <6/18) due to eye diseases and refractive errors. There has been a transition in usage of definition from 'best corrected' vision to 'presenting' vision in determining the extent of visual impairment. Best-corrected vision refers to visual acuity obtained with the best possible refractive correction whereas presenting vision indicates visual acuity obtained using currently available refractive correction, if any. (2)

Over the last 20 years, causes of blindness has changed both in proportion and actual numbers, however cataract has still remained the major cause of blindness globally and more so in Asia.

Available Indian estimates suggest that there are more than 12 million bilaterally blind persons in the country with visual acuity [VA] <6/60 in the better eye, of which nearly 7 million are with VA <3/60 in the better eye. National survey during 2001-04 indicated that prevalence of blindness stood at 1.1% and Rapid Assessment of Avoidable Blindness [RAAB] in 2006-07 showed that prevalence has come down to 1.0%.

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Main causes of blindness in the surveyed population indicated cataract [62.6%], refractive errors [19.7%], corneal blindness [0.9%], glaucoma [5.8%], surgical complication [1.2%], posterior capsular opacification [0.9%], posterior segment disorder [4.7%] and other causes [4.19%].(3)

The fundamental issue under any program is social mobilization for advancement of health objectives and increasing demand and utilization of services. It is expected that health personnel including community link worker like ASHA, Aanganwadi workers and 'motivated' members of civil society can play a critical role in this aspect. Village-wise blind register is a tool that facilitates in identification, recording, communication, referral and appropriate management of such cases.

National Programme For Prevention Of Blindness (NPCB) :- NPCB was launched in the year 1976 as a 100% Centrally Sponsored scheme with the goal to reduce the prevalence of blindness from 1.4% to 0.3%. Various activities/initiatives undertaken during the Five Year Plans under NPCB are targeted towards achieving the goal of reducing the prevalence of blindness to 0.3% by the year 2020.

NPCB has been able to deliver effective eye care services through successful and vibrant Public Private Partnership [PPP], through decentralized mode under integrated State/District Health Societies of National Rural Health Mission [NRHM], a win-win situation for all stakeholders and parties. The year 2008 recorded ever-highest 5.8 million cataract surgeries with 94% intraocular lens [IOL] implantation at national level inspite of continuation of ban on 'surgical camps' in makeshift operation theaters to prevent post-operative infections. The program has been able to achieve huge quantitative gains without compromising quality and the momentum thus generated has paved way towards a sustainable blindness free society in near future.

Curative ophthalmology can make a perceptible impact in the society only in conjunction with community ophthalmology. Such activities include need assessment, planning, mobilizing level appropriate resources, fact finding surveys, outbreak investigation in ophthalmic practices, targeted interventions through screening,operational research, clinical care, Vitamin-A supplement/rich food, complete vaccination [especially measles], training, ophthalmic surveillance; sensitization, counselling, motivation, ensuring compliance, referral, follow-up, rehabilitation of incurable blind, empowering community/individuals to utilize available government concessions/benefit for the welfare of blind; reducing myths and misconceptions, understanding and removing barriers for access to services, facilitating favourable environment for growth and development; local leadership and coordination amongst stakeholders under various governmental departments of health, social welfare, education and ICDS, establishment of intra and inter-linkages, information, education and communication activities [IEC], promotion of eye donation improving efficient client movement and logical disposal within health facilities, feedback/reminders for action, monitoring, supervision and evaluation.

Our Services

Various projects and activities are being carried out at our institution GSVM Medical College , Kanpur among which A Cross Sectional Study On Prevalence Of Ocular Morbidity among school going children was done from January 2015 to December 2015. in this study 1149 urban and 956 rural school going children of 6 - 16 years of age of Kanpur city were screened with Snellens-E-chart , Ishihara chart , pin hole , cover uncover test along with comprehensive ocular examination with torch light , slit lamp with 90 D and direct ophthalmoscope. After the study in the result it was found that the prevalence of refractive error was

maximum (26.19%) followed by squint (2.78%), Vitamin A deficiency (1.91%), blepharitis(1.83%), colour-blindness(1.2%), stye(0.78%) and ptosis(0.35%) in urban area.

In rural area prevalence of refractive error was 15.9% but prevalence of Vitamin A deficiency (12.86%) blepharitis (5.43%) and stye (2.40%) was highly significant (P<.0001). for the rest of the ocular morbidities prevalence did not vary significantly.

Prevalence of ocular morbidity in males (Rural-63.52% and Urban -57.81%) was more than females (Rural-36.48% and Urban - 42.17%).

We are providing community ophthalmic services through various means like organising school health programmes on regular basis where we provide promotive and preventive measures. Children are screened for various ocular morbidities and are provided medications and those requiring major interventions are referred to our institution.

Awareness is being spread on maternal and child nutrition like including vitamin A rich sources in their diet, face washing, safe water and environmental sanitation. Preventive and curative measures are also being taken like nutrition supplementation, vision screening, measles vaccination , treatment for vitamin A deficiency and referral for surgery

As cataract being one of the leading cause of avoidable blindness *'screening camps'* are held in rural , remote and underprivileged areas of Kanpur. Patients are provided comprehensive eye care services including refraction and cataract patients are being transported to our institution and undergo surgery.

Glaucoma week is celebrated every year from 6th - 12th March where we organise free eye camps where patients are screened thoroughly and given treatment accordingly. Public awareness for eye care , eye donation , glaucoma and prevention of blindness is achieved by organising different rallies ; frequent press releases and articles in leading newspaper and scientific journals.

Rehabilitation of the blind is as important as the prevention and control of blindness. In Rehabilitation services we have provision of low vision services and certification of blind and to sensitise them about concessions.

Conclusion

To conclude, it should never be forgotten that, one of the basic human rights is the right to see. The strategy makers MUST ensure that:

- No citizen goes blind needlessly due to preventable causes.
- All avenues are exhausted to restore the best possible vision to curable blinds.
- Blinds not amenable to curable measures receive comprehensive rehabilitation.

And various activities and services should be enhanced at a community level for the prevention of blindness.

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2. Resnikoff S, Pascolini D, Mariotti SP, Pokharel GP. Global magnitude of visual impairment caused by uncorrected refractive errors in 2004. Bull World Health Organ 2008;86:63-70.
3. www.npcb.nic.in

Current Concepts in the Management of Subluxated Lens- An overview

- Prof.S.P Singh*, Dr. Chandraprakash Oli**

Management of subluxated lens poses a great challenge to the surgeon planning to perform phacoemulsification with PCIOL in the bag, as each step of the surgical procedure may complicate the situation and every case may require different surgical technique. The different surgical strategy depends on the extent of subluxation, position of subluxation and presence or absence of vitreous prolapse.

The adoption of new devices (various type of endocapsular rings) and techniques that minimize the stress on compromised zonules have gained acceptance over the conventional approaches i.e intracapsular cataract extraction or pars plana vitrectomy/lensectomy.

Some important anatomical facts related to lens

- Lens is suspended in its anatomic position by ciliary zonule s(suspensory ligament of Zinn). These zonules are inserted till 1.5mm anterior and 1mm posterior to equator.
- Mean lens diameter is 9.72±0.31mm with a central zone(6.83±0.35mm) free of zonular insertion. This diameter (i.e central zone free of zonules) remains constant irrespective of the age and diameter of lens.
- It has been shown that the lens capsule displays considerable elasticity. The circumference of an intact capsulorhexis may expand upto 62% before a radial tear occurs and capsular elasticity does not seem to be related to the age.
- A radial tear rarely extends beyond the equator, provided that the zonules situated above and adjacent to tear remain intact.

Etiology:

Subluxation of lens may be congenital or acquired. Congenital subluxation of lens can occur as an isolated anomaly or associated with heritable disorders (like Marfan's, Weil- Marchesani, homocystinuria). Acquired subluxation of lens may occur due to hypermaturity of cataract, trauma, pseudoexfoliation, high myopia, previous scleral buckling surgery and staphylomas.

Preoperative evaluation:

Detailed ocular examination should be done. Both near and distant BCVA should be determined, keeping in mind that the patient may best see with an aphakic correction if the lens is markedly subluxated. The exact degree of zonular loss, location of defect and presence or absence of vitreous in the anterior chamber should be noted. Ultrasound biomicroscopy and anterior segment OCT, are especially useful for zonular and angle assessment in patients where the pupil fails to dilate. Gonioscopy is performed to note

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any developmental defects, pseudoexfoliative material and deformities secondary to trauma or as a sequlae to subluxation. The fundus examination is done to look for lattice degeneration, cyclitic membranes, retinal detachment or posttraumatic pathology. B-scan ultrasonography is indicated in opaque ocular media.

Besides the routine systemic examination, conscious efforts are directed towards detection of any cardiovascular abnormalities especially in Marfan's syndrome and Homocystinuria.

Indications for surgery:

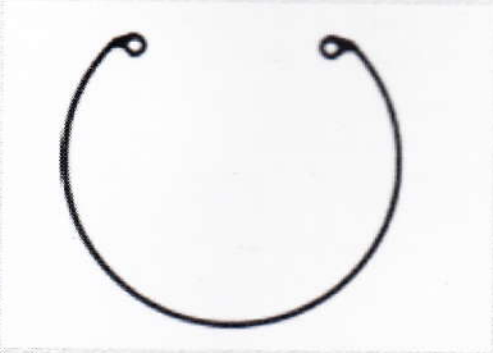
1. In younger children if there is significant or progressive dislocation or if amblyopia cannot be effectively treated by conventional means such as glasses, contact lens, and/or patching.
2. For older children and adults, if poor visual acuity is attributed to subluxated lens and is not amenable to spectacle correction, or if the lens is threatening to dislocate anteriorly or posteriorly.
3. Lens induced uveitis.
4. Significant cataract.
5. Lens induced glaucoma not controlled by medication

OPERATIVE PROCEDURE:-

Depending on the degree of subluxation the surgical procedure is chosen:-

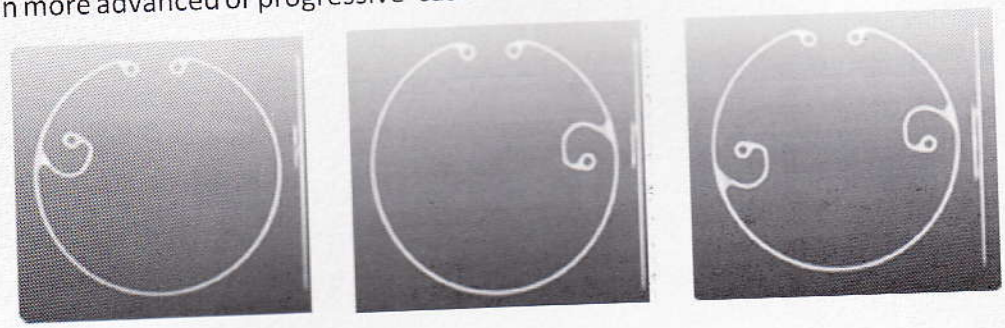
Degree of Zonular dehiscense	Procedure chosen
upto 3'o clock	CTR with IOL implantation
>3 to 6'o clock	Modified CTR with single loop
>6 to <9'o clock	Modified CTR with double loop
If 9 or >9'o clock/Generalised weakness of zonules	ICCE with scleral fixated IOL/Iris fixated IOL/ACIOL

In 1991, the CTR (capsular tension ring) was introduced by Dr Hara and subsequent studies demonstrated that CTR could provide both intra-operative and post-operative stabilization of capsular bag and IOL. These PMMA rings can be inserted anytime after the capsulorrhexis has been completed. CTRs are indicated in cases of small localized zonular dialysis of less than 3-4 clock hours.



Standard capsular tension ring

The modified CTR(MCTR), designed by Dr Robert Cionni, incorporates a unique fixation hook to provide scleral fixation without violating the integrity of the capsular bag. Depending on the extent of subluxation single or double loop models can be chose. The MCTR provides a good centration of capsular bag and are indicated in more advanced or progressive cases of zonular instability



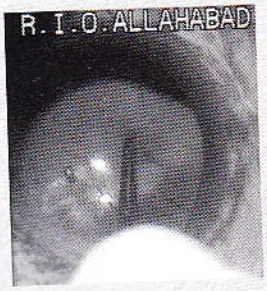
Various types of Cionni's ring

In 2002, Iqbal Ike Ahmed, MD, designed partial polymethylmethacrylate ring segments with 120º of arc length and a 5-mm radius of curvature. Like the Cionni CTR, Ahmed CTS have an anteriorly positioned eyelet for suturing to the sclera. The advantages of the CTS compared with the CTR are that the former can be implanted without a dialing technique, which minimizes trauma to an already compromised zonular apparatus. CTSs can be placed after the capsulorhexis and before cataract removal, and they can be slid into the area of greatest zonular weakness. CTSs can be used in cases of a discontinuous capsulorhexis, anterior capsular tears, or posterior capsular rents

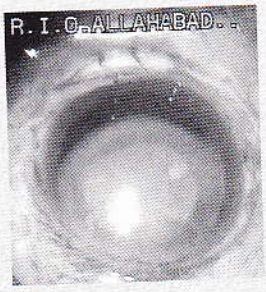
Capsular tension segment

Operative Technique:

Peribulbar anaesthesia is preferred. Incision should be away from the site of zonular dialysis & smallest possible to reduce stress on the existing zonules and minimize fluid egress through the incision and prevent anterior chamber collapse. After intial incision a generous amount of highly molecular weight viscoelastic is placed over the area of zonular dialysis to help tamponade the vitreous and to maintain a deep non collapsing AC. Capsulorrhexis in subluxated cataract may severly test the skill of the surgeon. Staining with 0.06 % tryphan blue dye gives better visualisation of capsule during rhexis. Initial relaxing capsulotomy is difficult because of lack of tractional forces. It is advisable to begin the capsulorrhexis where zonules are intact and the anterior capsule offers sufficient resistance. Capsulorrehxis forceps is preferred over the capsulotomy needle. A 5.5-6 mm of capsulorrhexis is usually adequate.



Initiation of capsulorrhexis

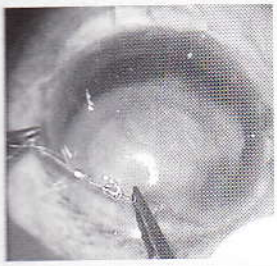


Capsulorrhexis completed

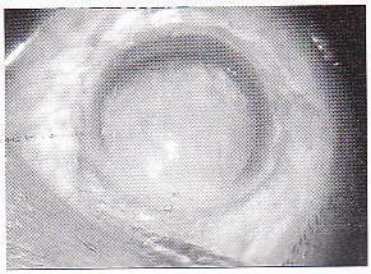
CTR/MCTR can be inserted into the capsular bag at any point after the capsulorrhexis; however the bulk of the nucleus can make visualization and placement of the CTR difficult but it is preferable to insert the CTR after capsulorrhexis and a good hydroprocedure as it reduces intra-operative herniation of vitreous in AC. The CTR is inserted using forceps or a specially designed injector.

Insertion before nuclear extraction

In this case a space is created between the peripheral capsular bag and remaining lenticular material with viscoelastic so as to prevent entrapment of cortex under the CTR. If the CTR is placed before phacoemulsification, a "safety-suture" (10.0 Prolene) is looped through the leading eyelet. This suture is left trailing out of the incision and can be used to retrieve the CTR in the event of a posterior capsular rent or if the CTR is difficult toplace.



Insertion of CTR



Centration of lens after CTR insertion

Fixation of Cionni's ring:- Steps in scleral fixation of cionni's ring is shown below in various photographs

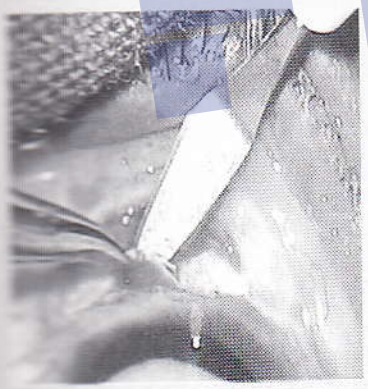


Fig. 1

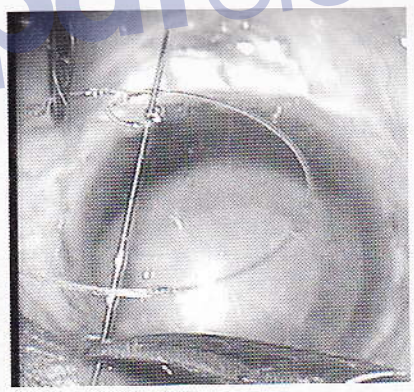


Fig. 2

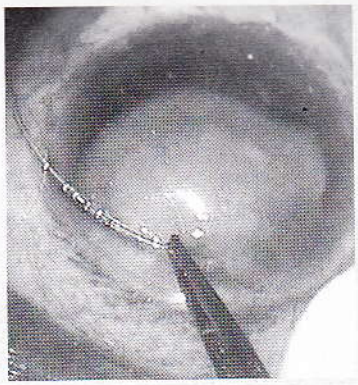


Fig. 3

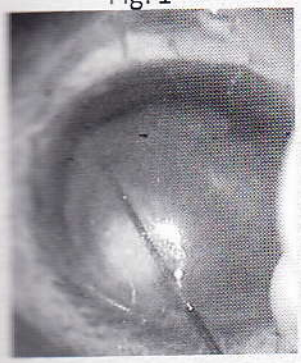


Fig. 4

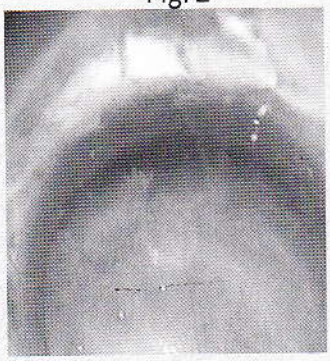


Fig. 5

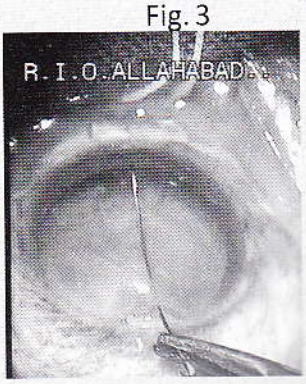


Fig. 6

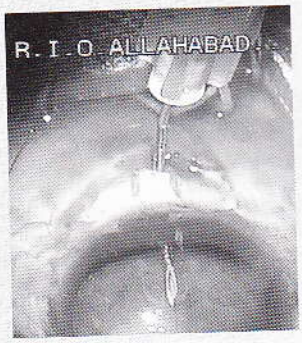


Fig. 7

Fig. 8

Fig. 9

Fig 10

Fig.1- *Partial thickness scleral flap created at point of maxmium subluxation*

Fig.2- *One end of double armed straight needle 10-0 polypropylene suture passed through fixation eyelet.*

Fig.3- *Cionnis ring is inserted in the capsular bag.*

Fig.4-*Cionnis ring dialled horizontally using sinskey hook.*

Fig.5-*Fixation eyelet is positioned at point of maximum subluxation.*

Fig.6-*Needle of the double armed 10-0 polyproplyene is passed through the main incision towards fixation site.*

Fig.7- *Bent curved 26- gauge needle is introduced 1.5 mm from the limbus through scleral bed into the posterior chamber under the iris.*

Fig.8- *Needle of 10-0 polypropylene suture is fed into the barrel of 26-gauge needle.*

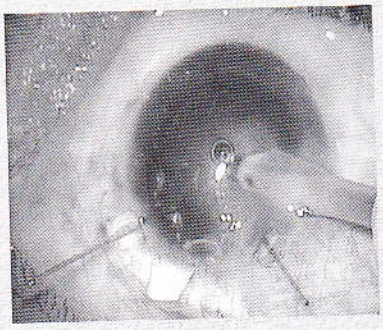
Fig.9- *Fed 26- gauge needle containing needle of 10-0 suture is then retracted through the sclera.*

Fig.10-*Similar technique is applied to other end of the double armed 10-0 polypropylene suture and then anchoring knot is placed and Suture knot is buried in scleral bed and covered with scleral flap and conjunctiva by 10-0 monofilament suture.*

Insertion after nuclear extraction

Once capsulorrhexis has been completed, if one plans to extract the nucleus prior to capsular tension ring implantation, if there is moderate subluxation, the capsular bag should be stabilized with iris retractors placed through limbal stab incisions.

