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Dear Friends,

We have reached the closing issue of this term of KJO. We had a memorable journey with a fantastic team of ophthalmologists from across the state, who have spared their time and effort in the midst of very busy schedules for successfully bringing out each edition of the journal. I would like to thank each and every member of his/her support. We have had very critical reviews of the articles, thought provoking letters to the editor and responses, brainstorming case discussions and cutting-edge articles from other states as well as guest articles from other specialities to add to the flavor of our cuisine. I would also like to specially mention the mentorship and timely guidance provided by the previous editors that has helped to shape the journal like it is today. All in all, it has been an enlightening experience where each article has added a little to our knowledge and we have been able to learn from many experiences of our veterans and peers. A significant change from previous times is that a lot of interactions have also taken place through social media, saving a lot of time and adding a new dimension to information exchange. Taking lessons from our past, we are now in a transition. We will be taking this journey forward with a new team that is ready with a lot of energy for the road ahead.

This issue brings in a different set of articles from less explored areas in our specialty. Dr. Joe Thomas has contributed an article that throws light on the ophthalmological perspective of rheumatoid autoimmune diseases. It is very important to have a strong statistical basis for any research study. To this end, we have an article from a statistics expert in the state, Mr. Krishnan that covers various important aspects rooted in fundamentals of statistics and branching to the latest techniques. In addition we have articles from our own members and fraternity.

I thank you for your appreciation and acceptance of the new introductions to KJO in the running term, including "Diagnostic and Therapeutic Challenges ", "Letters to the Editor", "Photo Essay" and "Practical Tips for the Comprehensive Ophthalmologist". The feedback received has been encouraging and it has helped a lot of youngsters to come out with their new ideas and comments. The excellent cover photos contributed by our members have given a facelift to our journal as we today proudly stand at par with many international peer reviewed journals.

As we move on to the next step, we have many more challenges awaiting us and ever increasing expectations to keep up with. One major milestone for the coming term for KJO is indexing of the journal, for which the seeds have already been sown. An MOU has been signed with an international publishing house which publishes many peer reviewed journals including IJO. With this, our journal is sure to reach greater heights with all your blessings.

Jai KSOS!

Dr. Ashok Nataraj

Editor, KJO

Dr. K. Mahadevan MS

What ails our MBBS course teaching?

After 35 years of teaching and practice, I have realised that there exists the need to fill up some lacunae in the curriculum. In the modern world there is emphasis on medical graduates to be competent in Cardio Pulmonary Resuscitation, early diagnosis and prompt referral basic trauma care and first aid and publications in peer reviewed journals. In a high volume centre, all of the above aspects of training can be achieved within the four and a half and one year of course period, because there will be enough number of patients to give hands on training to all the students. In the institutions where, patient clientele is poor, the best the teachers can do is to impart good theoretical knowledge to the students and make them conscious of things and still incompetent for independent practice, then encourage them to learn, further in a institution with good number of patients to become competent. This is very much akin to the lack of exposure to Industry faced by Engineering and Pharmacy students. The fresh Lawyers and Chartered Accountants generally do internship under the guidance of a senior with good practice for a few years before launching themselves into solo practice. I have always felt that knowledge of 12th standard mathematics is very essential to make a complete and successful doctor especially to understand statistics and epidemiology and also present scientific papers. The MBBS level Ophthalmology text books should also include during special chapters on drug interactions, out-patient emergency treatment and first aid, certain important diseases that need early detection and prompt referral. Under graduate students should also be given opportunity to attend selected CMEs and conferences, so that they can learn theory and practice faster. These are some of the points that came to my mind regarding modifications to be made in the MBBS curriculum.

Best wishes to all for a prosperous future.

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Major Review

Thyroid Eye Disease - An Overview

Dr. Marian Pauly MS, DNB, FMRF, Dr. Mekhla Naik DOMS

Introduction

Thyroid eye disease (TED) is known by many synonyms such as Graves' disease, Infiltrative Ophthalmopathy, Endocrine Exophthalmos, Thyroid Associated/Related Ophthalmopathy, and Von Basedow Ophthalmopathy.[1] It is an organ-specific autoimmune process that is strongly associated with dysthyroidism. It is the principal extrathyroidal manifestation of autoimmune thyroid diseases such as Graves 'disease and Hashimoto thyroiditis.[1] Globally it is the most common orbital disorder and the commonest causes of acquired unilateral or bilateral axial proptosis, strabismus or lid retractions.[1] TED may cause significant decrease in the quality of life due to visual dysfunction, ocular discomfort and cosmetic problems.[1] TED may precede, coincide, or follow the systemic complications of dysthyroidism.

Epidemiology

TED is associated with 90% of patients with hyperthyroidism, 7% with Euthyroid, 3% with Hashimotos thyroiditis and 1% with primary hypothyroidism.[1,2] It is a self-limiting disease which stabilizes in 3-5years.[3]

TED is more common in females, with the female to male ratio being 4:1.[2] More severe disease is seen in males.[3] It is commonly seen in the age group of 20-50 years.[4] Severe cases are seen in age group >50 yrs. Familial tendency is seen in 30%. Intensive treatment or surgery is required in 3-5% of cases.[2]

Pathogenesis

It is an autoimmune mediated inflammation of the extra ocular muscles and periorbital connective tissues. The thyroid and orbital tissues share a common antigen. Antigens involved are still unknown. It is a cytokine mediated Type 2 Hypersensitivity reaction (ADCC). Autoreactive T lymphocytes migrate into the orbital soft tissue, fat and musculature reacting with the common thyroid and orbital antigen causing cellular infiltration of interstitial tissue by lymphocytes along with plasma cells, macrophages and mast cells. This in turn triggers a cytokine cascade causing fibroblast proliferation & secretion of glycosaminoglycans.[1,4] This results in retro orbital soft tissue proliferation & enlargement along with increase in size of the extra ocular muscles.[1,4] In the long run this process leads to fibrosis of the extra ocular muscles and permanent restriction of ocular motility.

The development & severity of TED is dependent upon a number of endogenous and exogenous factors. The endogenous or non – modifiable risk factors are genetic predisposition, male sex and age more than 60 years.[4] The exogenous or modifiable risk factors include increased TSH-R antibody levels, previous history of radio iodine treatment, cigarette smoking, diabetes and stress.[1,2,4]

Classification systems in TED

A number of systems have been used to classify TED

1) It is the simplest classification in which TED is classified into 2 groups :

Type I - patients are younger with minimal inflammation and restrictive myopathy.

Type II - older patient with significant orbital inflammation and restrictive myopathy.