Stabilisation of capsular bag with iris retractor



Phacoemulsification after stabilising capsular bag with iris retractor

Hydrodissection is then performed gently, yet thoroughly, to maximally free the nucleus and thereby decrease zonular stress during manipulation of the nucleus. Phacoemulsification should be performed using low vacuum and aspiration settings in order to keep the bottle height and flow rate at a minimum. Chop techniques are preferred for the dense nuclei to minimize zonular stress during phacoemulsification. Cortical viscodissection prior to aspiration will also limit the stress on remaining zonules. The cortex should be stripped along a vector tangential to the capsular bag periphery to decrease the risk of further damaging the zonules. The cortical entrapment can be prevented, by injecting the viscoelastic just under the surface of the residual anterior capsular rim before inserting the CTR or MCTR. This will create a space for the ring and dissect the residual cortex away from the peripheral capsule. Once the CTR/MCTR has been placed appropriately, the posterior chamber intraocular lens (IOL) is inserted in the bag. It is easier to inject a foldable IOL in comparison to a PMMA lens but either can be used. Hydrophobic acrylic lenses should be preferred as these lenses are associated with less anterior capsular fibrosis compared to silicon lenses. Three piece lens design with broad stiff PMMA haptic are considered better as they exert centrifugal tension against capsular contraction compared to soft pliable haptics of single piece lenses, thereby proving good stability and centration of IOL. It is safer to place the IOL haptics in the meridian of zonular disinsertion. Vitreous presents at any time during the procedure, it should be completely removed from the anterior chamber. Kenalog (Alcon) (triamcinolone suspension) can be used to identify vitreous in the anterior chamber

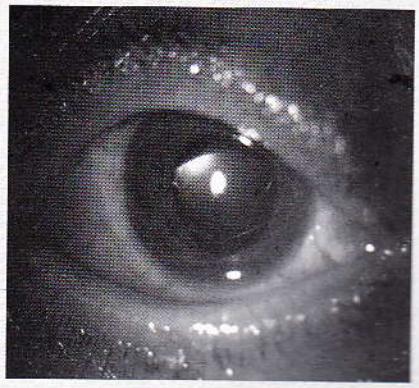
Complications:

Intra-operative complications include posterior capsule rupture, nucleus drop, CTR drop with the bag, and IOL drop. In addition there are usual complications encountered during lens extraction. Glaucoma, iritis, hyphaema, delayed IOL subluxation or decentration , capsular phimosis, capsulorrehxis contraction anterior capsular fibrosis, vitreous haemorrhage, retinal detachment and macular edema may be encountered postoperatively.

Contraindications of CTR/MCTR:

- Complete continuous capsulorrhexis is not attained
- Posterior capsular tear occurs since the expansile forces may cause the capsular bag to rupture.
- Extensive generalized zonular weakness.
- MCTR is not to be used in patients with scleral disorders.

In conclusion, with the use various types of endocapsular ring, it is now possible to save and re-centre the capsular bag, and implant a PCIOL within it. However, this requires a highly skilled surgeon and cannot always be completed. In cases where there is extensive subluxation (9 o'clock hrs or more), intraoperative extension of zonular dialysis, rupture of capsular bag, retropupillary fixation of iris claw lens can be done, the discussion of which is beyond the scope of this article.



Retropupillary fixated iris claw lens

Key points to remember:-

- Make the corneal incision in the meridian where the zonules are intact.
- For better visualisation of capsule stain with 0.06% tryphan blue dye.
- Make a large rhexis, starting at where zonules are intact.
- Do gentle hydroprocedure.
- Minimal rotation of nucleus to minimize zonular stress.
- During phacoemulsification decrease vaccum, flow rate and irrigation level to prevent undu turbulence in the AC and zonular disturbance.
- Use stop & chop or direct chop for minimal manipulation of the zonules.
- Place the IOL in the bag and avoid dialing the lens.
- Hydrophobic acrylic lenses with three piece lens design having broad stiff PMMA haptics a considered better.

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Descemet's Membrane Detachment

Kamaljeet Singh, S.P. Singh, Harsh Mathur, Kshama Dwivedi, Arti Singh, Sushank A. Bhalerao*

Descemet's membrane detachment (DMD) is an uncommon but serious complication of intraocular surgery[1]. It occurs when fluid enters the corneal stroma through a break in Descemet's membrane (DM) or an area of separation between the DM and the corneal stroma. Acute loss of vision from severe corneal edema can be the first sign and may also be the cause of a delayed diagnosis[2].

In 1928, soon after the advent of slit-lamp biomicroscopy, the first systematic description of DMD in the American literature was made by Bernard Samuels[3]. Samuels reported three patients with DMD after iridectomy, but he failed to realize its significance. Indeed, the subsequent literature reflected little interest in this entity until 1964, when Scheie[4] realized the potentially serious nature of this surgical complication in his report of three patients who did poorly with DMD after cataract extraction.

A review of literature revealed that only one report has determined the incidence of DMD. It was found to be 2.8% for extracapsular cataract extraction (ECCE) and 0.5% for phacoemulsification[5]. The presence of DMFags or scrolls along the interior lip of the sclera-corneal incision have been noted, with an incidence determined by gonioscopy to be 11% to 42%[6,7].

There is no clarity in the existing literature regarding the need for surgical reattachment[8-11] and the efficacy of various substances used as tamponade, such as 100% air, viscoelastic material, 14% isoexpansile perfluoropropane (C3F8) and 20% sulfur-hexafluoride[12].Potter and Zalatimo[13] have reported air to be the most efficacious tamponade for descemetopexy.

Predisposing Factors

- Shallow anterior chamber
- Complicated or repeated surgeries
- Inadvertent insertion of instruments between the corneal stroma and descemet's membrane
- Anterior and shelved incisions
- Blunt blades
- Engaging the descemet's membrane during intraocular lens implantation or with the irrigation/aspiration device (when mistaken as an anterior capsular remnant).

Causes of Descemet's Membrane Detachment

Surgical

- Complicated / uncomplicated Cataract surgery – Phacoemulsificaton, SICS, ECCE
- Glaucoma surgery – Viscocanalostomy, Deep sclerectomy, Trabeculectomy, Iridectomy, holmium laser sclerostomy

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3. Inadvertent intracorneal injections- Viscoelstics, Balanced salt solution, Adrenaline, Antibiotics
4. Penetrating keratoplasty
5. Pars plana vitrectomy

Non- surgical- Birth injury, Trauma- blunt/sharp, Congenital glaucoma, Corneal ectasia- keratoconus, Anatomical predisposition

The most common cause of descemet's membrane detachment is mechanical separation near the incision site by an instrument, fluid or viscoelastic substance.[15,16,17]

Classification

- **Mackool and Holtz Classification** based on clinical presentation - Classification by Mackool and Holtz helps in determining the prognosis of DMD. Planar detachments are likely to resolve spontaneously and non-planar should be repaired early. Iradier MT and Moreono E used this classification in studying the late spontaneous resolution of a massive detachment of Descemet's membrane after phacoemulsification.[14,15]
- Planar (<1mm separation from the stroma)
- Peripheral detachment only
- Combined peripheral & central detachment
- Non- Planar (>1mm separation from the stroma)
- Peripheral detachment only
- Combined peripheral & central detachment

Dr Jacob's Classification based on etio-pathogenesis[17]

- Stripped descemet's membrane detachment
- Taut descemet's membrane detachment

Stripped descemet's membrane detachment - Stripped descemet's membrane detachment is generally induced during viscoelastic injection or during insertion of blunt instruments or intraocular lens.

Taut descemet's membrane detachment - A long-standing stripped descemet's membrane detachment could sometimes adhere to intraocular contents with secondary fibrosis, thus turning into a taut descemet's membrane detachment. It could be due to inflammation involving the descemet's membrane, secondary incarceration of the descemet's membrane in an inflammatory process, eg, in peripheral anterior synechiae or within the graft host junction; or secondary incarceration in a wound/suture with subsequent contraction.

Morphological classification[18]

- DMD with non- scrolled edges
- DMD with scrolled edges

Role of Imaging Technology

Diffuse corneal edema can obscure the slit-lamp view into the anterior chamber, making the diagnosis and subsequent surgical planning difficult. Ultrasonographic biomicroscopy (UBM) has been advocated as a

means of imaging DMD through an opaque cornea, but this procedure requires a skilled technician, a cooperative patient, and substantial time investment.[19]

Anterior segment OCT may be superior alternative to UBM because of the speed and ease of image acquisition, the ability to acquire images without direct corneal contact, and the ability to image patients in the upright position.[20] It determines the extent of detachment (planar or non-planar) and degree of tautness. A stripped descemet's membrane detachment is seen as an undulating linear hyper-reflective echo in the anterior chamber whereas a taut descemet's membrane detachment is seen as a straight, taut line between two points of attachment.[17]

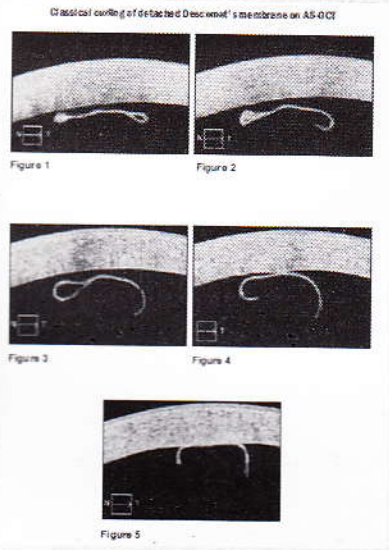

Fig. Classical curling of DMD on AS-OCT

Management

Conservative Approach: Planar DMDs are visually insignificant and resolve spontaneously (reattachment) within few weeks to few months. Conservative approach including medical treatment in the form of topical steroids and hyperosmotic agents is indicated with a close follow-up.

Reattachment: Spontaneous resolution of descemet's membrane detachment has been reported within days to 3 months. The actual nature of this reattachment is unclear. It has been hypothesized that the persistent pumping action of the healthy endothelium might exert an appositional force to appose detached corneal descemet's membrane. Fortunately, the viability of the endothelial cells is maintained, and they function well even after months of descemet's membrane separation. The descemet's ridges present following reattachment are usually visually insignificant.[21]

Interventional Approach: Non-planar DMDs may cause vision loss because of subsequent corneal decompensation. Swift action in nonplanar DMD is essential.

Internal tamponade : One should be vigilant enough to notice even a small DMD intra-operatively, immediately on its occurrence. If stripping of descemet's mem¬brane is recognised at the time of surgery attempt may be made to reposit the same using an iris repositor. Sterile air should be injected at the end of surgery. Due to its short life, air is reserved for small incision detachments. If anterior chamber gas injection cannot be carried out at the end of the surgery, it must be done on the first day after the surgery.

Descemetopexy: Intracameral injection with either iso-expansile sulfur hexafluoride (SF6) or iso-expansile perfluoropropane (C3F8) gas has gained increasing acceptance as an efficient and effective treatment option for descemet's membrane detachments. SF6 (20%) is the safest for the endothelium.[22] In addition, this procedure can be performed at the slit-lamp and may be repeated if necessary. It may also be combined with transcorneal suturing if DMD is very large or having scrolled edges.

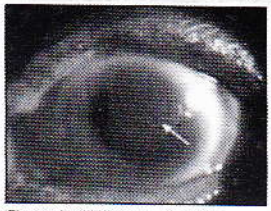

Figure 1- Slit-lamp examination image with postoperative severe corneal edema

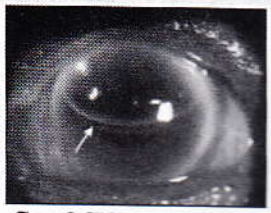

Figure 2- Slit-lamp examination image with C3F8 bubble in anterior chamber and attached Descemet's membrane. Day 3

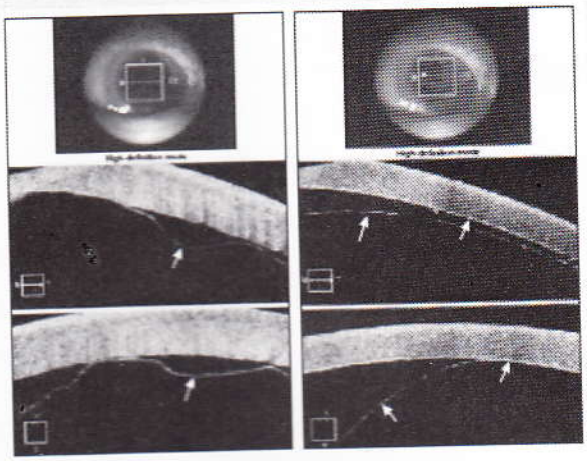

Figure 3- High-resolution cornea scanning with anterior segment optical coherence tomogram revealing central Descemet's membrane detachment

Figure 4- Post C3F8 injection gas bubble with attached Descemet's membrane and clear cornea on anterior segment optical coherence tomogram

Case 1. Management of DMD by Descemetopexy

Figure 1- High-resolution cornea scanning with anterior segment optical coherence tomogram revealing central Descemet's membrane detachment

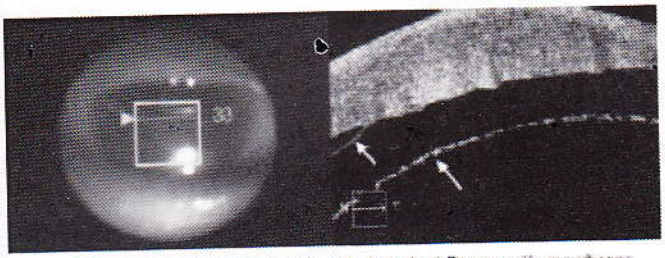

Figure 2- Post air injection gas bubble with detached Descemet's membrane on day 3 on anterior segment optical coherence tomogram

Figure 3- Re-descemetopexy- Post C3F8 injection with attached Descemet's membrane at 1 month on anterior segment optical coherence tomogram

Case 2 . Management of DMD- Re-Descemetopexy an option

Complications of descemetopexy

- Raised intraocular pressure due to pupillary block due to large gas bubble or because of movement of the gas bubble behind the iris. A simple paracentesis will relieve the pupillary block.
- Endothelial fallout may occur due to increased instrumentation associated with descemetopexy
- Despite successful reattachment, a horizontal opacity, or descemet's membrane haze may remain at the location of the original detachment.
- Irregular astigmatism may result owing to the formation of wrinkles in descemet's membrane.

Prevention

Descemet's membrane detachment is a remediable but potentially blinding cause of postoperative corneal oedema. Several factors should be borne in mind to help minimise the risk of DMD:

- Instrumentation should be gentle and minimal,
- Use of Blunt keratomes and blades should be avoided,
- Early intraoperative detection is imperative to avoid rapid progression,
- The incision's inner corneal aspect should be equal to, or slightly greater than, the incision's outer scleral aspect to prevent undue trauma during insertion and removal of phaco probes or irrigation/aspiration devices with irrigating sleeves.

Conclusion

A careful slit-lamp examination augmented by an anterior segment OCT if needed, can diagnose descemet's membrane detachment in cases of corneal oedema following cataract surgery, especially if the procedure has been uneventful. AS-OCT guided, endoilluminator assisted intracameral injection of sulphur hexafluoride(SF6) gas is the best way of management of DMD as compared to intracameral injection of air and perfluoropropane (C3F8) gas[23]. Descemetopexy should be undertaken even if detection of DMD is as late as 2 months postoperatively.

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CLASSIFICATION OF UVEITIS

Dr Abhishek Varshney*, Dr Manmath Kr. Das

Need for classification for any disorder/ disease arises because it enhances precision and comparability of clinical research from different centres, moreover it also helps in development of complete picture of course of disease and also aids in assessing the response to the treatment. Uveitis may be classified in numerous ways, according to several systems and multiple descriptors.

INTERNATIONAL UVEITIS STUDY GROUP (IUSG) CLASSIFICATION (1987)

It is the most widely used classification and was given by this committee in the year 1987. It is based on the anatomical location of the disease.

ANATOMICAL CLASSIFICATION OF UVEITIS (SUN Working Group Classification)

i) Anterior

- Iritis
- Anterior cyclitis
- Iridocyclitis

ii) Intermediate uveitis (formerly k/a pars planitis, posterior cyclitis, hyalitis, basal retinochoroiditis, peripheral uveitis)

iii) Posterior uveitis

- focal, multifocal or diffuse choroiditis, chorioretinitis
- retinochoroiditis or neurouveitis

iv) Panuveitis

In 2005, the Standardization of Uveitis Nomenclature (SUN) Working Group standardized the methods for reporting clinical data for uveitis under the headings of diagnostic terminology, inflammation grading schema and outcome measures. Anatomical classification of uveitis based on criteria defined by the International Uveitis Study Group (IUSG) was retained. A standardized grading schema for aspects of intraocular inflammation, that is, anterior chamber cells, anterior chamber flare, and vitreous haze, was developed.[1] Standardized definitions of outcomes, including reporting visual acuity outcomes, were reported.

Detailed clinical guidelines on anterior segment and posterior segment intraocular inflammation were also published by The International Ocular Inflammation Society (IOIS).[1,2]

CLINICAL CLASSIFICATION OF UVEITIS

The anatomical classification was further refined by SUN group by defining descriptions based on clinical

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onset, duration and course. This came to be known as the **CLINICAL CLASSIFICATION OF UVEITIS**

On the basis of **onset**:-

- Sudden
- Insidious

On the basis of **duration**:-

- Limited (duration not more than 3 months)
- Persistent (duration more than 3 months)

On the basis of **course** of Uveitis:-

- Acute (sudden onset and limited duration)
- Recurrent (repeated episodes of uveitis separated by periods of inactivity lasting at least 3 months without treatment)
- Chronic (persistent uveitis with relapse within 3 months after discontinuation of treatment)

INTERNATIONAL UVEITIS STUDY GROUP (IUSG) CLASSIFICATION (2008)

IUSG in 2008 proposed a newer classification based on the etiology of the disease. Three main categories were defined. They were:-

- Infectious (bacterial, viral, fungal, parasitic)
- Non-infectious (known systemic associations, no known systemic associations)
- Masquerade (neoplastic, non-neoplastic)

Other etiologies that have been included are

- Traumatic (surgical, non-surgical)
- Toxic (chemical, drug induced)

Few other classifications have also been proposed. They were

MORPHOLOGICAL CLASSIFICATION

This classification was given by Alan Churchill Woods hence also came to be known as Woods' classification. This classification is based on the clinical examination of the patient of uveitis.

Two categories were proposed in this group

- Granulomatous uveitis
- Non - granulomatous uveitis

Features	GU	NGU
Onset	insidious but prolonged	acute
Laterality	Bilateral	unilateral
Pain	none/slight	Marked
Photophobia	minimal	Marked
Recurrence	occasional	Common
Blurred vision	marked	moderate
Inflammation	mild	marked
KPs	Mutton fat greasy	Fine, dispersed
Iris nodules	seen	Not seen
Synechiae	Broad based, thick	Fine, filamentous
Post. segment involvement	Common	Generally absent

CLASSIFICATION PARAMETERS

For the formulation of complete diagnosis following parameters must be kept in mind

- **Patient demographics** (Age, sex, sexual orientation, race, geographic location, travel history, social habits, and occupation)
- **Location of the inflammatory process** (Anterior, intermediate, posterior and panuveitis)
- **Duration** (limited, persistent), **onset** (sudden, insidious), and **course of inflammation** (acute, recurrent and chronic)
- **Character of the inflammation** (granulomatous, non-granulomatous) including the nature of the inflammatory cells and deposits, distribution of lesions, and the presence of nodules, fibrin or synechiae
- **Etiology of the inflammation** (autoimmune, infectious, neoplasm, trauma, toxic, systemic diseases, idiopathic)

GRADING OF UVEITIS

The SUN Working Group standardized the grading of anterior chamber cells and flare to achieve better compatibility between data from different groups and different studies.

For anterior chamber cells, in a field size of 1X1-mm slit beam, the following grades were described[4]:

Grade 0	-	< 1 cell
Grade 0.5+	-	1-5 cells
Grade 1+	-	6-15 cells
Grade 2+	-	16-25 cells
Grade 3+	-	26-50 cells
Grade 4+	-	>50 cells

The presence of hypopyon was recorded separately.

The grading for anterior chamber flare was standardized as follows[4]:

Grade 0	-	none
Grade 1+	-	faint (barely visible)
Grade 2+	-	moderate (iris and lens details clear)
Grade 3+	-	marked (iris and lens details hazy)
Grade 4+	-	intense (fibrin or plastic aqueous)

SUN working group also classified the activity of anterior uveitis as[4]:

Inactive	grade 0 cells in anterior chamber
Improved activity	2-step decrease in the level of inflammation or a decrease to grade 0
Worsening activity	2-step increase in the level of inflammation or an increase from grade 3+ to 4+
Remission	inactive disease for at least 3 months after discontinuation of treatment

Vitreous inflammatory cells are graded as follows[4]:

Grade 0	-	no cells
Grade 0.5+	-	1-10 cells
Grade 1+	-	10-20 cells
Grade 2+	-	20-30 cells
Grade 3+	-	30-100 cells
Grade 4+	-	>100 cells

Vitreous haze is graded as follows[5]:

Grade 0	-	no haze
Trace	-	slight blurring of optic disc margin
Grade 1+	-	slightly blurred optic disc and vessels
Grade 2+	-	moderately blurred optic disc and vessels
Grade 3+	-	optic disc blurry but visible
Grade 4+	-	optic disc not visible

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Setting Target IOP in Glaucoma

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Glaucoma is a multi factorial optic neuropathy in which there is a characteristic acquired loss of retinal ganglion cells at levels beyond normal age related baseline and corresponding atrophy of optic nerve head.[1] Glaucomatous is associated with progressive visual field loss which can lead to total irreversible blindness if the disease is not diagnosed early and treated properly.[2] Various major studies on Glaucoma have concluded that lowering of IOP delays the progression of Glaucomatous damage[3,4,5,6]. This knowledge has given rise to the concept of target IOP in management of Glaucoma patients.

Target IOP:

It is the highest IOP level expected to prevent further Glaucomatous damage or that can slow progression to a minimum. It has to be individualized in every patient and in each eye of the same patient. Also it is dynamic, means we have to redefine target IOP if Glaucoma progresses despite an apparently low IOP. Baseline IOP and diurnal variation in IOP should be recorded before setting target IOP. Correction for corneal thickness should be done for Goldman applanation tonometry.

Target IOP Depends On:

- Pretreatment IOP or Baseline IOP
    - IOP at which damage has occurred e.g. if baseline IOP was 20 mm Hg, then target has to be near early teens like 12 mm hg. If the baseline IOP was in 30s, then target can be around 18. Though it also depends on type of disc & field damage.
- Disc and VF changes
    - Mild Glaucoma i.e. early disc damage, isolated VF defect outside central 10° of VF, MD on VF <= 6 db, the target IOP should be ~ 18 mm hg.
    - Moderate Glaucoma – arcuate VFD not encroaching on central VF, MD -6 to -12 dB, target IOP should be ~ 15 mm Hg.
    - Advanced Glaucoma – CDR 0.8 to 0.9, VFD on Central VF threatening fixation, MD >= -12 dB, target IOP should be <= 12 mm Hg.
- Normal tension glaucoma--decrease by 30%.
- Ocular HTN & Glaucoma suspects - < 20mm Hg.
- Age and life expectancy– more the life expectancy lower the IOP
- Severity of disease at presentation– more severe the disease at presentation, lower the IOP
- Presence of other risk factors (Target IOP to be lowered):
    - Family History

- Exfoliation Syndrome
- Thin Cornea is an independent risk factor for conversion of ocular hyper tension into POAG.
- Disc Hemorrhage
- Diabetes Mellitus
- Migraine
- Hypotension - it decreases ocular perfusion pressure.
- Patient on Anti Hypertensives - antihypertensive drugs especially beta blockers may cause fall in BP at night at thus a corresponding fall in ocular perfusion pressure.

- Quality of Life
- Compliance
- Cost Evaluation

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Role of OCT in Glaucoma

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Glaucoma is an optic neuropathy which involves loss of retinal ganglion cells and their axons leading to characteristic optic nerve head (ONH) appearance for which intra ocular pressure (IOP) is one of the main risk factors.[1] This leads to functional deterioration, apparent in the form of visual field loss. Several studies have provided evidence that RNFL defects (structural loss) precedeONH and visual field alterations (functional loss).[2]OHTS results show that without optic disc assessment,up to 55 % of glaucoma patients may be missed.[3]

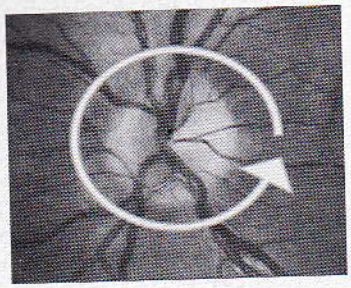
Role of OCT

OCT is an imaging technology that uses low coherence interferometry to acquire cross sectional images of ocular tissues. It has evolved from Time domain technology to the recent Spectral domain technology, which boasts of higher speed, better axial resolution and 3-dimensional imaging.

OCT Software Analysis

- Retinal Nerve Fibre Layer (RNFL)
- Optic Nerve Head (ONH)
- GCC Mapping

RNFL analysis



- Circular scanning is done around the centre of ONH at a radius of 3.45 mm.
- Three scans are acquired and data averaged and compared with normative data base of age matched subjects.
- Scan begins temporally.

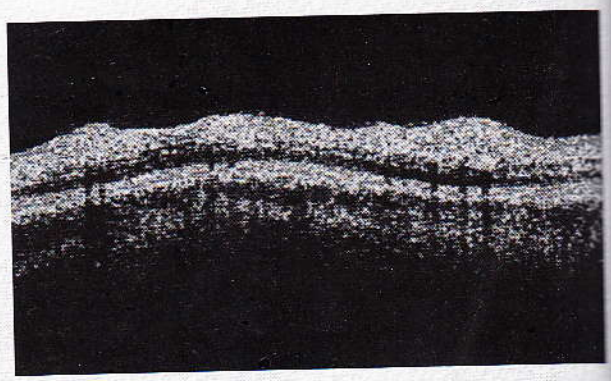


Fig 1: Peripapillary RNFL scan

*Consultant (Glaucoma Services) C L Gupta Eye Institute, Moradabad,UP.

RNFL thickness average analysis printout -7 zones

Zone 1 : Patient ID

Zone 2 : TSNIT with age matched normative data-base

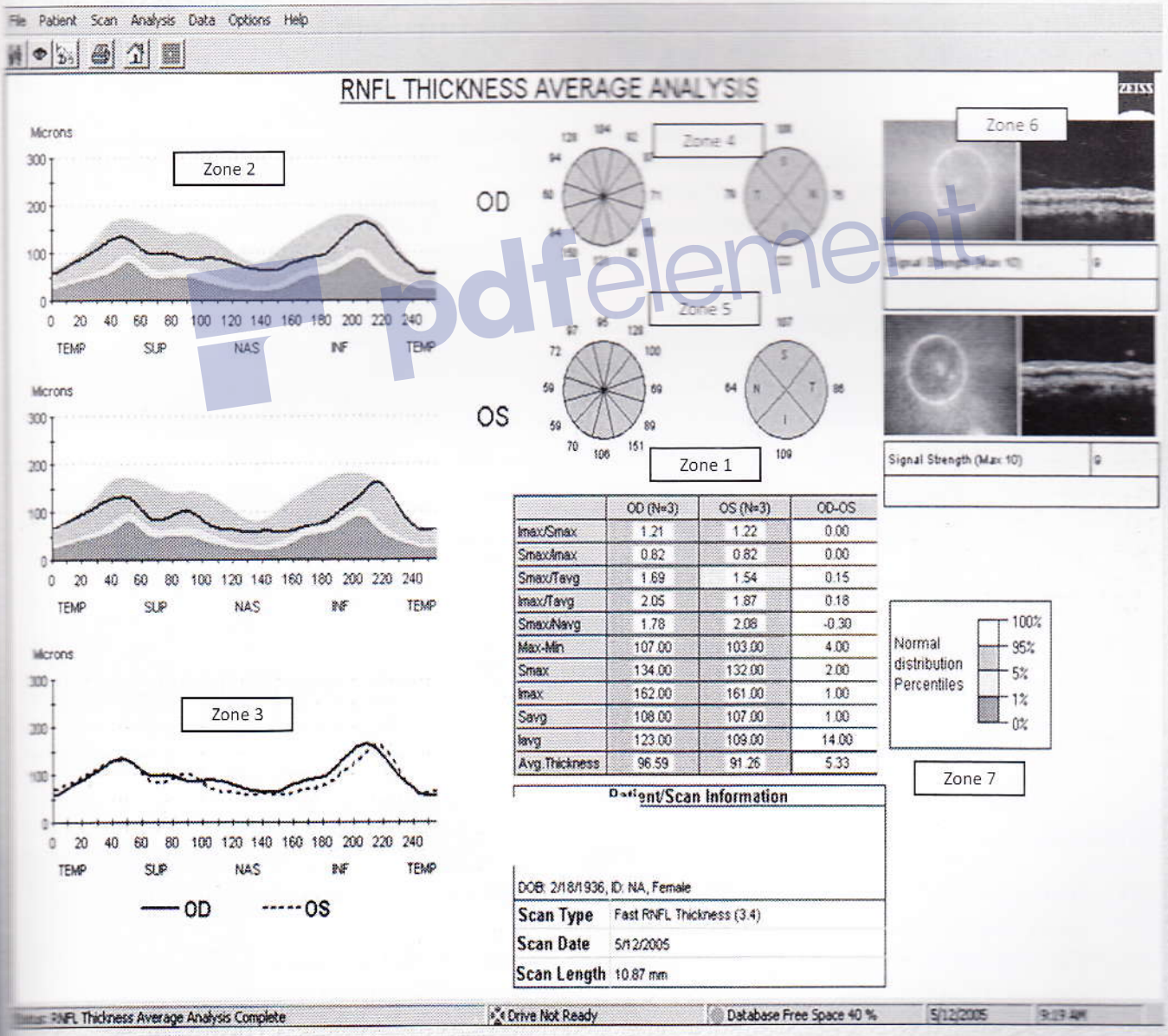
Zone 3: TSNIT overlap of 2 eyes

Zone 4 : Circular scan-quadrant/clockwise

Zone 5 : DATA TABLE-ratio/average

Zone 6 : RED FREE PHOTOGRAPH-position

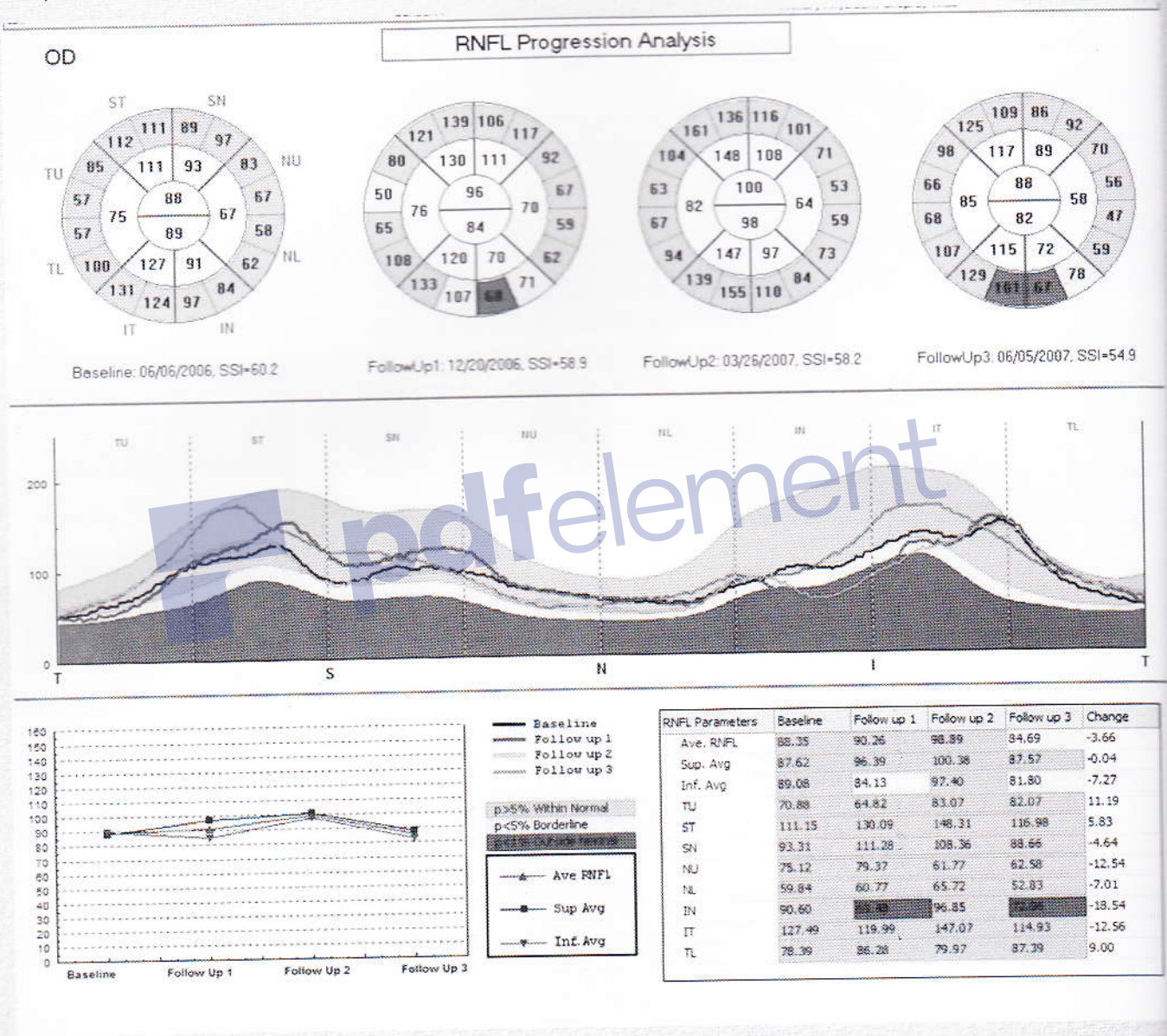
Zone 7 : PERCENTILE COLOR CODING



	OD (N=3)	OS (N=3)	OD-OS
Imax/Smax	1.21	1.22	0.00
Smax/Imax	0.82	0.82	0.00
Smax/Tavg	1.69	1.54	0.15
Imax/Tavg	2.05	1.87	0.18
Smax/Navg	1.78	2.08	-0.30
Max-Min	107.00	103.00	4.00
Smax	134.00	132.00	2.00
Imax	162.00	161.00	1.00
Savg	108.00	107.00	1.00
Iavg	123.00	109.00	14.00
Avg.Thickness	96.59	91.26	5.33

RNFL PROGRESSION ANALYSIS

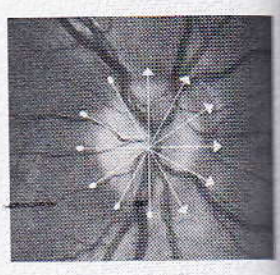
It compares the change detected over time to the variabilities of the measurements seen in a patient with glaucoma of the same stage. Areas of statistically significant changes are colour coded yellow when noted first, and red if it persists on subsequent scans.