2) Van Dyk's soft tissue classification or the RELIEF classification:

- Resistance to retropulsion
- Edema of conjunctiva
- Lacrimal gland enlargement
- Injection of conjunctiva
- Edema of lids
- Fullness of lids

Disease severity and activity

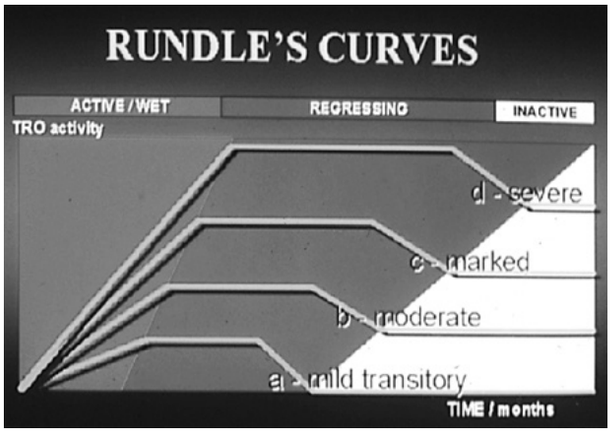
The natural course of the disease has 3 phases which are:

- Active phase
- Regressing phase
- Inactive phase

This pattern of TED was first described by Rundle in 1944 &

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the plot of the orbital disease severity against time is called the Rundles curve.[2,4]



The NOSPECS & EUGOGO classification assess the clinical severity.

1) Werner classification or NOSPECS classification: the ophthalmology index is based on this classification.[2,4,5]

CLASSES	GRADES	OCULAR SYMPTOMS AND SIGNS
0		No signs or symptoms
1		Only signs, no symptoms (signs limited to upper lid retraction & stare, with or without lid lag &proptosis)
2		Soft tissue involvement with symptoms & signs
	0	Absent
	A	minimal
	B	Moderate
	C	Marked
3		Proptosis 3mm or more in excess of upper normal limit, with or without symptoms
	0	Absent
	A	3-4 mm increase
	B	5-7 mm increase
	C	8 mm or more
4		Extraocular muscle involvement (usually with diplopia , other symptoms and /or signs)
	0	Absent
	A	limitation of motions at extremes of gaze
	B	evident restriction of motion
	C	fixation of globe or globes
5		Corneal involvement (primarily due to lagophthalmos)
	0	Absent
	A	stippling of cornea
	B	Ulceration
	C	clouding, necrosis & perforation
6		Sight loss (due to optic nerve involvement)
	0	absent
	A	disc pallor or choking, or visual field defect; vision 20/20 – 20/60
	B	same, but vision 20/70 – 20/200
	C	blindness i.e. failure to perceive light , vision less than 20/200

2) EUGOGO classification of disease severity has 3 categories[6,7]

a) Sight-threatening TED: warrants immediate intervention and includes patients with dysthyroid optic neuropathy, eyeball subluxation, choroidal folds and/or corneal breakdown.

b) Moderate to severe TED: includes patients without sight-threatening disease, but whose eyes have sufficient impact on quality of daily life to warrant the risk of rehabilitative surgery (if inactive) or the risks of immunosuppression and/or orbital radiotherapy (if active). Common symptoms are lid retraction >2 mm, exophthalmos >3 mm above normal for race and gender, moderate to severe soft tissue involvement and intermittent or constant diplopia.

c) Mild TED: are patients with features that have minor impact on quality of daily life. Watchful waiting is appropriate. Risk of immunosuppression or surgery is typically not justified in this group unless there is progression.

Common symptoms include minor lid retraction <2 mm, exophthalmos <3 mm above normal for race and gender, mild soft tissue involvement, transient or no diplopia and corneal exposure responsive to lubricants.

The VISA & CAS classifications were intended to evaluate the clinical activity.[6]

1) VISA classification

Vision loss (optic neuropathy) score

- Yes
- No

Inflammation / congestion & activity in TED score (total 0-8)
- Orbital pain 0-2 (none, with gaze, at rest)
- Chemosis 0-2
- Eyelid edema 0-2
- Conjunctival injection 0-2
- Eyelid injection 0-1

Strabismus / motility score
- Strabismus 0-3
- Restriction 0-2

Appearance / exposure score
- Mild
- Moderate
- Severe

2) Clinical Activity Score system: it is based on the 4 classic signs of inflammation i.e. dolor, rubor, tumor & loss of function. A score of 1 is given for each feature present. A CAS score of < 3 indicates inactive disease& poor response to immunosuppressive therapy.[2]

Pain	Painful, oppressive feeling on or behind the globe, during the last 4 weeks
	Pain on attempted up, side or down gaze during the last 4 weeks
Redness	Redness of the eyelid(s)
	Diffuse redness of the conjunctiva, covering at least one quadrant
Swelling	Swelling of the eyelid(s
	Chemosis
	Swollen caruncle
	Increase of proptosis of >2 mm during a period of 1–3M
Impaired Function	Decrease of eye movement in any direction 5 deg B/N 1–3 months
	Decrease of visual acuity of 1 line(s) on the Snellen chart (using a pinhole) during a period of 1–3 months

Clinical features

Ocular symptoms include dry eyes, puffy eyelids, angry-looking eyes, bulging eyes, diplopia, visual loss, field loss, dyschromatopsia, photopsia on upgaze, ocular pressure or pain.[5]

The symptoms of hyperthyroidism include tachycardia/ palpitations, nervousness, diaphoresis, heat intolerance, skeletal muscle weakness, tremors, weight loss, hair loss, irritability & goitre.[5]

The symptoms of hypothyroidism are bradycardia, drowsiness, poor mentation, muscle cramps, weight gain, dry skin, husky voice, depression & cold intolerance.[5]

Ocular signs can be divided into lid signs, proptosis, soft tissue involvement, restrictive myopathy & optic nerve involvement.

1) Lid signs include:
- Dalrymple Sign Upper - lid retraction in straight gaze
- Von Graefe sign - lid lag in downgaze
- Kocher sign - staring look on fixation
- Means sign -superior scleral show on upgaze
- Griffiths sign - lower lid lag in upgaze
- Vigouroux sign - eyelid fullness
- Stellwag sign - incomplete and infrequent blinking
- Grove sign - resistance to pulling down the retracted upper lid

Mechanisms for the lid signs include Sympathetic drive of Müller muscle, fibrosis of the levator, adnexal fibrosis, contracture of LPS aponeurosis or inferior rectus, contracture lower lid retractors or superior rectus & contralateral ptosis (myasthenia).[1,2,5]

2) Proptosis: is due to the increase in the intraorbital volume as a result of swelling of the extraocular muscle bellies and other soft tissues.[1,2,5]

3) Restrictive myopathy signs include:
- Ballet sign - restriction of one or more extraocular muscles
- Braleys sign - increase in intraocular pressure more than 4-6 mm Hg on upgaze
- Mobius sign - poor convergence

Mechanism for restrictive myopathy is due to soft tissue involvement.1,2,5

4) Conjunctival involvement can be in the form of superior limbic keratoconjunctivitis, conjunctival injection usually over the rectus muscle insertions,conjunctival chemosis.[2]

5) Corneal signs include superficial punctate keratitis, corneal exposure & corneal ulceration.[2,5]

Causes for exposure keratopathy: proptosis, lagophthalmos, lid retraction, infrequent blinking, and absence of Bell's – IR tethering, dry eye –lacrimal gland involvement.[5]

6) Pupillary signs include:
- Knies sign - uneven dilatation of pupil
- Cowens sign - extensive hippus of consensual light reflex
- Loewis sign - dilatation of pupil with 1:1000 adrenaline

7) Strabismus: the extraocular muscles are affected in the following order IR>MR>SR>Obliques>LR & confirmed with forced ductions or elevated intraocular pressure with eye movement.[2,8] The patient may present with convergence insufficiency, hypotropia or esotropia or pseudo 3rd, 4th Nerve Palsy.