RNFL Parameters	Baseline	Follow up 1	Follow up 2	Follow up 3	Change
Ave. RNFL	88.35	90.26	98.89	84.69	-3.66
Sup. Avg	87.62	96.39	100.38	87.57	-0.04
Inf. Avg	89.08	84.13	97.40	81.80	-7.27
TU	70.88	64.82	83.07	82.07	11.19
ST	111.15	130.09	148.31	116.98	5.83
SN	93.31	111.28	108.36	88.66	-4.64
NU	75.12	79.37	61.77	62.58	-12.54
NL	59.84	60.77	65.72	52.83	-7.01
IN	90.60	[redacted]	96.85	[redacted]	-18.54
IT	127.49	119.99	147.07	114.93	-12.56
TL	78.39	86.28	79.97	87.39	9.00

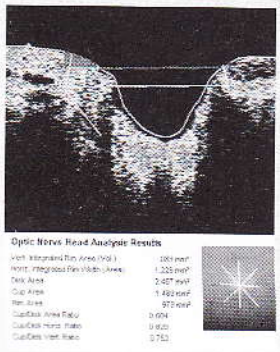
ONH Analysis

- ONH scans are composed of six linear scans in a spoke pattern separated by 30-degree interval centered on the ONH.
- The algorithm detects and measures all features of the disc anatomy based on the anatomical markers on each side of the disc where the RPE ends.



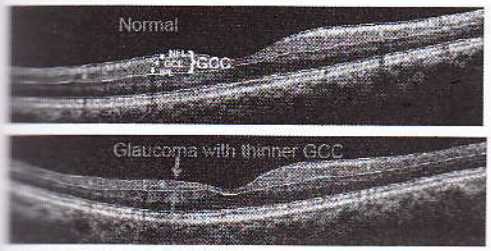
ONH scan

- Disc line: At the terminal ends of choroid, at level of pigment epithelium
- Cup line: 150 micron above disc line
- Nerve head volume: area above disc line
- Rim volume: area above cup line



GANGLION CELL COMPLEX (GCC)

Glaucoma preferentially thins the Ganglion Cell Complex (GCC) which includes the axons, cell bodies, and dendrites of retinal ganglion cells

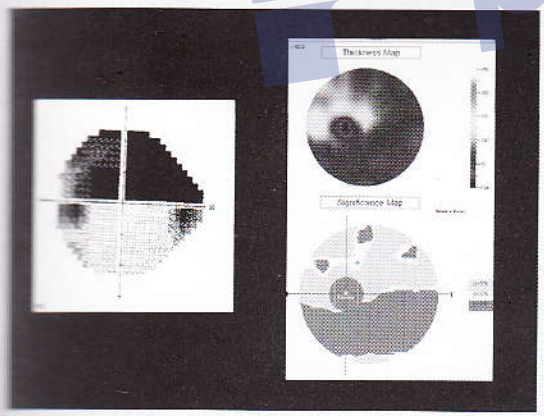


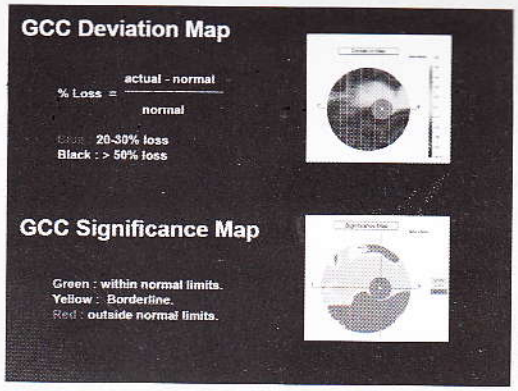
Ishikawa H., et al., *IOVS* 2005
Tan O, et al., *Ophthalmology*, 2008;115:949-56.

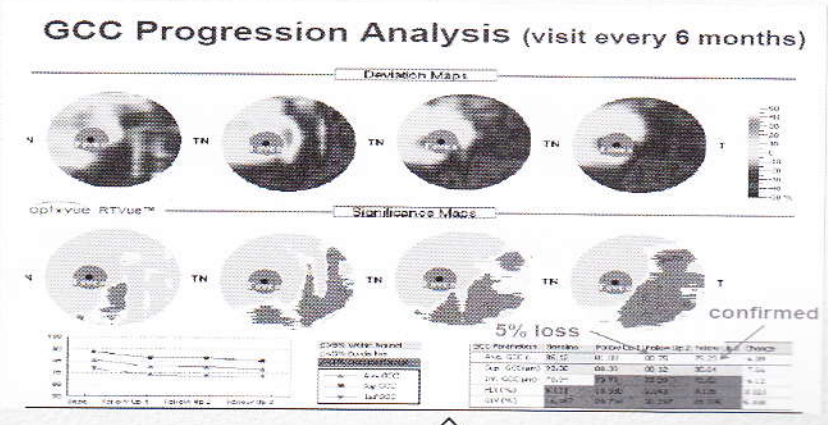
GCC includes the retinal nerve fibre layer (RNFL), the ganglion cell layer (GCL) and the inner plexiform layer (IPL), which becomes thinner in glaucoma. The thickness of GCC in macular region gives an analysis compared to a normative database.

The GCC map is colour coded, where the hot colours (red and yellow) represent thicker areas and cooler colours (blue and green) represent thinner areas.

Inferior GCC thinning corresponding with superior arcuate defect seen on field analysis.





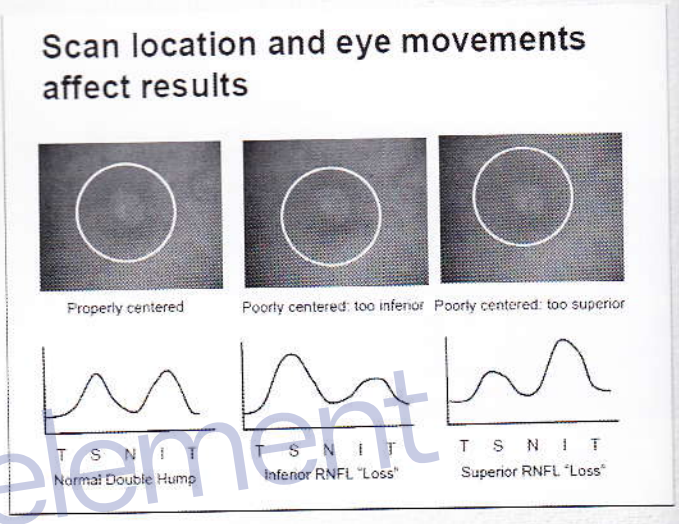


CLINICAL APPLICATIONS OF OCT

- It is a useful tool for baseline and follow up RNFL assessment in disc suspects and ocular hypertensives.
- In glaucoma patients with poor fixation or macular pathology, where field test may not be possible, OCT can help in determining progression.
- OCT has good sensitivity and specificity from differentiating normal from glaucomatous eyes.

LIMITATIONS OF OCT

- Scan location and eye movements affect results.
- Inaccurate detection of disc and RNFL borders due to optical opacities.
- Localised NRR/ optic cup changes can be missed by the interpolation algorithm.



CONCLUSION

Inspite of being a useful adjunct in the diagnosis and follow up of glaucoma patients, it is important to remember that OCT cannot replace a good clinical examination. The clinician must correlate the IOP, ONH and NFL appearance, visual field data with the quantitative data by OCT to detect glaucoma and its progression.

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Optical Coherence Tomography - Principle and Clinical Application

*Ravindra kumar, S.P.Singh, K.J Singh, Santosh Kumar**

Optical coherence tomography (OCT) is an outstanding example of applied physics in medicine. Over the last decade, OCT has become an essential tool in ophthalmology. Optical coherence tomography is a low-coherence, interferometer-based, non-invasive medical imaging modality that can provide noncontact, high-resolution, cross-sectional images of biological tissue.

Generations

Several generations of the commercial version of the OCT device have been developed. The first generation OCT 1 has transverse and axial resolutions of approximately 20µ and 10 to 15µ, respectively. The second generation OCT 2 has similar hardware with an improved user interface. Both generations acquire 100 vertical scans in a standard OCT scan in an acquisition time of approximately 1.2 seconds. The recently released third generation OCT 3 machine has improved resolution of 8 to 10µ and acquires 512 vertical scans. An experimental ultra high resolution OCT system has been developed using Ti: Al2O3 laser that provides an improved axial resolution of 2 to 3µ. This resolution makes it possible to identify otherwise unseen intermediate retinal layers, such as the retinal ganglion cell layer.[2]

Principle & Procedure -

OCT is based on the principle of **"low coherence interferometry"**. The OCT device uses a light source consisting of a near – infrared, low coherence super luminescent diode laser of 850nm wave length. This diode source connects with Michelson interferometer. In low-coherence interferometry, an interferometer is used with a broadband (white) light source. The beam of light from the source is split into two at a half mirror, which creates a measurement and a reference path. The light is then reflected, by the mirror in the reference arm and the sample in the measurement arm, and recombined to create interference before it hits a detector, usually a photodiode, measuring the field strength of the interfering beams of light. Figure 1 below illustrates this setup. Since the spectrum of the light used in low coherence interferometry is broad, interference is only be observed when the lengths of the measurement and reference arm are matched to within the small coherence length of that light, allowing for very good axial resolution.[3]

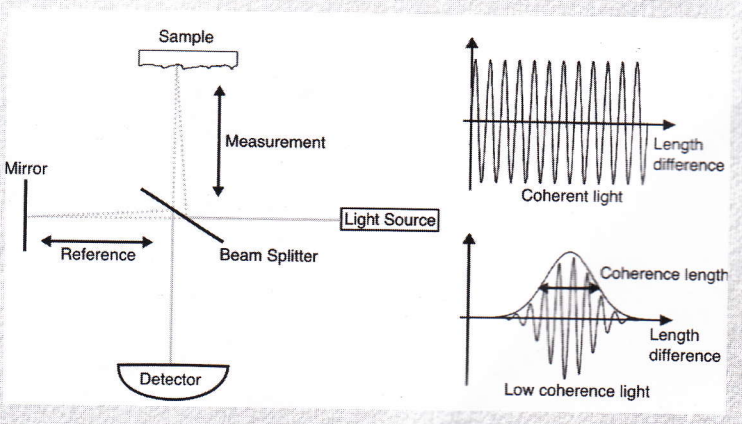

fig.1

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Infrared light from the source is divided at an optical beam splitter into reference beam and measurement beam. The measurement beam is directed onto the patient's eye and is reflected from intraocular structures at different distances. The reflected measurement beam is composed of multiple echoes which include the information about the range or distance and thickness of different intraocular structures. The reference beam is reflected from a reference mirror. The reflected reference beam returns to beam splitter where it combines with reflected measurement beam. Both beams are combined resulting in a phenomenon called **Interference**. The interference is measured by means of a photo sensitive detector. The echo time delay of the measurement and reference beam is compared and then signal is sent, which is processed electronically and used within OCT's internal computer data acquisition bank for analysis and storage.

On Z axis, 1024 points are captured over a 2 mm depth to create a tissue density profile, with resolution of 10µ. On X–Y axis, tissue density profile is repeated up to 512 times. every 5 – 60 microns to generate a cross sectional image. Several data points over 2mm of depth are integrated by the interferometer to construct a tomogram of retinal structures. Image thus produced has an axial resolution of 10µ and a transverse resolution of 20µ. The tomogram is displayed in either gray scale or false color on a high resolution computer screen.

Interpretation of Normal OCT Imaging

The physical basis of imaging depends on the contrast in optical reflectivity between different tissue microstructures. The proportion of incident light which is directly back scattered by a tissue structure defines the reflectivity of that structure. The OCT signal from a tissue layer is a combination of its reflectivity and the absorption and scattering properties of the overlying layers.The intensity of the reflected optical signal is represented on a logarithmic scale with varying degrees of brightness. The maximal optical reflection and back scattering are represented by Red – Yellow colors. Theminimal signals are represented by Blue – Black colors.

OCT Imaging of Normal Retina

The OCT can scan the macula, paripapillary region including retinal nerve fiber layer and optic nerve head region. There are 10 layers of the retina and cross sectional OCT image of the retinal layers are represented like fig2.

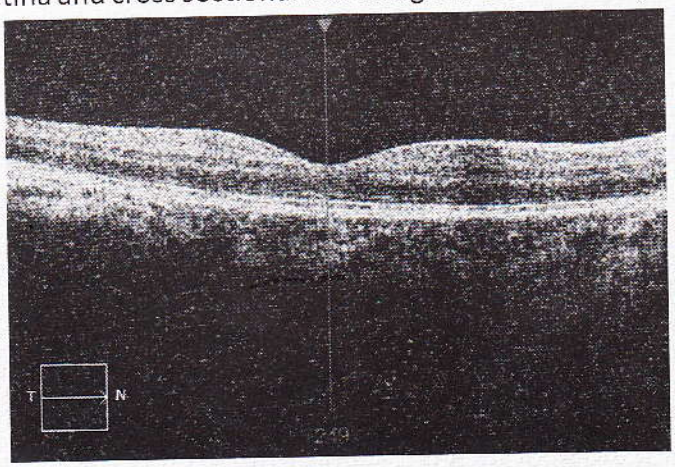


fig.2

The vitreous being non reflective is seen as a dark space. The vitreoretinal interface is demarcated by the

contrast between the non reflective vitreous and the backscattering surface of the retina. The inner margin of retina shows area of bright back scattering, a red layer that corresponding to the nerve fiber layer. A highly reflective red layer delineates the posterior boundary of the retina and corresponds to RPE and choriocapillaries. A dark layer of minimal reflectivity appears just anterior to choriocapillaries layer and represents the outer segment of retinal photoreceptors. The intermediate layers exhibit moderate back scattering. Fovea is identified by the characteristic thinning of the retinal layers.

(1)**The Optic nerve head**: It can be identified on the basis of its contour – central depression of cup and the stalk. OCT is provided with two scan protocols for detailed evaluation of optic nerve head.

Optic disc scan consists of equally placed lines scans 4 mm in length, at 30° intervals, centered on the optic disc.

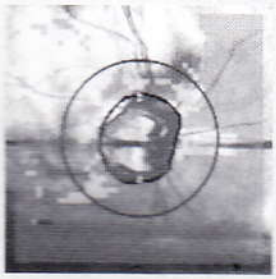


fig.3

The point at which choriocapillaris terminates at lamina cribrosa determines the disc boundaries. Extrapolation of these points to retinal surface defines a line segment which measures disc diameter. The points at which nerve fiber layer terminates determines the Cup. By this scan OCT images can measures the optic nerve head and its parameters like Rim area, Disc diameter, Rim volume disc area, Cup disc ratio and Cup volume. (Fig 4)

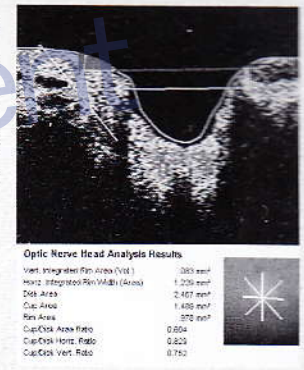


fig.4

(2) **The Retinal Nerve fiber Layer**: OCT measures the thickness of the retinal nerve fiber layer in the peripapillary region. RNFL thickness increases from macula to the optic disc. OCT 3 offers a variety of RNFL thickness measurement and analysis protocols like RNFL thickness Circle scan, Fast circle scan, Concentric 3 rings protocol, RNFL map and Proportional circle. RNFL measurement with a circular scan of 1.34 mm radius, centered on the optic nerve head has been shown to have a maximum reproducibility. Mean RNFL thickness is calculated using age adjusted RNFL thickness average analysis protocol. (Fig. 5)

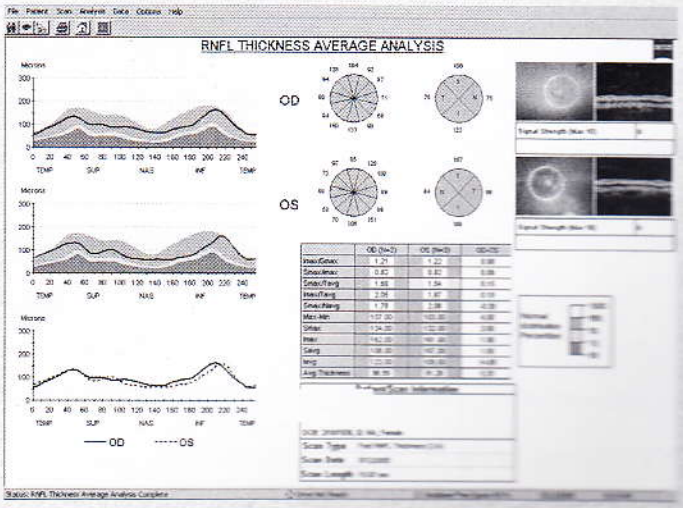


fig.5

(3) Macula : The normal fovea is identified by its characteristic depression of the inner retinal border secondary to the lateral displacement of tissue anterior to Henle's layer. The macular scan is composed from six linear scans in a spoke pattern configuration equally spaced 30º apart. In the color coded macular thickness map blue color represents thinner retina and yellow green, thicker retina. OCT has become part of routine imaging modality with suspected or known macular pathology. (Fig. 6)

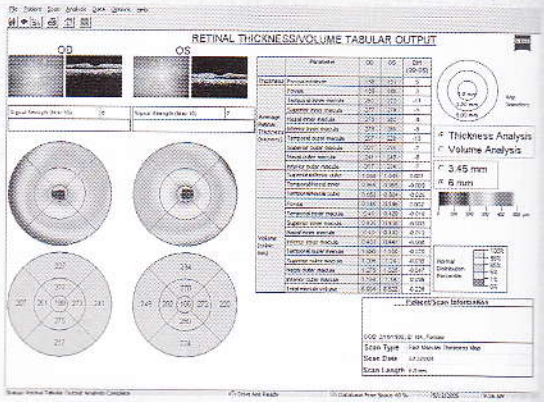


fig.6

Interpretation of Abnormal OCT Imaging

Reflectivity pattern of the scanned images is used to interpret abnormal finding as follows:

Hyperreflectivity: It can be caused by inflammatory infiltrate into any layer of retina, fibrosis like disciform or other scar, hard exudates, and hemorrhages. Thin hemorrhages appear as thin, high reflective bands with little effect on underlying tissue. Thick hemorrhages completely attenuate reflections from underlying structures.

Hyporeflectivity: It can be caused by retinal edema, serous fluid, hypopigmentation of RPE.

Nature of Fluid: It is based on the basis of reflectivity. Serous fluid is either optically clear or hyporeflective, blood has both enhanced reflectivity and increased attenuation of incident light. Exudate typically has intermediate appearance between blood and serous fluid.

Applications

Application of OCT can be summarized as:

(a) Follow up of the clinical course, understanding the pathogenesis of the disease.

(b) For assessing the response to medical, surgical, laser therapy.

(c) For documentation and explaining the prognosis of a particular disease.

OCT in Glaucoma: OCT provides high resolution measurements and cross sectional imaging of the retina, optic disc and RNFL. Recent studies indicate that RNFL thinning to be the first sign of early glaucoma. The main uses are

To evaluate the RNFL for early (pre perimetric) glaucoma detection

To detect, study and follow the macular changes in hypotony induced maculopathy after glaucoma surgery

To evaluate cystoid macular edema after combined cataract and glaucoma surgery.

OCT in Macular diseases: OCT provides reproducible, high resolution, cross-sectional imaging of the retina allows diagnosis, monitoring, and quantitative assessment of macular pathology.

(a) **Macular Hole:** Diagnosis and staging of macular holes by biomicroscopy can be difficult for even the most experienced examiners owing to simulating conditions, such as a lamellar hole, vitreomacular tractional syndromes, and cystoid macular edema with central cyst. It is also useful in monitoring the course of disease, whether spontaneous resolution or progression to a full thickness macular hole, and the response to surgical intervention. (fig.7)

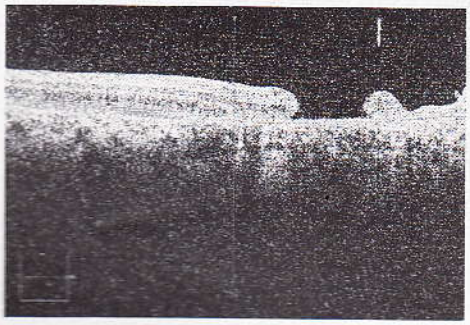
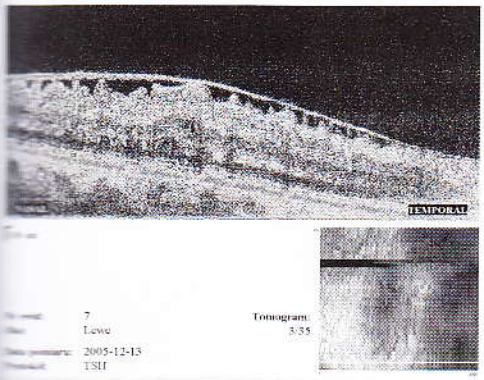


fig.7

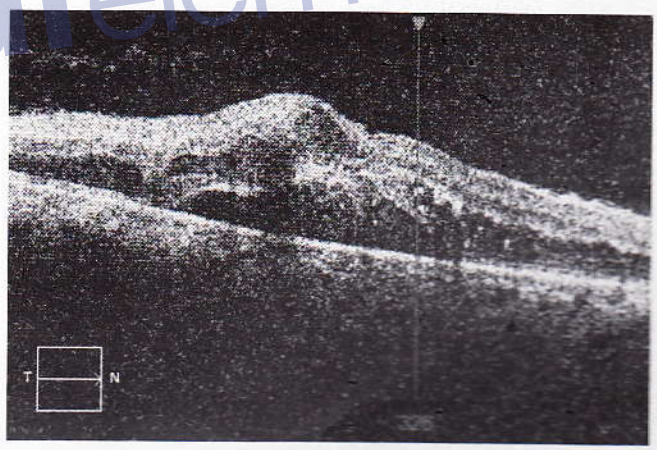


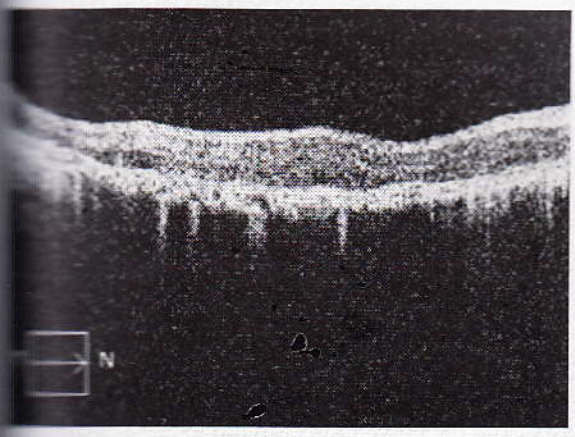
(b) Epiretinal membrane: OCT images confirm the diagnosis of faint, diaphanous membranes and provide a cross sectional assessment of factors contributing to vision loss. It provides information about membrane thickness, cystic changes and its adherence to retinal surface.

fig.8

(d) **Cystoid macular edema:** Although cystoid changes are visible by slit lamp biomicroscopy and fluorescein angiography, only OCT can quantitatively assess retinal thickness and demonstrate any associated RPE structural anomalies beneath the edematous retina, which can be obscured by leakage on angiography. Measurements of retinal thickness by OCT correlate more strongly with visual acuity than the presence of leakage on angiography.

fig.9





(e) Diabetic retinopathy: Clinically Significant Macular Edema is the leading cause of treatable vision loss in patients with diabetic retinopathy. OCT may be more sensitive than biomicroscopy in detecting macular edema. OCT almost gives the in vivo histopathology of the retinal layers that helps in a better understanding of the pathogenesis of the disease process.It is a useful tool in monitoring response to an intervention in CSME.

fig.10

(g) Central Serous Chorioretinopathy: It is effective in quantifying the amount of serous fluid accumulation in CSR. It is also used to monitor the course of CSR. It exhibit well defined reflection at fluid RPE interface , whereas elevation of RPE reflection above an optically clear space occurs when the pigment epithelium is detached.

fig. 11

Limitations

Presence of conditions like asteroid hyalosis, cloudy media, high astigmatism, decentred lens implant and dense cataracts can compromise quality of the tomograms.

Limited transverse sampling

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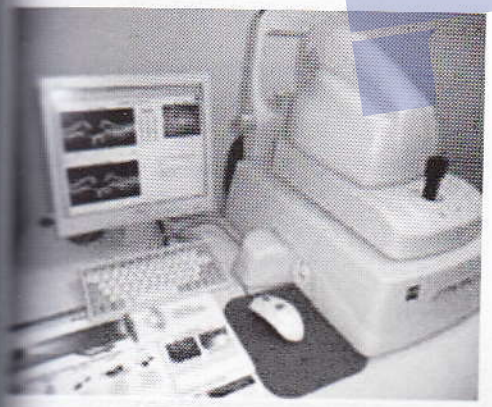
Optical Coherence Tomography: Basics & Applied Aspects

Dr.Sujit Deshmukh*, Prof. Shrikant*, Dr. Shraddha Pandey*, Dr. Anushree Agrawal**

What is OCT?

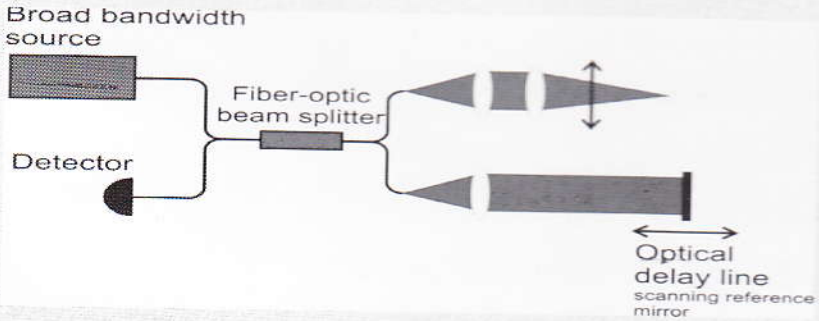
- It is Live histopathology of retinal tissue.
- It is Diagnostic imaging technique that examines living tissue non-invasively. It is based on a complex analysis of the reflection of low coherence radiation from the tissue under examination.
- It gives Real time cross sectional analysis
- OCT allows both qualitative and quantitative analysis of the retina
- Qualitative analysis includes description by location, a description of form and structure, identification of anomalous structures, and observation of the reflective qualities of the retina.
- Quantitative analysis involves measurements of the retina, specifically retinal thickness and volume, and nerve fiber layer thickness. This is possible because the OCT software is able to identify and "trace" two key layers of the retina, the NFL and RPE.

The OCT system comprises



Fundus viewing unit.
interferometric unit.
Computer display.
Control panel.
Color inkjet printer.

OCT principle



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**Resident (DNB), Arvind Eye Institute, Pondicherry

Evolution

How does it work?

128 to 768 axial samples (A-scans) in a single "scan pass"
Each A-scan has 1024 data points and is 2mm long (deep).

Resolution

When all of the A-scans are combined into one image, the image has a resolving power of about 10 microns vertically and 20 microns horizontally ,spectral domain has a resolution of 5 microns ,an edge over time domain.

Compare that to the resolution of a good ophthalmic ultrasound at 100 microns

Optical coherence tomography-The process is similar to that of ultrasonography, except that light is used instead of sound waves.

OCT

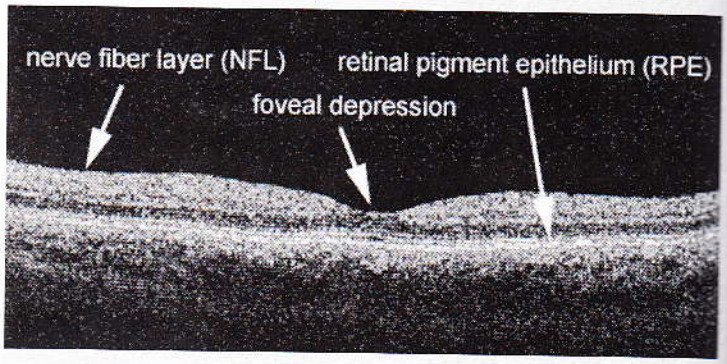
USG

Retinal Anatomy Compared to OCT

The vitreous is the black space on the top of the image

We can identify the fovea by the normal depression

The nerve fiber layer (NFL) and the retinal pigment epithelium (RPE) are easily identifiable layers as they are more highly reflective than the other layers of the retina



This higher reflectivity is represented by the "hotter" colors (red, yellow, orange, white) in the false color representation of the OCT .

The middle layers of the retina, between the NFL and RPE, are much less easily identifiable in the scan.

What makes a good OCT scan?

A good quality OCT scan has good reflectivity from edge to edge.

The "hotter" colors (orange, red, white, yellow) are maximized

Generally, the retina should be in the lower portion of the scan window so that the vitreous can be images as well.

Scanning Tips

Refer to other images of the pathology, e.g. color photos and FA.

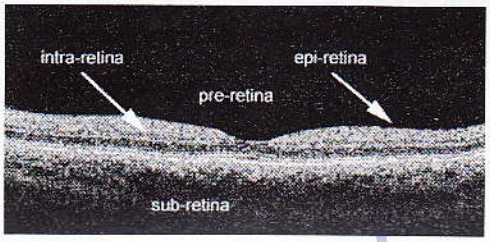
Review past OCT exams and repeat scan types used before.

Dilate the eye well??????

The patient must keep the forehead against the bar and the chin in the chinrest, with teeth together. Use the marker on the headrest to align the patient vertically. The outer canthus should be even with the lineMinimize patient fatigue by keeping scan time to a minimum. Never scan an eye for more than 10 minutes (FDA regulation).

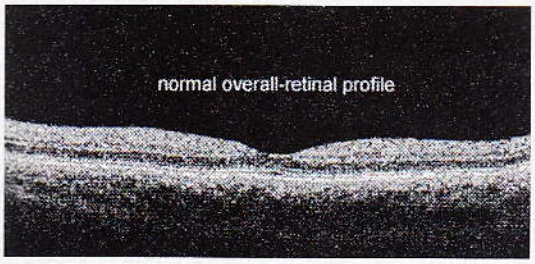
Move the instrument on the x and y axis (using the joystick) to work around opacities

For purposes of analysis, the OCT image of the retina can be subdivided vertically into four regions
the pre-retina
the epi-retina
the intra-retina
the sub-retina

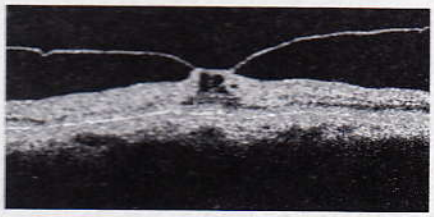


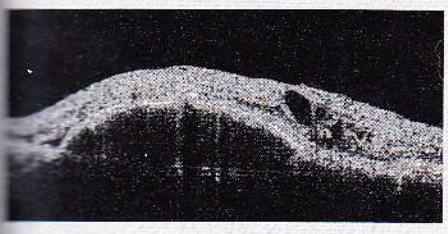
Anomalous structures

- pre-retinal membrane
- epi-retinal membrane
- vitreo-retinal strands
- vitreo-retinal traction
- pre-retinal neovascular membrane
- pre-papillary neovascular membrane



Apre-retinal membrane with traction on the fovea



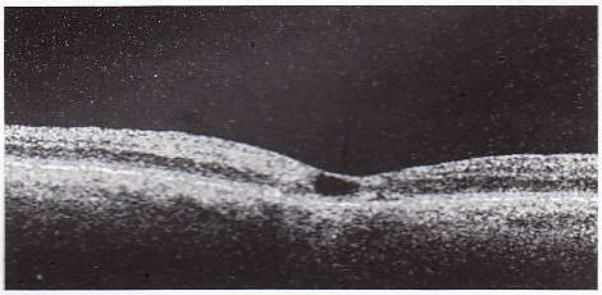


a pigment epithelial detachment is causing the convexity

Deformations in the foveal profile

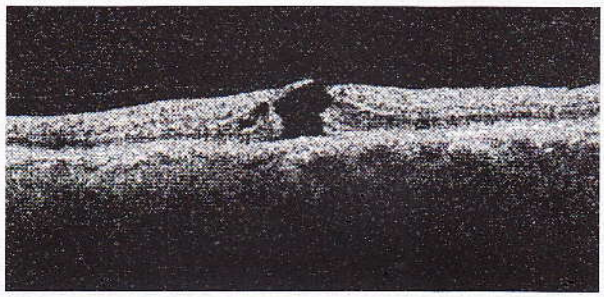
- macular pucker
- macular pseudo-hole
- macular lamellar hole
- macular cyst
- macular hole, stage 1 (no depression, cyst present)
- macular hole, stage 2 (partial rupture of retina, increased thickness)
- macular hole, stage 3 (hole extends to RPE, increased thickness, some fluid)
- macular hole, stage 4 (complete hole, edema at margins, complete PVD)

Macular cyst

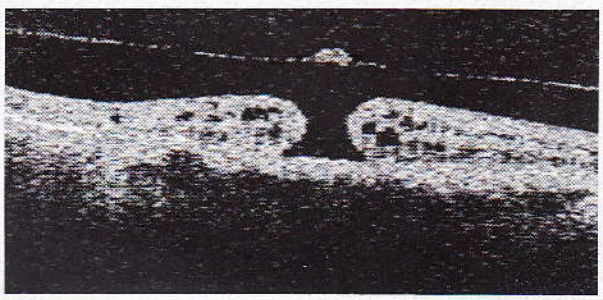


Macular hole, stage 2

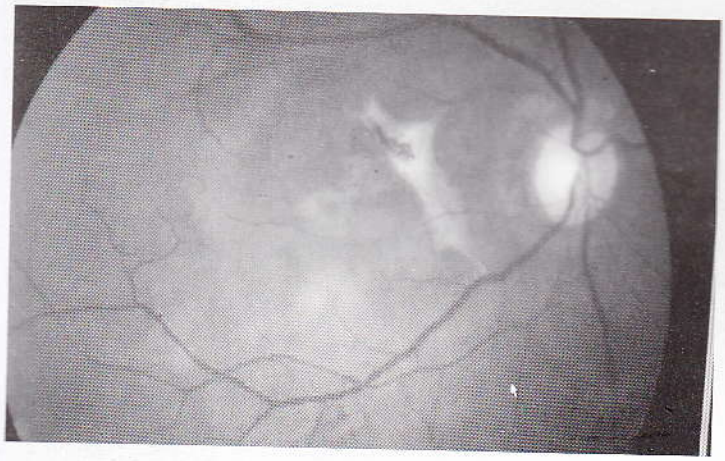
Macular hole, stage 3



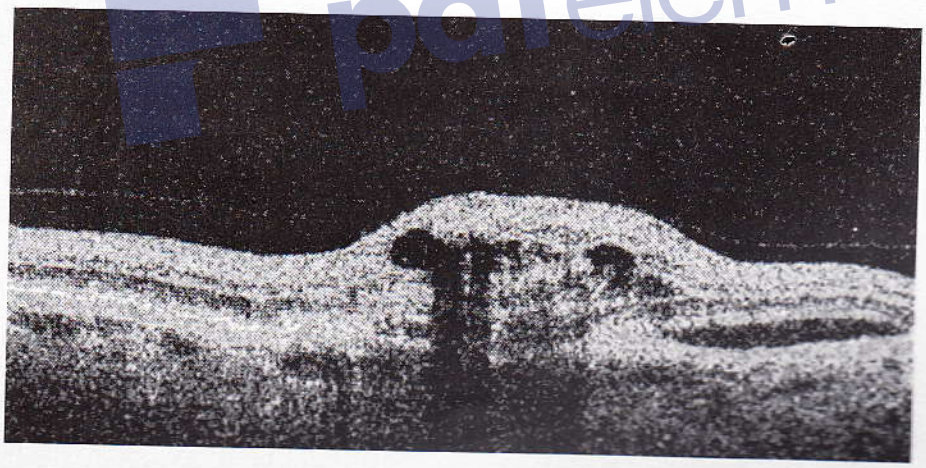
Macular hole, stage 4, operculum suspended by the hyaloid membrane



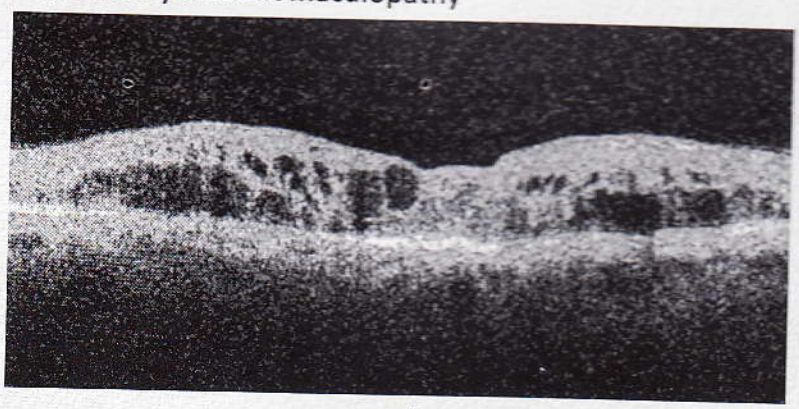
CAN YOU SEE ANY MACULAR HOLE???WAIT....