Inferior rectus muscle restriction may mimic double elevator palsy. If a patient presents with exotropia one should always rule out myasthenia gravis.

8) Dysthyroid optic neuropathy affects 5% of TED patients who may present with blurry vision, visual loss, dyschromatopsia, or field loss.[1,2,5] Optic disc edema/optic atrophy occurs due to direct compression of nerve or its vascular supply.[1] It may occur without significant proptosis. Glaucoma can occur due to multiple mechanisms like decreased episcleral venous outflow, restrictive myopathy-intraocular pressure may rise more than 4-6 mm Hg on up gaze, MPS deposition in aqueous outflow channels.[2,5]

9) Other signs include:
- Joffroy sign - absent creases in the forehead on superior gaze
- Riesman sign -bruit over the lid
- Donder sign-bruit over the eye

Differential diagnosis[1,2,5]

Orbital Cellulitis
Orbital inflammatory disease (OID)
Carotid cavernous fistula (CCF)
Other causes of thickened muscles are sarcoidosis, metastases, lymphoma, amyloidosis and acromegaly.

Evaluation of TED

1) Evaluate the disease phase: the activity & severity of the disease is determined using the above mentioned classifications.[1,2]

2) Serum markers: free T4, FT3, TSH, Antithyroid antibodies Antithyroid peroxidase(TPO),TSH –R antibody.[1,2]

3) Imaging: Optic neuropathy, Rule out orbital SOL, Euthyroid Ophthalmopathy, before decompression, brain imaging in suspected cases of CST and Carotico – Cavernous Fistula.

Routinely a CT scan of the orbit is done. The coronal view is the most preferred as it can show proptosis, muscle enlargement with tendon sparing, crowding of apex with loss of perineural fat at the apex, increased orbital fat, anterior displacement of lacrimal gland and dilated superior ophthalmic vein.[1,2,5]

An MRI may be done to know the disease activity. An active disease will show a prolonged T2 relaxation time.[1]

Orbital scintigraphy, positron emission tomography (PET) scan and recently digital infrared thermal imaging have also been used as imaging modalities to assess disease activity.[1]

4) Endocrinology consultation: is mandatory as uncontrolled thyroid function is associated with more severe thyroid eye disease.[1,2,5] Anti-thyroid medications like carbimazole, methimazole and propylthiouracil reduce orbit-directed autoimmune reactions but do not alter the course of existing TED.[5]

The various drug regimens are:

- block-replace regimen where a higher dose of anti-thyroid drug is given with a replacement dose of thyroid hormone
- titration regimen where the anti-thyroid drug is reduced by titrating treatment against thyroid hormone concentrations.12–18 months of the titration regimen had fewer side effects but had the same efficacy as compared to the block-replace regimen.

Radioactive iodine (RAI) or I 131, given orally. It is rapidly concentrated by thyroid follicular cells. The ionizing effect of b particles induces an inflammatory response and subsequent necrosis of follicular cells. 5–15 mCi can be given to yield an absorbed radiation dose of 50–100 Gy. However it can precipitate TED. The use of steroids during and following the course of radioiodine therapy reduces the risk of exacerbation in patients with active TED.2 In patients with inactive TED, risk of eye disease exacerbation is minimal after the administration of RAI.

Management of TED

Rescue therapy for acute stage: consists of moderate to severe inflammation CAS >4 or compressive optic neuropathy. 1 g of intravenous methylprednisolone for three consecutive days followed by dose titration based on the response.2 If there is no response in 2 weeks surgical decompression has to be done. Oral corticosteroids 1mg/

kg/day in tapering doses. It can have pronounced long term consequences due to the longer duration of treatment. 60% of patients have favourable effects.[2]
\

Management of active TED without optic neuropathy includes intravenous or oral glucocorticoids. Studies have shown intravenous steroid pulse therapy to be better tolerated and more effective as compared to oral steroids.9 The Positive Response Rate is 80% as compared to 50% with oral steroids.[10] But this treatment carries a risk of liver damage/cardiac failure. Bisphosphonates should be considered to reduce the incidence of osteoporosis.[2]

Combination therapy with RT/ Non-steroidal Immunosuppressants.[1]

Supportive treatments are aimed at reducing dry eye due to exposure resulting from decreased blink, widened palpebral fissure, increased evaporative surface. They include artificial tear supplement and gel at bed time.[7] Head end elevation. The patient should be advised to stop smoking immediately.[2,7] Sunglasses. Fresnel prisms or patching for diplopia.[2,5]

- Orbital Radiation: Indications are active disease and cases that are steroid resistant or steroids are contraindicated. Young age is a relative contraindication whereas diabetic retinopathy and severe hypertension are absolute contraindications.2 It has anti-inflammatory action & it is based on the radiosensitivity of lymphocytes. A dose of 20GY over 2 weeks is delivered.1,2,3,7 A positive response is seen in 4 weeks and maximum effect in 4 months. Approximately 60% of patients have favorable response to Orbital Radiation.

Combined treatment of Orbital Radiation with oral glucocorticoids is more effective than either treatment alone.[1]

Immunosuppressives such as Azathioprine, Methotrexate, Cyclosporine have also been used in combination with Steroids and Radiotherapy.[1,2,7]

Surgical management

1) Thyroidectomy has not demonstrated any advantage in the outcome of TED but is indicated for long-term control of thyroid function. Total or near total thyroidectomy is typically performed. Recurrence is directly related to the size of thyroid remnant, initial TSHRAb level and the presence of TED.[1,5]

2) Orbital Decompression: is indicated in cases of compressive optic neuropathy, cases not responsive to IV Steroids, exposure keratopathy, congestive orbitopathy and for cosmesis.[1,2,7,8]

It is of two types i.e.

BROD (Bone Removal Orbital Decompression): was first described in 1911. Post-operative complications include strabismus, sinusitis, infraorbital anaesthesia, loss of vision and CSF leak. It has three further subgroups depending on the amount of proptosis reduction required.

a) 2 wall decompression / Antral ethmoidal- achieves 3-6 mm reduction in proptosis. It includes removal of orbital floor and medial wall.

b) 3 wall decompression- achieves 6-10 mm reduction in proptosis and includes removal of orbital floor, medial wall & lateral wall.

c) 4 wall decompression- achieves 10-16 mm reduction in proptosis and includes removal of orbital floor, medial & lateral walls plus lateral half of orbital roof.