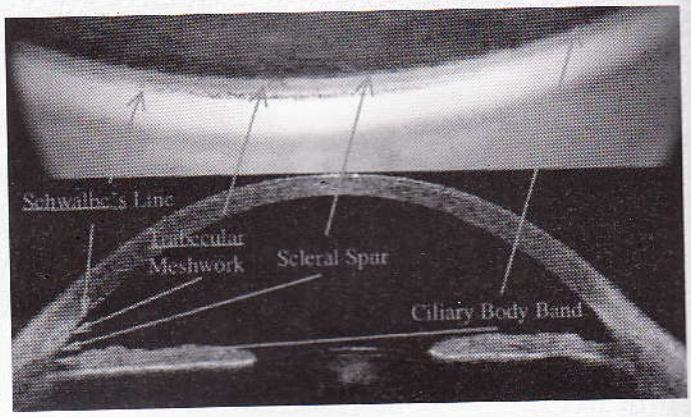
Choroidal neovascular membrane



Cystoid macular edema cause by diabetic maculopathy



Anterior segment optical coherence tomography (OCT)



High-speed anterior segment optical coherence tomography (OCT) offers a non- contact method for high resolution cross- sectional and three-dimensional imaging of the cornea and the anterior segment of the eye.

Anterior Segment Optical Coherence Tomography enhances surgical planning and postoperative care for a variety of anterior segment applications by expertly explaining how abnormalities in the anterior chamber angle, cornea, iris, and lens can be identified and evaluated

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Nanoparticulate Drug Delivery: A Newer Drug Delivery Concept

Prof. Shri Kant*, Dr. Narendra Kumar Regar**, Dr. Anushri Agrawal***, Dr. Sanjay Singh****

Abstract

Aim: To compare change in intravitreal drug concentration with time for pristine (plain) and nanoparticulate drug.

Method: Pristine drug solution & liposome nano-particulate prepared. Pristine & Nano particulate administered by topical, subtenon and intravitreally. Vitreous sample were collected at different interval & drug concentration was measured by High Performance Liquid Chromatography (HPLC).

Results: The concentration of drug in vitreous was more in intravitreal group as compared to subtenon group at different time interval. Nano particulate drug was present for long duration in vitreous as compared to pristine.

Conclusion: Nano particulate drug prolong the drug action and can reduce number of intravitreal injections as compared to pristine.

Introduction

Eyeball is divided as anterior and posterior segments. Drug delivery to the eye can vary in case from the simple topical eye drop, which rapidly penetrates to the anterior chamber, to the complicated engineering skills required to develop intravitreal implants. The anterior segment and the posterior segment are two entirely different ocular regions and the challenges faced in delivering therapeutic drugs to each of these areas are unique.

Drug delivery to eye can be by topical, subconjunctival, subtenon, periocular, intravitreal and systemic routes. To reach the drug in posterior segment in maximum concentration we have to inject drug by intravitreal injections. Many times intravitreal injections have to be repeated like in age related macular degenerations, diabetic macular edema...etc.

To prevent multiple intravitreal injection related complications either we may decrease the frequency of intravitreal injections or we may change the route of administering the drug.

Nanoparticle are very small size particle the formulations which can incorporate drug inside it or over its surface. Nano particulate drug provide the slow drug release so it prolong the drug action and that may decrease the frequency of intravitreal injections.

Aim of study

To compare change in intravitreal drug concentration with time for pristine(plain) and nanoparticulate drug after administering dexametha-sone and it's liposomal formulation by following routes:

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- Topical
- Subtenon
- Intravitreal

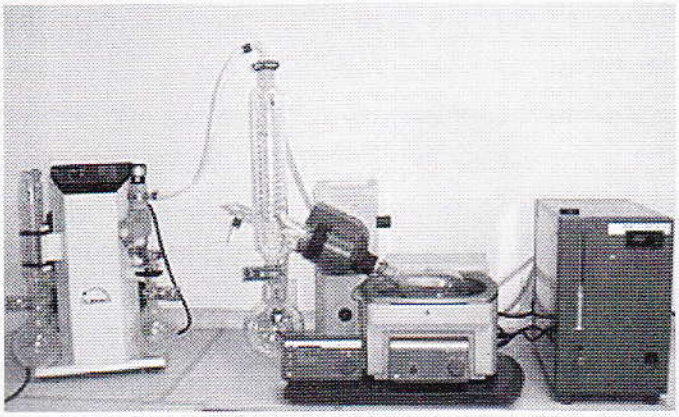
Material and method:

- Material:
  - Dexamethasone sodium phosphate.
  - Drugs for liposomal nano formulations.
  - HPLC machine.
  - New Zealander Rabbits
- **Nanoparticle preparation :**

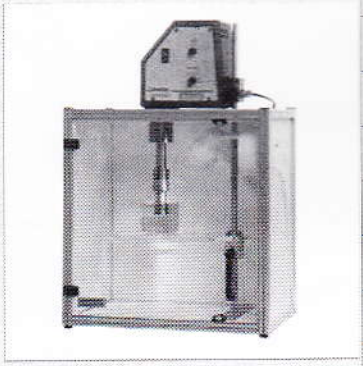
After weighting following contents were mixed in a round bottle flask.

Content name	Amount
Phosphatidylcholine	70mg
Cholesterol	18mg
Tocopherol polyethylene glycol (Vitamin E TPGS)	14mg
Chloroform	2ml
Methanol	4ml

Organic solvents were removed completely by a rotary flash evaporator (IKA® RV 10) above the lipid transition temperature (51 °C) at 75 rpm for 3 h to obtain a uniform thin lipid film on the wall of the flask. 10 ml distilled water was added to make it 1 mg/ml sample and mixed by the same.



Small unilamellar vesicles (SUV) were obtained by subjecting the dispersion to probe sonication (Ultrasonic Processor, UP200S, Hielscher Ultrasound Technology) for 1, 3, 5 min using 6 mm ultrasonic probe at 60 % amplitude and 0.5 cycles per second.



Sample	Dexamethasone (in mg)	Probe sonification time (minutes)
A1	10	1
A2	10	3
A3	10	5
B1	20	1
B2	20	3
B3	20	5
C1	30	1

- **Characterization of nanoparticles:**

Nano formulation was subjected to **particle size and polydispersity index analysis** using Photon Correlation Spectroscopy (PCS) Delsa Nano C (Beckman Coulter Counter, USA) particle Size analyzer.

Zeta potential of nano suspension was measured using a Delsa Nano C (Beckman Coulter, conter, USA).

The **per cent encapsulation** of DEX in DEX-Lipo was determined by direct method using Ultra Violet Spectroscopy.

- **In vitro release:**

In – vitro drug release study of selected batches were determined in distilled water as a dissolution medium using dialysis bag diffusion method.

Sample was analyzed using Ultra violet spectroscopy at 260 nm.

- **In vivo administration and vitreous sampling**

After taking institutional animal ethical clearance the procedure was performed on rabbit eyes.

- Groups: Total 24 rabbits were included in this study.
  - Species/Common name :New Zealander Rabbits
  - Weight : 2-2.5 KG
  - Gender : Male
  - Total Number of rabbits : 24
  - Number of day rabbit housed : 30 days.

Total number of groups were 4 and in each group 6 rabbits were included.

Group A : Rabbits in this group were applied with 100µl of topical pristine dexamethasone.

Group B : Rabbits in this group were applied with 100µl of subtenon liposomal nano formulation of dexamethasone.

Group C : Rabbits in this group were applied with 100µl of subtenon pristine dexamethasone.

Group D : Rabbits in this group were applied with 100µl of subtenon liposomal nano formulation of dexamethasone.

Group E : Rabbits in this group were applied with 100µl of intra vitreal pristine dexamethasone.

Group F : Rabbits in this group were applied with 100µl of intra vitreal liposomal nano formulation of dexamethasone.

100µl of vitreous humor was aspirated from all rabbits at day1st, day3rd, day7th, day14th and day 21st from each study included eye.

B. Anaesthesia

C. Drug administration

- We instilled few drops of standard povidine iodine solution in eye and washed with balanced salt solution.
- After this in each group according to the study we administered the drug in eyes by insulin syringe.

D. Vitreous sample taking:

- Anaesthesia given first as mentioned earlier .
- With proper technique, aspiration of vitreous done.
- Vitreous samples were collected through pars plana approach at predetermined time on day 1st, 3rd,7th,14th and 21st after dose under proper anaesthesia.

Sample analysis by HPLC

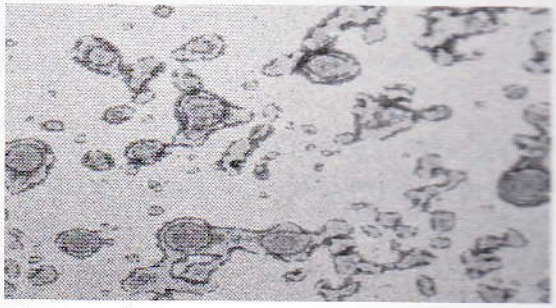
The collected Vitreous samples were stored at −20 ºC until the analysis. The Vitreous samples were with 100 of mobile phase and was injected in to HPLC for analysis

Observation and Results:

- **Characterization of nanoparticles:**

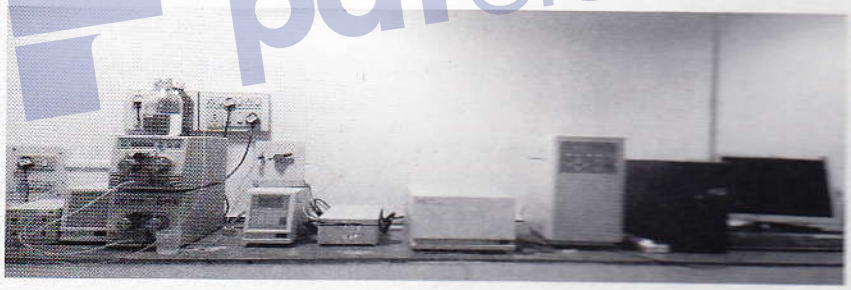
Formulation	Composition Dexamethasone (In mg)	Ultra Sonification time(in minutes)	Size(in nm)	Zeta potential	% Entrapment Efficiency
1	10	1	83.8	-9.74	74.04941
2	10	3	76.6	-5.91	65.74901
3	10	5	58.9	-6.95	62.7253
4	20	1	128.4	-11.11	50.45257
5	20	3	75.6	-10.84	44.64229
6	20	5	71	-6.83	17.48814

Liposomal nano formulation TEM (Transmission Electron Microscopy) image:



Vitreous sample analysis: (done by HPLC)

After the injection as mentioned earlier, vitreous sample was withdrawn on day 1st, 3rd, 7th, 14th and 21st and analyzed by the help of HPLC.



Results of Vitreous Sample Analysis (µl/ml)

Time in days	DEX-Lipo intravitreal	Pristine DEX intravitreal	DEX-Lipo subtenon	Pristine DEX subtenon	DEX-Lipo Topical	Pristine DEX Topical
1	30	27	13	9	9	5
3	23	13	10	4	7	3
7	15	5	7	0	3	0
14	4	0	0	0	0	0
21	0	0	0	0	0	0

- Overall the drug concentration was maximum for intravitreal injections at the time of injections on day 1.

- Subtenon administered drug also reached to the posterior segment but its concentration was less as compared to intravitreal injections.
- With time the pristine drug clearance was faster than the liposomal nano formulations.

Discussion:

- In our study we found that the drug concentration was more for intravitreal injections as compared to subtenon injections.
- The eyes where we injected nano particulate dexamethasone drug, concentration was more as compared to pristine drug and for longer duration
- Our study show that we can inject the drug by the subtenon route also for posterior segment diseases but the bioavailability is less in vitreous so we have to inject the more concentrated drug solution.
- These days endophthalmitis is most highlighted issue these days realated to intravitreal injections so this mode of drug delivery will decrease the number of injections and it may replace completely the requirement of intravitreal injections.

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Nanomedicine: Future of Corneal diseases

- Ansari NN*, Akhtar N#, Ahmad S^, Waris A&, Jahan S@

Abstract: Nanomedicine tools have been explored to successfully treat various corneal diseases for the restoration of normal vision. The barrier properties of the ocular surface can successfully be overcome through nanodelivery, thereby, enhancing the permeability and pharmacological properties of the drugs. Also, transporting genes into desired corneal cells to interfere with the pathologic process helps cater the disease at a molecular level. With the nanomedicine tools being explored, a targeted approach to treat will definitely improve the corneal disease outcome.

Keywords: corneal diseases; infection; nanoparticles; nanomedicine; nanomaterials; nanodelivery

1. INTRODUCTION:

Nanotechnology has been used in almost every field of medical science including: imaging, diagnosis, biosensing, drug delivery. Nanomedicine is the application of nanotechnology in medicine. It is used to study the functioning of the living cells at the molecular level and nanomaterials to develop newer drug delivery modalities for the treatment of human diseases.

2. NANOMEDICINE TECHNIQUES FOR CORNEAL DISEASES:

2.1 Nanoparticles: Nanoparticles ranging from 1 to 100 nm are widely useful for the nanomedicine. Nanoparticles are broadly classified into: **Metallic nanoparticles** include gold (Au-NPs), sliver (Ag-NPs) and platinum (Pt-NPs) [1]. The **polymeric nanoparticles** are usually prepared from polyethyleneimine (PEI) and have been reported to deliver transgene into human corneal epithelial cells and endothelial cells *in vitro* [2,3]. **Hybrid nanoparticles** are the most widely used metallic nanoparticles conjugated with polymeric compounds and can bind large therapeutic genes, for which they are being explored in corneal nanomedicine development [4]. **Non-metallic nanoparticles** such as calcium phosphate nanoparticles (CaP-NPs) functionalized with pcDNA3-EGFP (CaP/DNA/CaP/PEI0.5) have been shown to be an effective tool for transfection in cells.

2.2 Nanofiber scaffolds: They are self-assembling peptides that provide framework and optimal conditions for the **cells and tissue regeneration**. One such example is the cell-sheet engineering approach **to culture corneal endothelial cells under optimal conditions [5].**

2.3 Nanodevices: include the **nanospheres** which contain ciprofloxacin coated on to contact lenses and helps prevent Staphylococcus aureus and Pseudomonas aeruginosa infection [6].

2.4 Nanoadhesives : These are **biomimetic materials** used in tissue engineering to **heal, seal and repair** ocular tissues[7].

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2.5 Nanosponges: provide an **excellent solubility and corneal penetration for drugs** such as dexamethasone [8].

2.6 Single-/multiple-walled Carbon nanotubes (CNTs): The high surface areas and reactivity of the surfaces of CNTs provide **both non-covalent and covalent functionalization of the drugs and fluorescence probes**, thus expanding its potential as a drug carrier as well as for diagnostic purposes [9].

2.6 Nanodelivery: Nanodelivery methods can be broadly classified based on drug packaging as: polymeric nanoparticle, liposomes, dendrimers, nanoemulsions. **Polymeric nanoparticles** (PNs) are colloidal carriers with diameters ranging from 10 to 1000 nm and are used as **topical ocular drug delivery** systems [10,11], as eyedrops which make them ideal candidates for the treatment of corneal diseases. **Liposomes** are composed of one or more phospholipid bilayer membranes encapsulating a volume of aqueous medium. They deliver the active drugs to the target cells in addition to the wounded sites. **Dendrimers** are typically 1–10 nm in size [12-16], packaged with antimicrobial agents have been found to be effective against gram-negative and gram-positive pathogens often associated with lens-related bacterial keratitis [15]. **Polymeric micelles** (PMs) are self-assembled nanoparticles, ideally suited for ocular drug delivery[16,17]. **Nanoemulsions** (NEs) are nanometer droplets made by **the heterogeneous dispersions** of two immiscible liquids (oil-in-water or water-in-oil) to provide a transparent ocular drug delivery system [18]. The first FDA approval was awarded to ophthalmic nanoemulsion of Restasis (Allergan Inc., Irvine, CA, USA) for chronic dry eye conditions. In 2008, the FDA approved another similar nanoemulsion formulated drug called Durezol (Alcon Laboratories, Fort Worth, TX, USA) for the treatment of ocular inflammation. Similarly, two other products, a drug-free nanoemulsion called Lipimix (Tubilux Pharma, Italy) and Soothe XP Emollient (Bausch and Lomb, Rochester, NY, USA), have been used for the restoration of the lipid layer of the lacrimal fluid [19].

3. CONCLUSION:

The future of corneal nanomedicine greatly depends on **the innovative design and smart packaging of nanoparticles better suited for sustained drug-delivery in the eye.** It will revolutionize the way **we diagnose, monitor and treat corneal diseases** by **eliminating the need for repeated applications to achieve sustained drug effect**. The idea of **"Theragonostics"** [20] where nanoparticles deliver therapy and provide disease monitoring should be looked forward to [21].

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Vitamin K Deficiency Bleeding Masquerading as Capillary Hemangioma: Case report

Naheed Akhtar*, Shairin Jahan**Abdul Waris*,Nada Nadeem Ansari*, S.A.R. Rizvi***

Abstract:

Capillary hemangiomas are common primary benign tumors of the orbit in children but very rarely bleeding disorders may mimic capillary hemangioma. We present a case of bleeding disorder in a two and a half month old female of Indian origin masquerading as capillary hemangioma. The rarity of such a presentation led us to report the case.

Key Words:

Capillary hemangioma, benign tumors, Vitamin K deficiency

Introduction:

Capillary hemangioma, also known as a benign hemangioendothelioma, is the most common benign periorbital vascular tumor of childhood. It is present in 1-2% of all births. There is a 3:1 ratio of females to males. The incidence of orbit and eyelid hemangiomas is 1/10 that of systemic hemangiomas, which occurs in 10% of all children by 1 year of age.[1]

A periorbital hemangioma may appear as a superficial cutaneous lesion, subcutaneous lesion, deep orbital tumor, or combination of these types. Approximately one-third of lesions are visible at birth, with the remainder manifest by 6months of age. There is typically an initial rapid growth phase within 6 months of diagnosis, followed by a period of stabilization and subsequent involution over several years. It is estimated that approximately 75% regress to some extent by the time the child reaches 7 years of age.

This is in contrast to another known group of childhood vascular anomalies, vascular malformations. Vascular malformations, such as lymphangiomas and arteriovenous malformations, are present at birth and are characterized by very slow growth with persistence into adult life.[2,3]

Case Report:

A two and a half month old female infant was brought to the Emergency Department of Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh on 2nd May,2016 with the chief complaints of fever for the last 7 days, nodular bluish swelling over parietal area of scalp, sternum and back for the last 5 days, bluish discoloration and progressive swelling over right upper eyelid for 1 day.There was also history of nasal bleed 7 days back. There was no history of similar complaints or any spontaneous bleeding episode in the past or in any of the family members.

On examination:

Vitals and systemic examination were within normal limits.

Anthropometry:- Weight- 4 kg, Height- 56 cm, Head circumference- 36 cm, Chest circumference- 35 cm, Mid upper arm circumference- 11 cm.

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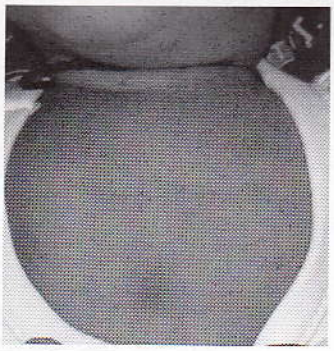
Indices:- W/A- 78%, H/A- 98% and W/H- 83%.

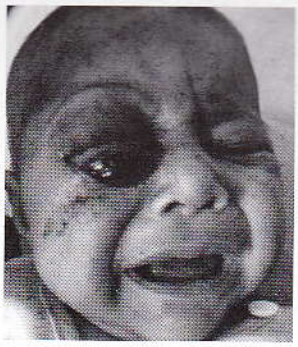
The infant was partially immunized for her age and was exclusively breastfed.

Ocular examination:

Right Eye- Swelling and ecchymosis of upper eyelid was present along with bulging out of upper palpebral conjunctiva due to sub-conjunctival hemorrhage. Cornea was clear and pupil was slightly sluggish reacting. Red glow was faint.

LE- Anterior segment was within normal limits, pupil was of normal size and normally reacting. Red glow was present.





On the basis of history and examination, differential diagnosis of capillary hemangioma and lymphangioma were made and patient was prescribed beta-blocker for local application.

The patient was advised bleeding profile, contrast enhanced MRI brain and orbits.

Haemogram- Within normal limits

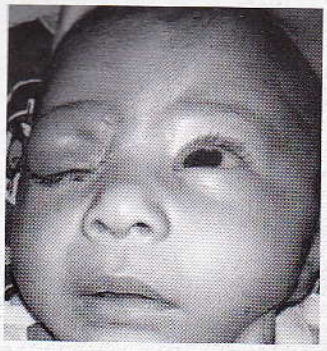
Bleeding profile-

PT-INR :- 6.1, BT :- 2 min 40 seconds, CT :- 2 min 50 seconds

MRI findings revealed-

- A peripherally enhancing altered signal intensity lesion in pre-septal space of right orbit with small loculated hematoma in intraorbitalextraconal component on superior aspect.
- Patchy bleeding foci in B/L deep frontal lobes, occipital horn of left lateral ventricle and 4th ventricle.

On the basis of bleeding profile and MRI report, diagnosis of bleeding disorder due to vitamin K deficiency was made and patient was infused 1 unit of Fresh Frozen Plasma and 2mg of vitamin K was given intravenously for 5 days.



After 5 shots of vitamin K, PT-INR was 1.283 and the right upper eyelid resolved slowly.

Discussion:

Prevention of vitamin K deficiency bleeding (VKDB) with intramuscular vitamin K is of primary importance in the medical care of neonates. A single dose of intramuscular vitamin K after birth effectively prevents classic vitamin K deficiency bleeding. Conversely, oral vitamin K prophylaxis improves coagulation test results at 1-7 days, but vitamin K administered by this route has not been tested in randomized trials for its efficacy in preventing either classic or late vitamin K deficiency bleeding.[4,5]

Immediately administer vitamin K subcutaneously (hold pressure on the site) for any infant in whom vitamin K deficiency bleeding is suspected or who has serious, unexplained neonatal bleeding.

Note the following:

- IM administration can result in a hematoma because of the coagulopathy.
- Intravenous (IV) administration of vitamin K has been associated with anaphylactoid like reactions.
- Fresh frozen plasma may be considered for moderate-to-severe bleeding.
- Life-threatening bleeding may also be treated with prothrombin complex concentrates (PCC).
- Because the bleeding in classic vitamin K deficiency bleeding usually is not life threatening, a single dose of parenteral vitamin K is sufficient to stop the bleeding and return prothrombin time (PT) values to the reference range.

Infants with evidence of intracranial bleeding may require transfer to a level III nursery after stabilization with subcutaneous vitamin K and other aspects of supportive care.

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Surgical Management of Keratoglobus: A Case Report

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Abstract

Keratoglobus is a rare noninflammatory corneal thinning disorder characterised by generalised thinning and globular protrusion of the cornea. Both congenital and acquired forms have been shown to occur, and may be associated with various other ocular and systemic syndromes including the connective tissue disorders. Managing this condition may be challenging due to lack of definitive procedures.

Introduction

Keratoglobus is the rare form of corneal ectasia group of disorders characterised by corneal thinning, protrusion, and scarring. Though primarily considered a congenital disorder[1,2], in recent years, there have been reports of acquired forms of keratoglobus. The congenital form of the disorder is always bilateral, exact genetics has not been described. It is assumed to be autosomal recessive, as described by Poliquenet al.[3]

Acquired form has been seen associated with disorders of the connective tissue such as Ehlers–Danlos syndrome, Marfan syndrome, and osteogenesis imperfecta and others such as Leber's congenital amaurosis, vernal keratoconjunctivitis, chronic marginal blepharitis, idiopathic orbital inflammation and dysthyroid eye disease[4].

Clinical findings include globular protrusion of the cornea associated with diffuse thinning from limbus to limbus. The thinning is commonly maximal at the periphery and may be up to one-fifth the normal corneal thickness. Vogt striae and Fleischer's rings are not associated with keratoglobus.[5,6] As a result of the thinning and protrusion, there is highmyopia with irregular astigmatism, which is the main cause of poor vision in these patients, and is difficult to treat with refractive correction. The diagnosis of keratoglobus is essentially a clinical one owing to the characteristic clinical findings, corneal pachymetry may supplement in cases with clinical dilemma.

Case report

52 year old male farmer presented to us with complaints of both eye gradual progressive, painless diminution of vision for near and distance for last 20 years. No significant past or family history.

Unaided visual acuity in right eye was counting finger at 1 meter which improved to 20/50 with pin hole. Retinoscopy finding was -12.00 D sph / -10.00 D cyl @140°. The vision in left eye was 20/60 improving to 20/30 with pinhole. Retinoscopy finding was -2.50 D sph / -5.00 D cyl @40°. Near vision was N10 with +1.25 D in both eyes.

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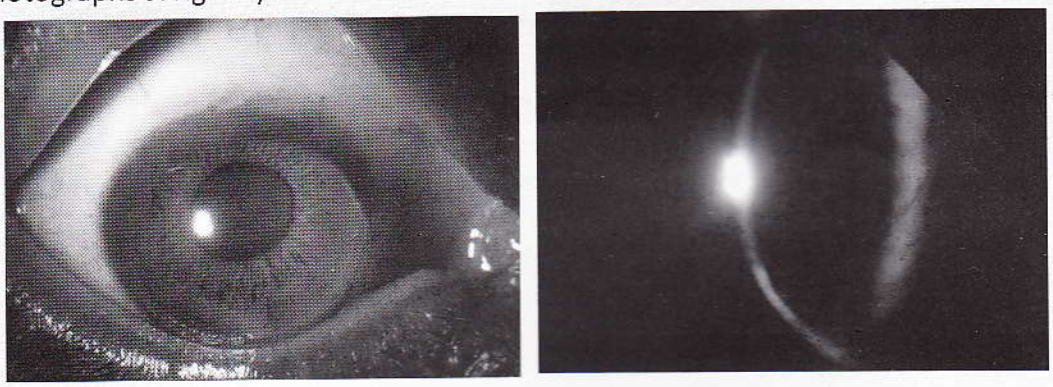
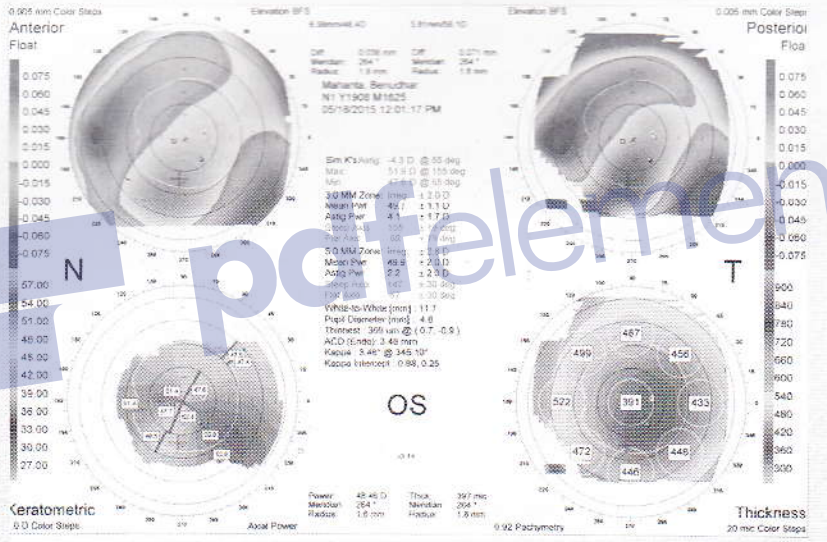
*** Director, Chandra Eye Care, Lanka, Varanasi

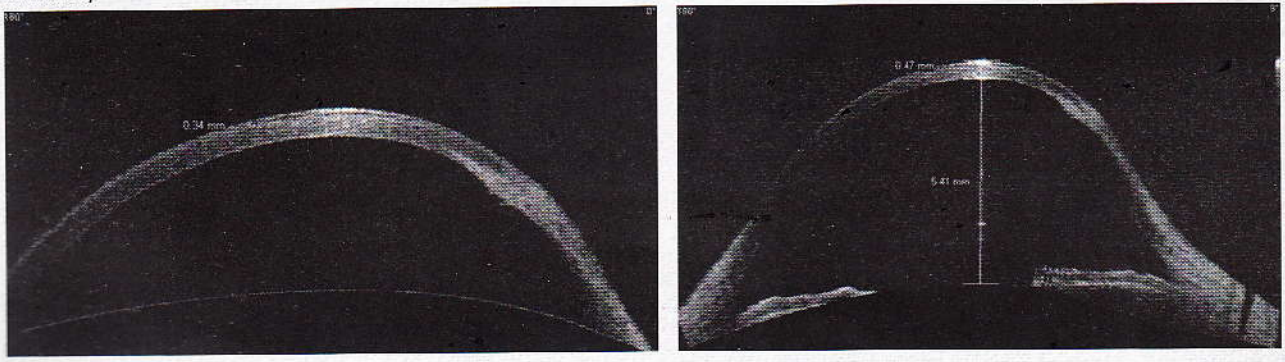
Slit lamp examination of right eye shows diffuse globular corneal thinning with generalized ectasia and inferior scarring as shown in the picture below. Left eye also showed globular protrusion. Rest of the ocular findings were within normal limit.

Clinical photographs of right eye





Orbscan of left eye showing generalized steepening with thinned out cornea (Right eye scan could not be obtained)



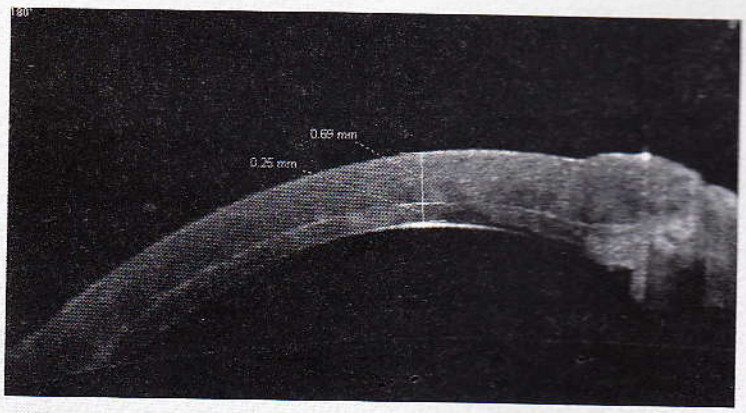
Anterior segment OCT photographs of right eye showing generalized thinning and globular protrusionof cornea

Based on following, clinical diagnosis of both eye keratoglobus was made.

Our plan of management in this patient was lamellar keratoplasty in form of tuck-inlamellar keratoplasty (TILK)[7]. A Hessburg-Baron vacuum trephine of 9.5 mm was centered and used to make an initial partial thickness groove of approximately 200 microns and anterior partial thickness lamellar dissection was done. 360 degree stromal pocket was created in peripheral cornea using a crescent knife. A full-thickness graft of10.0 mm diameter was punched, and the donor endothelium was scraped off. The peripheral part of the donorwas thinned from the posterior aspect to create a bevel-shapedflange in the periphery to complement the pocket created in thehost. The inner aspect of the donor button rim was held with aPierse Hoskins forceps and this was trimmed with the help of a fine-curved Vannas scissors to create a bevel or flange of approximately 1 mm width all around the rim. This button was placed overthe host bed. A paracentesis was done in the recipient cornea at the 9 o'clock position with a MVR blade to flatten the central dome ofthe host bed. The flange of the graft was tucked into the peripheralpocket of the host created previously, and the graft was suturedtightly with sixteen radial, interrupted, 10–0 nylon sutures.

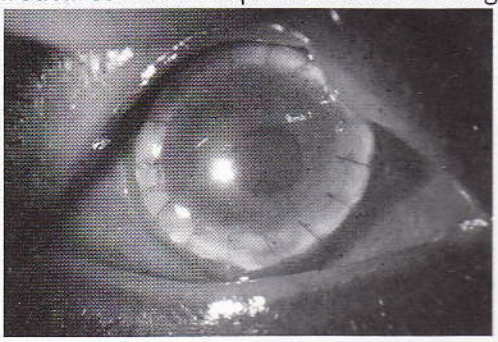
On postoperative day 1, patient was doing fine with vision of PL+ and PR accurate. Air bubble was in AC. Graft host junction was well apposed with all sutures intact. We started on prednisolone acetate 1% eye drop six times/day and ofloxacin 0.3% eye drop four times a day. Patient was asked to review after 1 week.

Clinical photograph at post op day 1

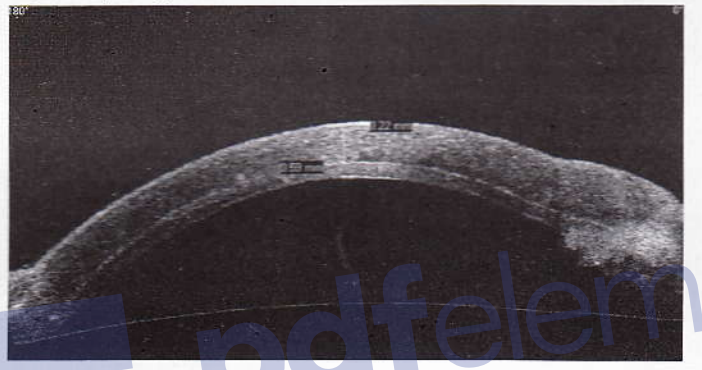


Anterior segment - OCT at post op day 1 showing graft thickness of 690 microns and bed thickness of 250 microns.

After 1 week, vision in right eye was counting fingers at 1m improving to 20/400 with pin hole. Graft host junction was well apposed with all sutures intact. Topical steroids were gradually tapered and patient was asked to review after 1 month.

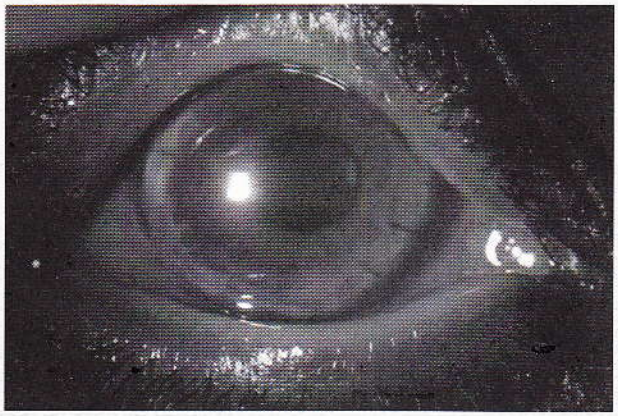


Clinical photograph at post op day 7.