FROD (Fat removal orbital decompression) for TED was first reported in 1988. Along with proptosis it has been reported to cause improvement in diplopia too.

3) Combined decompression

Strabismus surgery: is challenging due to the fibrotic nature of the extraocular muscles. A Goals of squint correction include fusion of images in primary and reading position and to improve diplopia.[7] The timing of the surgery is very important and should be done only when there is presence of inactive disease and the angle of deviation has been stable for >6 months.[7] Surgery involves recession of IR/MR with usage of adjustable sutures.7 Botulinum toxin has also been used to weaken the opposing muscle.[2]

Lid surgery: is indicated for correction of lid retraction and to prevent corneal exposure. The various surgeries that are practised are:[1,2,5,7]

- Mullerotomy
- Levator recession
- Lower lid retractor disinsertion with spacer graft
- Blepharoplasty

Recent advances:

1. Botox: for temporary treatment of lid retraction in active/

inactive phase.[2] 5-10 units are given but results can be variable. Ptosis can develop in upto50% of the patients.

2. omatostatin Analogues: such as lanreotide and octreotide. They act on type 4 somatostatin receptor subtypes and decrease adipogenesis.[2] A new drug SOM 230 is under trial.
3. TNF alpha inhibitors: Target cytokines and may help by decreasing the auto immune response. A few case reports have shown positive results with the use of infliximab and subcutaneous entanercept 25 mg twice weekly for 12 weeks.
4. Pentoxyfiline: it inhibits cytokine induced GAG Synthesis
5. Plasmapharesis: it helps by removal of humoral factors in acute Graves' disease but rebound is likely.
6. Rituximab: it interferes with cytokine synthesis, dendritic cell function, and antibody levels,including the TSH-receptor and IGF-1 receptor antibodies. However only few case reports are available as supportive evidence.[2]
7. Selenium and thyroid: Low levels of selenium have been found in thyroiditis. Selenium supplementation helps in early stabilisation of TED.[7]

References:

1. Kelvin KL C. Thyroid Eye Disease: a Comprehensive Review. The Hong Kong medical diary 2010; Vol.15,10:4-8
2. Bothun ED, Scheurer RA, Harrison AR, Lee MS. Update on thyroid eye disease and management. Clin Ophthalmol. 2009;3:543-51.
3. Sonam Angmo Bodh, Saurabh Kamal, Ruchi Goel et al. Thyroid Associated Ophthalmopathy. Del J Ophthalmol 2012;22(4):249-255.
4. Naik VM, Naik MN, Goldberg RA, Smith TJ, Douglas RS. Immunopathogenesis of thyroid eye disease: emerging paradigms. Surv Ophthalmol. 2010 May-Jun;55(3):215-26. doi: 10.1016/j.survophthal.2009.06.009.
5. Sergott RC, Glaser JS. Graves' ophthalmopathy. A clinical and immunologic review. Surv Ophthalmol. 1981 Jul-Aug;26(1):1-21.
6. http://download.lww.com/wolterskluwer_vitalstream_com/PermaLink/WNO/A/WNO_2014_03_14_BHATTI_00034_SDC1.pdf
7. Current Protocol for the Management of
8. Pinto C.N. Current Protocol for the Management of Thyroid Eye Disease. DOS Times - Vol. 20, No. 10 April, 2015; 81-85
9. Bartalena L, Baldeschi L, Dickinson A et al. European Group on Graves' Orbitopathy (EUGOGO). Eur J Endocrinol. 2008 Mar;158(3):273-85. doi: 10.1530/EJE-07-0666.

Major Review

Rheumatologic Investigations in Eye Diseases

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Rheumatologic diseases can affect the eye, periorbital structures or orbit posing a serious threat to vision. Ocular manifestations include conjunctivitis, scleritis, keratitis, uveitis, retinal vasculitis, and optic neuritis. A literature review indicated that the most common ocular manifestations of rheumatic diseases include keratoconjunctivitis sicca, anterior uveitis, and scleritis. The most serious eye complications of the inherited connective tissue disorders are lens involvement with cataract formation or subluxation. The most significant side effects of the drugs used to treat rheumatic diseases are the maculopathy associated with anti-malarial agents and cataracts and glaucoma associated with corticosteroid use.[1] In this brief review we will look into common rheumatological investigations for various eye diseases. However it has to be stressed that there is no replacement to a detailed clinical history and physical examination. Investigations only help to confirm the clinical suspicion.

Rheumatoid factor (RF)

Rheumatoid factors are antibodies directed against the Fc region of immunoglobulin G. They have different isotypes and affinities, were first detected more than 70 years ago, but there is still much to discover about the mechanisms underlying their production, physiological role, and pathological effects.[2] Automated techniques such as nephelometry and enzyme-linked immunosorbent assays are methods more commonly used for detection of rheumatoid factor. A positive rheumatoid factor (RF) test can be found in many rheumatic disorders and few nonrheumatic disorders, but also in healthy subjects.[3] Frequency of rheumatoid factor in various diseases is given in table 1.[4] The RF has a higher positive predictive value if ordered more selectively in patients with a modest or higher chance of having an RF-associated rheumatic disease such as rheumatoid arthritis (RA), Sjögren's syndrome, or the mixed cryoglobulinemia syndrome.

Table 1

Disease	Frequency, %
Rheumatoid arthritis	70–90
Psoriatic arthritis	<15
Primary Sjögren's syndrome	75–95
Mixed connective tissue disease	50–60
Systemic lupus erythematosus	15–35
Systemic sclerosis	20–30
Subacute bacterial endocarditis	40
Tuberculosis	15
HCV infection	40–76
Malaria	15–18
Malignancy	5–25

Antinuclear antibody (ANA)

Antinuclear antibodies (ANAs) are autoantibodies directed against nuclear specificities, such as DNA or small nuclear ribonucleoproteins (snRNPs), but since the advent of the now widely used fluorescent antinuclear antibody test (FANA), which can detect autoantigens throughout the entire cell, the spectrum of ANAs has expanded to include a diverse spectrum of nuclear and cytoplasmic specificities.[5] FANA provides a rapid, highly sensitive and is considered as method choice for ANA detection. The detection of antinuclear antibodies (ANA) in serum facilitates the diagnosis of patients with systemic lupus erythematosus (SLE) and related autoimmune diseases. Conditions associated with a positive antinuclear antibody and there relevance are given in table 2.

Table2: Conditions associated with a positive antinuclear antibody (ANA)[6]

ANA very useful for diagnosis	Systemic lupus erythematosus Systemic sclerosis

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ANA somewhat useful for diagnosis	Sjogren's syndrome Polymyositis-dermatomyositis
ANA is a critical part of the diagnostic criteria	Drug-associated lupus Mixed connective tissue disease Autoimmune hepatitis
ANA not useful or has no proven value for diagnosis, monitoring or prognosis	Rheumatoid arthritis Multiple sclerosis Thyroid disease Infectious disease Idiopathic thrombocytopenic purpura Fibromyalgia

In most clinical laboratories, FANA serves as a screening test, with a positive result often prompting "cascade" testing by the laboratory, ordering physician, or both consisting of ELISAs or other assays for specific autoantibody specificities, such as anti-ds-DNA, anti-Ro, anti-La, anti-RNP, and anti-Sm. The higher the prior probability that a patient has a systemic autoimmune disease, the more likely the results of an ANA test will assist in establishing the diagnosis. As an example, if there is clinical evidence of systemic lupus erythematosus (SLE) (eg, photosensitivity, pleurisy), systemic sclerosis (eg, Raynaud phenomenon, skin changes), or Sjögren's syndrome (eg, unexplained dry eyes, dry mouth), the ANA results are likely to be helpful. By contrast, if the ANA test is ordered indiscriminately, it may false positive in a significant majority and may potentially distract the clinician from the correct diagnosis.

Anti-CCP antibodies (Anti-CCP)

In 1998, the interesting finding that patients with RA produce antibodies against peptides and proteins containing citrulline, a modified form of the amino acid arginine, was first published.[7] Based on this finding, a commercial test was developed using synthetic cyclic citrullinated peptide (CCP) as an artificial antigen.[8] Subsequently, a large number of publications have demonstrated that the use of this test enables early diagnosis and treatment of RA.[9] The best data regarding test performance characteristics of ACPA come from a 2010 systematic review and meta-analyses of 151 studies. Sensitivity of ACPA in was 67 percent, and the specificity was 96 percent for diagnosis of rheumatoid arthritis.[10] ACPA have also been found in 8 to 16 percent of patients with psoriatic arthritis; they are most frequently found in patients with erosive and/or polyarticular disease, but may be present in patients with severe psoriasis in the absence of arthritis.

Anti-neutrophil cytoplasmic antibodies (ANCA)

ANCAs were first described in 1982 by Davies and colleagues11 in eight patients with necrotizing pauci-immune glomerulonephritis who were suspected of having viral infections. A few years later, Hall and colleagues[12] identified ANCA in four patients with systemic vasculitis. In 1985, van der Woude and colleagues[13] were the first to suggest an association between ANCA and Granulomatosis with polyangiitis (Wegener's Granulomatosis). Since that time, subsequent studies have established a close association between ANCA and three major vasculitis syndromes: Granulomatosis with polyangiitis (Wegener's Granulomatosis), Microscopic polyangiitis (MPA), and Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).[14] ANCAs are antibodies directed against primary granules of neutrophil and monocyte lysosomes. Without ethanol fixation, all ANCAs stain in a cytoplasmic distribution. However, following ethanol fixation, two distinct patterns are described, cytoplasmic (cANCA) and perinuclear (pANCA), depending on their relative charge. ANCA positive by immunofluorescence (IIF) should be followed by confirmation by both protease-3 ELISA and myeloperoxidase-ELISA. Disease association with PR3-ANCA and MPO-ANCA is given in the table 3.

Table 3

Disease entity	PR3-ANCA (%)	MPO-ANCA (%)
Granulomatosis with polyangiitis (Wegener's)	66	24
Microscopic polyangiitis	26	58
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	< 5	40
Idiopathic crescentic glomerulonephritis	30	64

HLA-B51/B5

HLA, located on chromosome 6p21.3, is the major histocompatibility complex in humans. HLA encodes genes involved in antigen processing and the presentation of antigenic peptides to T cells, and is instrumental in many innate and adaptive immune responses. The HLA class I molecule HLA-B*51 allele is strongly associated with Behçet's disease (BD) in many different ethnic groups.[15] Meta-analyses done by Maldini C et al showed that, in BD, HLA-B51/B5 carriage predominates in males and is associated with moderately higher prevalences of genital ulcers, ocular and skin manifestations, and a decreased prevalence of gastrointestinal involvement.[16]

HLA-B27

Possession of the human leukocyte antigen (HLA) class 1 allele HLA-B27 is strongly associated with development of the spondyloarthritides, a group of related diseases including ankylosing spondylitis and reactive arthritis. Approximate frequency of HLA-B 27 in various diseases is given in table.[17] Positive testing for HLA-B27 is especially useful in patients without plain radiographic evidence of sacroiliitis,

where its presence may aid in making the; it should be obtained when the diagnosis or exclusion remains uncertain despite the findings of the history, physical examination, and plain radiographic imaging of the pelvis and sacroiliac (SI) joints, and thus plays an important role in making the diagnosis.[18] Traditionally the lymphocytotoxicity assay was used to determine HLA status, though time consuming and expensive to perform. Alternate methods that have been developed to speed up HLA-B27 screening have included: flow cytometry, DNA-based typing using polymerase chain reaction (PCR) assays and enzyme-linked immunosorbent assays

Disease	HLA-B27 frequency (%)
Ankylosing spondylitis	96
Undifferentiated spondyloarthropathy	70
Reactive arthritis	30–70
Colitis-associated spondyloarthritis	33–75
Psoriatic spondyloarthritis	40–50
Juvenile enthesitis-related arthritis	70
Iritis	50
Cardiac conduction defects with aortic incompetence	Up to 88

Conclusion

Rheumatologists and ophthalmologist share a mutual responsibility for patients with systemic illness whose vision requires their combined efforts. No screening test is ideal for detecting rheumatic diseases; a good history and detailed clinical examination of patient are extremely important for proper diagnosis of over 100 types of arthritis. Laboratory investigations may be useful in confirming or ruling out rheumatic disease after a clinical diagnosis is considered. Once a rheumatic disease has been diagnosed, certain laboratory tests can help in assessing prognosis or determining the extent of the disease.