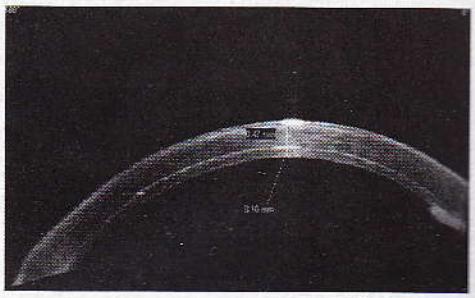


Anterior segment - OCT at post op day 7 showing graft thickness of 590 microns and bed thickness of 220 microns.

At 3 months follow up, best corrected visual acuity (BCVA) in right eye was 20/100 (+3.50 D sph / -6.00 D cyl @40°).



Clinical photograph at 3 months



Anterior segment - OCT at post op 3 months showing graft thickness of 470 microns and bed thickness of 160 microns

Discussion

Various methods for the management of keratoglobus has been described. Conservative management[8] includes patient counselling for use of eye protection because of thin cornea associated with high risk of perforation, spectacle wear to correct high myopia and astigmatism in the early stages. Contact lens fitting may be difficult because of corneal shape and itself is associated with risk of trauma inflicted by contact lens.

Surgical management includes penetrating keratoplasty, epikeratoplsty and lamellar keratoplasty[9]. Though penetrating keratoplasty is conventional, it is limited by peripheral graft host thickness disparity, large irregular astigmatism and poor visual outcomes. Taking large limbus to limbus corneal graft is an option but is limited by loss of immune privilege, limbal stem cell disruption and angle structure disruption.

The technique of tuck-in keratoplastyby Vajpayee et al, effectively reduces the corneal ectasia, not only centrally but also peripherally, and decreases the corneal-induced myopia and astigmatism and thus visually rehabilitates the patient in a single stage. It provides tectonic support, so that the structural integrity of the globe is maintained. Since no surgical intervention is done on the overlying limbal area or the angle, it preservesthe host stem cells and prevents any damage to the trabecularmeshwork of the host. Being an extraocular procedure, problems of graft rejection and vision-threatening complicationssuch as endophthalmitis are avoided.

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Infectious Crystalline Keratopahthy – A Rare case

Mohan Shalini*, Goel Rajat**, Khattri Mohit***, Sachan Surendra Kumar****

A crystalline appearance within the stroma of cornea may be caused by a variety of conditions including lipid and metabolic disorders such as cystinosis and monoclonal gammopathy in association with multiple myeloma. It rarely occurs as a complication of Penetrating Keratoplasty following either infection or rejection.[1-4]

Infectious Crystalline Keratopathy (ICK) is characterised by an indolent infectious keratitis in which needle-like, branching crystalline opacities are seen within the corneal stroma, in the absence of appreciable corneal or anterior segment inflammation.

We report a patient who developed crystallinekeratopathy following a graft. The cause of keratopathy was considered to be infective and the condition resolved on antibacterial treatment. After that, the patient underwent cataract surgery with a toric posterior intraocular lens implant.

CASE REPORT

A 44-year-old woman with right eye leucomatous corneal opacity underwent an uneventful optical Penetrating Keratoplasty in November 2010. The postoperative examination revealed an epithelial defect that healed within 48 hours. Anterior chamber was maintained and all interrupted sutures were in situ and buried. Patient was in regular follow up and at 4 months postopertaive follow up she came with loose sutures at 3o'clock and 7o'clock which were removed.

In the 9th month, patient came with complaints of foreign body sensation, dimunition of vision and some white opacification in graft. Decrease in vision was very gradual painless and progressive. Past history did not reveal any significant point. The patient was using topical prednisolone eye drops (twice daily) and lubricants eye drops (twice daily).

On examination the best corrected visual acuity (BCVA) of patient reduced from 6/24 to 5/60. Slit lamp examination showed white eye i.e. no congestion with a focal area of non-suppurative intrastromal white opacities (3.1 /4.8 mm^2) in branching pattern with crystalline deposits (figure 1). The lesion extended from the graft-host interface at 3 o'clock to 5 o'clock. Its extension was noted towards the centre and at approximately 60% of stromal depth. The epithelium was intact and the anterior chamber had occasional cells and flare (Grade 1). The area of involvement corresponded to the area of suture removal. Differential diagnosis of following diseases were made:

- Herpes simples keratitis due to branching pattern. But crystalline nature of the opacity was against this differential. Moreover stain was negative and corneal sensation showed normal senstivity.
- Graft rejection was another diagnosis due to differential corneal edema. But mnimal cells and no congestion ruled out the diagnosis.
- Clinically the diagnosis of crystaline keratopathy was made due to typical crystalline opacities in branching pattern.

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The biopsy of lesion could not be taken as the epithelium was intact and pupillary area was clear moreover suture biopsy could not be taken as suture was already removed from that area.

Fig. 1

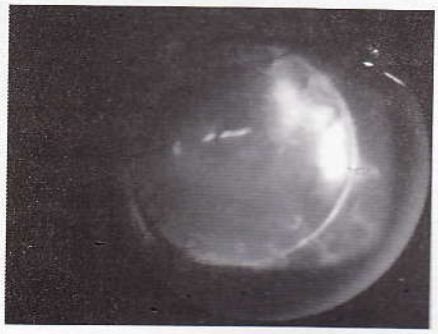

Fig. 2

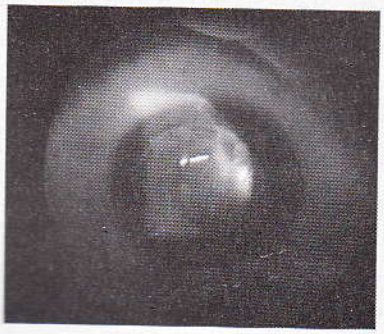

Fig. 3

So the patient was put on broad spectrum antibiotics assuming infectious etiology because spectrococcus viridans is the most common organism implicated.[2] So Azithromycin (1%) ophthalmic drops with fortified Tobramycin (1.3%) and Vancomycin (5%) was started every hour. Topical prednisolone was reduced to once daily. Topical homatropine (2%), three times daily was also added. Lubricants were continued. The patient was kept under strict follow up by monitoring her symptoms and the size of the lesion and crystals by slit-lamp examination and photographs. Initially the lesion did not show any regression although it did not increase either. The medications were continued in view of resistant nature of the disease. At 2 weeks follow up the patient showed some response to the treatment and improved symptomatically. On slit lamp examination, the density length of the lesion decreased although size remained the same (figure 2). The continued treatment showed reduced crystals size at 2 months follow up. The course of treatment was uneventful with no worsening of symptoms or any signs of rejection. The ICK resolved in 5 months and 15 days duration (figure 3). Topical antibiotics were then tapered in 6 months. The BCVA regained to 6/36 as there was increased astigmatism with lenticular opacity. She had astigmatism of -3.00D cylinder at 40°. So cataract surgery by Phacoemusification and toric posterior chamber intraocular lens implant was planned. Surgery went as planned and was uneventful. At first day post surgery media was clear, anterior chamber was well defined with no cells, lens implant was in place, fundal glow was good. The final BCVA was 6/9 with -0.5 D of sphere.

DISCUSSION

Infectious crystalline keratopathy may occur with a bacterial infection. The infection can arise de novo or as a sequelae of surgical procedures, such as refractive surgery and corneal transplants, if the cornea is traumatized chemically or mechanically. Infectious crystalline keratopathy is a rare complication typically following penetrating keratoplasty, but it can occur in an ungrafted cornea in patients with herpes simplex, herpes zoster, *Acanthamoeba*, or local anesthetic abuse.[2,3] It was first described by Gorovoy et al. in patients of corneal transplant who received prolong corticosteroids.[5]

The various predisposing factors are Penetrating keratoplasty long term steroid, previous HSV keratitis, neurotrophic keratopathy, topical anaesthetic abuse, persistent epithelial defects, loose sutures, contact lenses, radial keratotomy scars, post-LASIK etc.[1]

Many organisms have been isolated in cases of ICK, but the most common are gram positive aerobic streptococci which have been reported in 42% of cases, of which *S. viridans* is the most common (1,4). Another 12% of cases are reported with staphylococci as the organism isolated, including *Staphylococcus aureus* and *haemolyticus*. Fungi have been implicated in 8% of cases, including *Candida tropicalis, albicans*, and *parapsilosis*, and *Alternaria*. Additional organisms that have been isolated include *Mycobacterium fortuitum*, *Peptostreptococcus*, *Corynebacterium*, *Pseudomonas* and *Acanthamoeba*. Often, multiple organisms are isolated. Eyes undergoing refractive surgery are at higher risk for infections with atypical organisms such as mycobacteria (acid-fast bacteria) and *Alternaria* (fungi). With the increasing number of patients undergoing refractive surgery and the relevance of early intervention, it is important to recognize ICK. The organisms gain access along the suture track or through the micro defects in epithelium and form a biofilm that prevents proper penetration of antibiotics.[6]

Infection-related crystalline deposits have a fine branch like shape, develop over time and may be associated with inflammation. Diagnostic testing such as gram staining, acid-fast staining, routine bacterial and fungal cultures, as well as mycobacterial cultures, should be obtained whenever feasible.

The treatment of choice for ICK is with intensive topical antibiotics. Most treating surgeons use "fortified" antibiotics such as cefazolin,vancomycin or tobramycin.[4] When the organism has not been identified, broad-spectrum antibiotics should be used. The antibiotics as persensitivity should be switched and tailored once the organism and antibiotic sensitivities have been obtained. If symptoms do not resolve, it is reasonable to expand coverage or one can start systemic antibiotics. It is common for treatment of ICK to be continued for weeks or even months. In some cases it can even do not regress at all and compel the surgeon to repeat the keratoplasty.

Legends:

Figure 1: ICK lesion at presentation

Figure 2: Reduced density of lesion at 2 weeks of treatment

Figure 3: Resolved lesion at 6 months with corneal opacity

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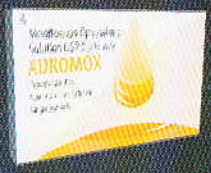

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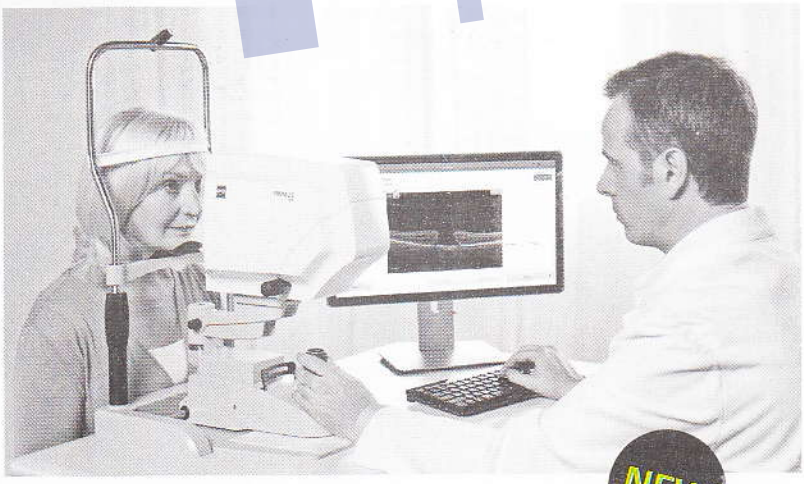

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Basic Succinct Statement

Accentrix®

Presentation: Vial: Ranibizumab. Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution.

Indications: •Improvement and maintenance of visual acuity and function and for reduction of vascular leakage and retinal oedema, in patients with neovascular age-related macular degeneration (AMD), •the treatment of visual impairment due to diabetic macular edema (DME), •the treatment of macular edema following retinal vein occlusion (RVO) •the treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM).

Dosage: •The recommended dose is 0.5 mg (0.05 mL) given as a single intravitreal injection. The interval between two doses injected into the same eye should not be shorter than 1 month. Wet AMD, DME, RVO, PM: •Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. •Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity as assessed by visual acuity and/or anatomic parameters. •Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). •While applying the treat-and-extend regimen, the treatment interval should be extended by two weeks at a time for wet AMD and central RVO, or by one month at a time for DME and branch RVO. •Accentrix and laser photocoagulation in DME or in branch RVO: Accentrix has been used concomitantly with laser photocoagulation in clinical studies. When given on the same day, Accentrix should be administered at least 30 minutes after laser photocoagulation. Accentrix can be administered in patients who have received previous laser photocoagulation. •Accentrix must be administered by a qualified ophthalmologist using aseptic techniques. Broad-spectrum topical microbicide and anaesthetic should be administered prior to the injection. •Not recommended in children and adolescents.

Contraindications: Hypersensitivity to ranibizumab or to any of the excipients, patients with active or suspected ocular or periocular infections, patients with active intraocular inflammation.

Warnings/Precautions: •Intravitreous injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Therefore proper aseptic injection techniques must be used. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. •Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Accentrix. Sustained IOP increases have also been reported. Intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. •There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5 mg compared to ranibizumab 0.3 mg or control, however, the differences were not statistically significant. Patients with known risk factors for stroke, including history of prior stroke or transient ischemic attack should be carefully evaluated by their physicians as to whether Accentrix treatment is appropriate and the benefit outweighs the potential risk. •Available data do not suggest an increased risk of systemic adverse events with bilateral treatment. •As with all therapeutic proteins, there is a potential for immunogenicity with Accentrix. •Accentrix has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. •There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischemic branch RVO (BRVO) and central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischemic visual function loss, treatment is not recommended. •Should not be used during pregnancy unless the expected benefit outweighs the potential risk to the fetus. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child; use of effective contraception recommended for women of child-bearing potential; breast-feeding not recommended. •Following treatment patients may develop transient visual disturbances that may interfere with their ability to drive or use machines. Patients should not drive or use machines as long as these symptoms persist.

Interactions: No formal interaction studies have been performed.

Adverse reactions: •Very common adverse reactions are: intraocular inflammation, vitritis, vitreous detachment, retinal hemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival hemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperemia, eye pruritus, intraocular pressure increased, nasopharyngitis, headache, arthralgia. •Common adverse reactions are: retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous hemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctuate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site hemorrhage, eye hemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid edema, eyelid pain, conjunctival hyperemia, stroke, influenza, urinary tract infection*, anemia, anxiety, cough, nausea, allergic reactions (rash, pruritus, urticaria, erythema). •Uncommon adverse reactions are: blindness, endophthalmitis, hypopyon, hyphema, keratopathy, iris adhesions, corneal deposits, corneal edema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation. •Serious adverse events related to intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract.

*observed only in the DME population

Packs: Pack of 1 vial

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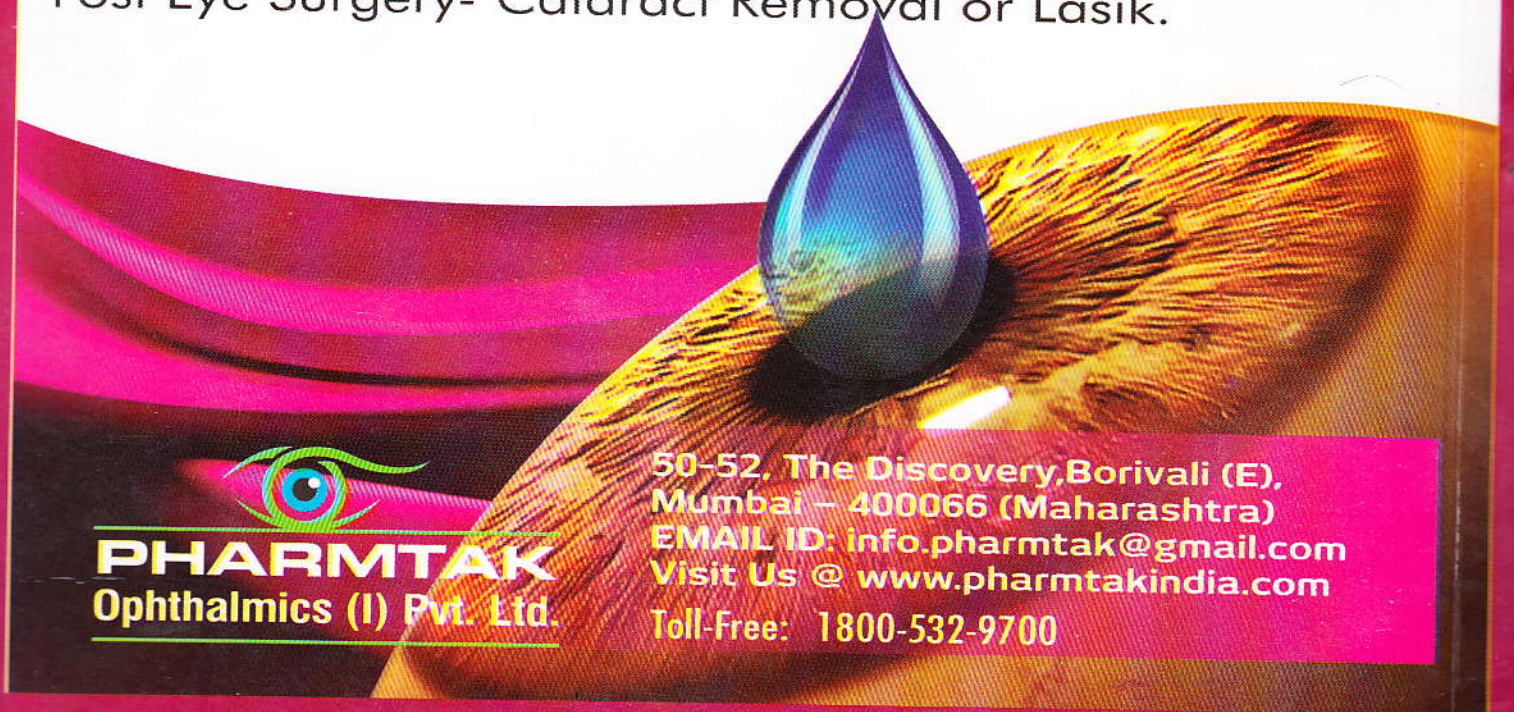

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