1. Hamideh F, Prete PE. Ophthalmologic manifestations of rheumatic diseases. Semin Arthritis Rheum. 2001 Feb;30(4):217-41.
2. T.D¨orner, K. Egerer, E. Feist, and G. R. Burmester, "Rheumatoid factor revisited," Current Opinion in Rheumatology, vol. 16, no. 3, pp. 246–253, 2004
3. Shmerling RH, Delbanco TL. The rheumatoid factor: an analysis of clinical utility. Am J Med 1991; 91:528.
4. R. H. Shmerling and T. L.Delbanco, "Therheumatoid factor: an analysis of clinical utility," American Journal ofMedicine, vol. 91, no. 5, pp. 528–534, 1991
5. Peng S.L., Craft J: Antinuclear antibodies.In: Harris E.D., Budd R.C., Firestein G.S., et al ed. Kelley's Textbook of Rheumatology, Philadelphia: WB Saunders; 2005:311-331.
6. Solomon DH, Kavanaugh AJ, Schur PH; American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines.Evidence-based guidelines for the use of immunologic tests: antinuclear antibody testing.Arthritis Rheum. 2002 Aug;47(4):434-44.
7. Schellekens, G. A., de Jong, B. A., van den Hoogen, F. H., van de Putte, L. B. & van Venrooij, W. J. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. J. Clin. Invest. 101, 273–281 (1998).
8. 2. Schellekens, G. A. et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 43, 155–163 (2000).
9. 3. Avouac, J., Gossec, L. & Dougados, M. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. Ann. Rheum. Dis. 65, 845–851 (2006).
10. 4. Whiting PF, Smidt N, Sterne JA, et al. Systematic review: accuracy of anti-citrullinated Peptide antibodies for diagnosing rheumatoid arthritis. Ann Intern Med 2010; 152:456.
11. Davies D.J., Moran J.E., Niall J.F., et al: Segmental necrotizing glomerulonephritis with antineutrophil antibody: Possible arbovirus aetiology. BMJ 1982; 285:606.
12. Hall J.B., Wadham B.M., Wood C.J., et al: Vasculitis and glomerulonephritis: A subgroup with an antineutrophil cytoplasmic antibody. Aust N Z J Med 1984; 14:277.
13. van der Woude F.J., Rasmussen N., Lobatto S., et al: Autoantibodies against neutrophils and monocytes: Tool for diagnosis and marker of disease activity in Wegener's granulomatosis. Lancet 1985; 1:425.
14. Jennette J.C., Falk R.J.: Small-vessel vasculitis. N Engl J Med 1997; 337:1512-1523.
15. de Menthon M, Lavalley MP, Maldini C et al (2009) HLA-B51/B5 and the risk of Behçet's disease: a systematic review and meta-analysis of case-control genetic association studies. Arthritis Rheum 61:1287–129
16. Maldini C, Lavalley MP, Cheminant M, de Menthon M, Mahr A. Relationships of HLA-B51 or B5 genotype with Behcet's disease clinical characteristics: systematic review and meta-analyses of observational studies. Rheumatology (Oxford). 2012 May;51(5):887-900. doi: 10.1093/rheumatology/ker428. Epub 2012 Jan 11. Review.
17. McMichael A, Bowness P.HLA-B27: natural function and pathogenic role in spondyloarthritis.Arthritis Res. 2002;4 Suppl 3:S153-8. Epub 2002 May 9.
18. Rudwaleit M, van der Heijde D, Khan MA, et al. How to diagnose axial spondyloarthritis early. Ann Rheum Dis 2004; 63:535.

Major Review

Statistics: For Forming Generality in Medical Research Beyond Subjects

Dr. S. Krishnan PhD

The advent of statistics in medical research as a potent tool in transforming the enumerable data into useful information has laid a better ramification in medical research owing to the wide range of statistical tools pertinent to the growing requisites. This pace in medical research has made considerable implications in the fore-front which has made the then impossibilities in clinical curation as today's possibilities; though critically viewed by some. Statistics has an imperative role in medical research, where it has assumed statistics as a vital tool to master research concepts. Statistical tools are employed in accomplishing a research work to arrive at a valid conclusion, arising from myriads of numerical figures.

Various clinical examinations can be performed to diagnose a disease; however it is of utmost value to properly diagnose a diseased condition when it is actually present. Owing to this the clinical examinations are subjected to statistical comparisons through various statistical measures like specificity, sensitivity, negative predictive value, positive predictive value; leading to the selection of a robust clinical examination and thus facilitate the medical community in adopting the same in the frontline. Cohen's Kappa test is also used as an efficient tool in this regard. Yet other implications of statistical tools in medical research had been for testing the potentiality of various drugs, attaining an optimum dosage etc.

Cohen's Kappa test is an efficient tool in knowing the agreements of results obtained through different testing procedures. Cohen's kappa coefficient is a statistic which measures the inter-rater agreement for qualitative items and hence can be used in medical research where categorical items are also of major concern.

$$K = \frac{p_o - p_e}{1 - p_e}$$

Where p_o is the relative agreement among results in two different tests and pe is the hypothetical probability of chance agreement. Value of k ranges from 0 to 1, denoting the degree of agreement among raters. Viera and Garret (2005) has studied the relative prominence of Kappa coefficient in medical research for assessing inter-observer agreements compared to other methods. Schlenker et al.(2010) has used kappa coefficient to investigate the effectiveness of a traditional flip-chart optotype test, the Sheridan Gardiner test (SGT), in measuring visual acuity and detecting amblyopia, over computer-based test

The researcher will always be anticipating a clinical outcome such as a disappearance of tumour or survival of trabeculectomy after surgery. The survival rate can be known using Kaplan Meier survival analysis test. This survival analysis can be however affected as the patient refuse to involve in a trial in the midway, and this can be regarded as a censored observation. Kaplan Meier estimate is the simplest and efficient way of computing the survival over a period of time irrespective of the previously mentioned difficulty. When the desired outcome is the survival of a patient, variable of interest is the length of time before the same event occurs. To generate a Kaplan Meier estimator, at least two pieces of data are required for each patient, the status of last observation and the time to the event. It involves computing probabilities of occurrence of event at a certain point of time. The survival probability at any particular time is computed as

$$S_t = \frac{\text{No. of subjects living at start - No. of subjects died}}{\text{No. of subjects living at start}}$$

There are quite many statistical tools available for data analysis in medical research. The right choice depends on the scale of measurement of data. There are four scales of measurement, viz; Nominal, Ordinal, Interval and Ratio. The terminology of these scales can be had from any standard source.

The size as also the number of samples ultimately determines the test statistic to be co-opted in a situation. In addition the sample size also is most important. Now a days because of rapid development of electronic media similar works in the same field is easily accessible, so that an overall conclusion is possible even when the present sample size is low. The non parametric tests are widely used than parametric tests.

The statistical methods of estimation and testing involve a number of assumptions about the population. For example in carrying out t-test, a common assumption is that the

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samples come from a normal population. Also the sampling distribution of the statistic depends on the parameters. Such methods based on assumptions about parameters are called the parametric methods (Eg. Z test, t test, F test ANOVA etc.). The reliability of such methods depends on the validity of the assumptions which they hold. Moreover these methods require data of at least interval scale of measurement. In many practical situations, we may be using data with ordinal or even nominal scale of measurement. In such cases, we go for non parametric methods for testing and drawing inference. Here the tests are carried out without many assumptions about the parameters or the form of the distribution. Also the sampling distribution of the test statistic is independent of the distribution of the population and they do not involve parameters. Hence they are generally known as non – parametric or distribution – free methods.

However certain mild assumptions are associated with most of the non parametric methods. The usual assumptions are
(i) Observations are independent
(ii) The variable under study has underlying continuity

But these assumptions are fewer and weaker than those associated with parametric tests.

Advantages

Non parametric methods can be used in situations where the distribution of parent population from which the sampling is done is not known

Non parametric methods are more flexible since they do not depend on population parameters and we can very easily generalize the results

Moreover non parametric tests do not require measurements so strong as that required by parametric methods. NP test can be applied to data in an ordinal scale or even in a nominal scale. As non- parametric tests may be used with non-numerical data many of them are often referred to as “ranking tests” or “order tests”. (Siegel, 1956). Due to this fact, non parametric tests are commonly used in behavioral sciences

Disadvantage

If all the assumptions of the parametric tests are satisfied, the parametric methods are much more powerful than the non parametric tests.

Parametric tests	Non Parametric tests
1. Information about population is completely known 2. Specific assumptions are made regarding the population	1.No information about the population is available 2. No assumption is made regarding the population
3. Null hypothesis is made on parameters of the population distribution 4. Test statistic is based on the distribution 5. Parametric tests are mostly used for variables 6. No parametric tests exist for nominal scale data 7. Parametric test is more powerful if it exists	3.The null hypothesis is free from parameters 4. Test statistic is arbitrary 5. It is applied both for variables and attributes 6. Non parametric test do exist for nominal & ordinal scale data 7. It is not so powerful and efficient like parametric test
Examples	
Single mean Z, t tests in parametrics paired t test in parametrics Independent samples t test in parametrics One way ANOVA Two way ANOVA	Wilcoxon signed test Wilcoxon signed rank test Mann-Whitney U test Kruskal wallis test Fried man test

Regarding the test used in statistics (whether parametric or non-parametric), we have to be clear about
a. whether you wish to make decisions about differences between the populations from which your samples come, or whether you wish to make decisions about associations between features wthin the population from which your sample come.
b. whether your measurements are at the interval, ordinal or categorical level
c. whether your measurements are matched or unmatched

Once you are certain about these things, you might use the appropriate test according to the rationale of test. Indeed, all the statistical techniques have both advantages and disadvantages, and it is up to you to weigh them up in the context of your own project.

References

1. Schlenker, M.B., Christakis, T.J.,and BragaMele, RM. 2010. Comparing a traditional single optotype visual acuity test with a computer-based visual acuity test for childhood amblyopia vision screening: a pilot study. Can J Ophthalmol.45 (4):368-74.
2. Siegel,S. 1956. Nonparametric Statistics for the Behavioral Sciences International Student Edition. McGraw-Hill ,Kogakusha Ltd. 312p
3. Viera J. A., Garrett,M.J. 2005. The Kappa Statistic Understanding Inter observer Agreement. Fam Med 37(5):pp360-363.

Original Article

Cataract Progression After Intravitreal Pharmacotherapy – A Long term Study

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Abstract

Purpose: To assess the cataract progression rates and cataract surgery rates after intravitreal injection of steroids and anti VEGF drugs and analyze the risk factors leading to progression of cataract.

Methods: Retrospective chart analysis of patients undergoing intravitreal steroid/anti VEGF injection. Lens changes were documented by LOCS 3 grading system. Lens status in the other eye was used as a control. Any ocular surgeries and use of systemic steroids were excluded from the analysis to reduce the confounding effect. Patients were followed up till their last visit or till they underwent cataract surgery. Progression of cataract, rate of cataract surgery and risk factors for progression of cataract were analyzed statistically. Patients were divided into 3 groups

Results: Group (1) Bevacizumab (39 eyes, Mean age 58.6, Mean follow-up 27.9 months, mean injections 3.1) Group (2) Ranibizumab (28eyes, Mean age 67.1, Mean follow-up 26.7 months, mean injections 2.6) Group (3) Triamcinolone (48 eyes, Mean age 54.6 years, mean follow-up 39.3 months, Mean injection 1.0). Patients with progression of cataract in the other eye were excluded from analysis. . Ranibizumab group had similar cataract progression in either eye. Bevacizumab group had 23.1% more progression of cataract compared to control. In the Triamcinolone group 79.1% required cataract surgery. Risk analysis for age and systemic diseases were done.

Conclusion: Cataract progression rate was highest in the triamcinolone group with almost everyone above 50 years progressing. Off label use of Bevacizumb had marginal increase in the cataract progression compared to control eyes while Ranibizumzb was the safest in terms of progression of lenticular change.

Introduction

Intravitreal pharmacotherapy has become the primary line of management in an array of retinal conditions including metabolic diseases like Diabetic Retinopathy, Degenerative diseases like Age Related Macular Degeneration, Vascular diseases like retinal vein occlusions and Inflammatory diseases like posterior uveitis. Drugs used as injections in the posterior segment included steroids like Triamcinolone acetonide, anti vascular endothelial growth factor like Ranibizumab, Bevacizumab, Pegaptanib sodium, Aflibercept etc and antibiotics. Different complications of intravitreal injections are discussed in literature. This includes local adverse events like Endophthalmitis, Glaucoma, Cataract etc and theoretical over emphasized systemic adverse events like thromboembolic episodes. It has been shown in articles that a steroid injection results in secondary glaucoma, which is related to the dose and steroid responsiveness. It is estimated to occur in 20-30% eyes receiving triamcinolone acetonide[7]. Glaucoma is rare in anti VEGF injection. Commonest side effect of intravitreal injection is cataract progression[2,3,4,5,6,7]. This has been documented. But the rate of progression and risk factors for progression of cataract has not been studied. This assumes importance since the number of injection given in some of the diseases is many. It has to be informed to the patient that he or she may need cataract surgery in the course of treatment. This also has clinical implications since cataract surgery may alter the course of the original retinal disease. Diabetic macular edema and wet age related macular degeneration has been known to be worsened by cataract surgery. Visual outcome in phakics and pseudophakics are different for different drugs. Triamcinolone may be more useful in psudophakic eyes than phakic eyes in the treatment for diabetic macular edema. It becomes imperative to know the progression of lens opacities after intravitreal injections. This study was aimed at addressing this issue.

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Objective

To detect the cataract or lens opacity progression after the intravitreal injection of Triamcinolone acetonide, Ranibizumab and Bevacizumab

Methods

It was a retrospective chart review of patients undergoing intravitreal injections in one eye from the year 2004. Strict inclusion and exclusion criteria were designed and institutional review board approval was obtained. Inclusion criteria were 1. Phakic eyes receiving intravitreal injections with other eye used as control. Exclusion Criteria were 1. Any ocular surgery in the injected eye or other eye 2. Change of the drug used for intravitreal injection during the course of the treatment. 3. Use of systemic steroid. 4. Co existing or post treatment glaucoma. 5. Post treatment infections like Endophthalmitis. 6. Trauma to either eye. 7. Lack of follow up of at least one year or till cataract progression documented or cataract surgery performed.

Triamcinolone acetonide has been used only once and not repeated in any eyes. Both 2mg and 4 mg dosage has been used and the differences between the two dosages were analyzed. Both Ranibizumab and Bevacizumab had been used as multiple injections. Rate of cataract progression was studied in terms of number of injection. All the three drugs were compared with regards to the lens opacity progression. Lens Opacity Classification System III was used as a routine for grading the lens changes1. The grades of cataract as posterior sub capsular cataract, cortical cataract and nuclear sclerosis were noted. Cataract was found to be 'progressing' when at two occasions, the slit lamp examinations have noted down an increase in 2 grades as per the LOCS.

Follow up was terminated when the patient underwent cataract surgery in either eye. Follow up period included from the day of first intravitreal injection till the last visit/ when the patient underwent cataract surgery in one of the eyes. Cataract progression rate and cataract surgery rate was calculated in each arm and compared with the other two drugs. Un injected eyes were used as controls and compared with injected eyes. Risk factors for cataract surgery like dosage, number of injections and systemic diseases were also calculated. Statistical analysis was done using SPSS version 16. Multiple logistic regression analysis and ODDS ratio were calculated.

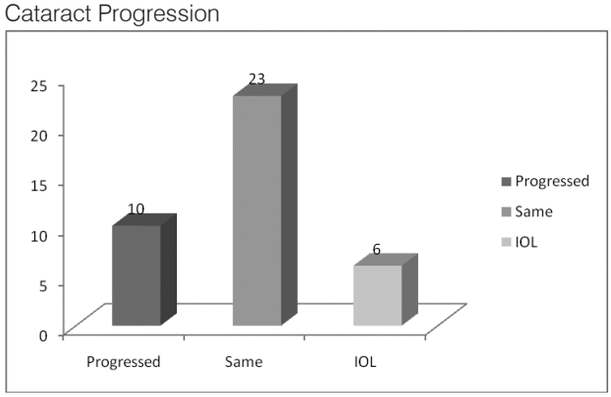
Results

A total of 115 eyes were included in the study. 39 eyes in Group 1(Bevacizumab or Avastin) and 28 eyes in Group 2(Ranibizumab or Lucentis) and 48 eyes in group 3 (Triamcinolone acetonide). Untreated other eye was used as control eye.

Group 1 (Bevacizumab or Avastin)

39 eyes of 39 patients were included. This had 21 males and 18 females. Mean age was 58.6 years. The mean follow up duration was 27.9 months. They had received a mean of 3.1 injections during the follow up. Cataract progressed in 16 eyes. Intra ocular lens implantation was done 6 eyes of these 16 eyes. Chi-square test did not show any difference between males and females (P=0.29). Number of injections and development of cataract were studied and it was found that the number of injections were not significantly related to cataract (P=0.15).

Cataract Progression



Univariate logistic regression analysis was done. One year increase in age resulted in 1.07 risk on getting cataract. The age and number of injections were not statistically significant (P=0.06).

Independent sample t test showed that there is a significant relationship between age and cataract. (P=0.02)
Mann – Whitney U test showed there is no significant relation between follow duration and cataract progression (P 0.28)
Chi square test showed sex (P 0.29) number of injections (P0.15) and etiology (P 0.36) did not have a significant relation to the progression of cataract

Univariate Logistic Regression

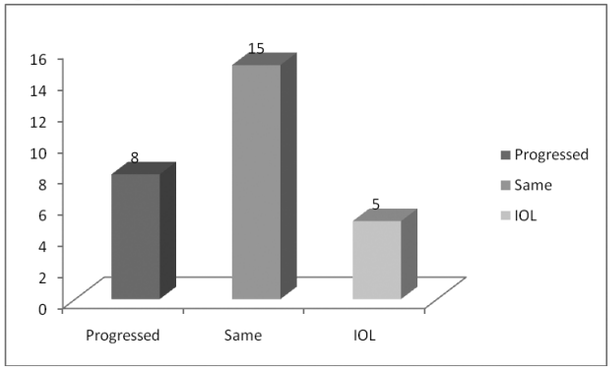
Characteristics	Odds Ratio	P-value	95% Confidence Interval	
			Lower	Upper
Age	1.07	0.06	0.99	1.15
Sex	2	0.29	0.54	7.30
No of Injections	2.24	0.06	0.96	5.22
Diagnosis	1.41	0.26	0.77	2.60
Follow up	1.03	0.24	0.98	1.08

With one-year increase in age there is 1.07 risk of getting the cataract.

Group 2 (Ranibizumab or Lucentis group)

28 eyes of 28 patients were included in the analysis. This had 16 males and 12 females. Mean age was 67.1 and mean follow up duration was 26.7 months and mean number of injections was 2.6. Cataract progressed in 13 eyes of which 5 eyes underwent Intra ocular lens implantation. In this group age was not found to be a significant variable for progression of cataract on independent sample t-test (P=0.86). Univariate logistic regression analysis and diagnosis were not having a significant P value in the progression of cataract.

Cataract Progression



Independent sample t test showed age was not related to cataract progression unlike group 1 (P 0.86)

Follow up duration was also not related to progression of cataract as shown by Mann Whitney U test (P 0.08)

Chi Square test showed Sex (P 0.74) Number of injections (P 1.00) and etiology (P 0.88) were not significantly related to the progression of cataract.

Univariate Logistic Regression

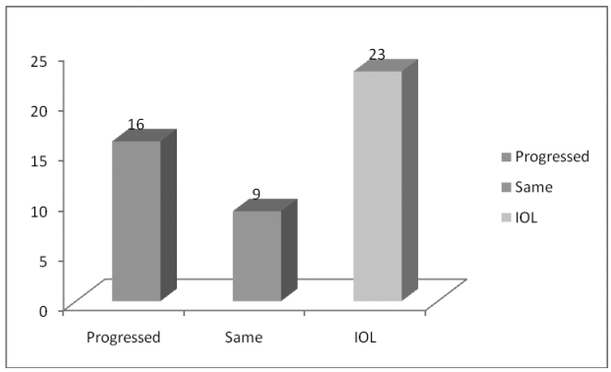
Characteristics	Odds Ratio	P-value	95% Confidence Interval	
			Lower	Upper
Age	1	0.85	0.94	1.07
Sex	1.28	0.74	0.28	5.77
No of Injections	0.76	0.67	0.21	2.65
Diagnosis	0.57	0.34	0.18	1.82
Follow up	0.96	0.10	0.93	1

Univariate logistic Regression analysis of different parameters did not reveal any significant relation with cataract progression

Group 3 (Triamcinlone acetonide)

48 eyes of 48 patients were included in the study. It contained 28 males and 20 females. The mean age was 54.6 years. The mean follow up was 39.1 months. In these cases follow up was terminated if the patient underwent cataract surgery. Otherwise the last date of follow up was taken as final follow up. Of the 48 eyes 38 eyes had progression cataract. 23 eyes underwent cataract surgery and follow up was terminated.

Cataract Progression



Independent sample t-test was done to find any relation between age and cataract development and it was found that age was significantly related with the progression of cataract (P Value = 0.04). There is no difference between males and females. Chi-square test was done for any difference between dosage of Triamcinolone, either 2mg or 4mg. 58.3% of eyes with 2mg injection developed cataract while 86.1% eyes with 4mg-developed cataract. This was statistically significant (P=0.04). Systemic disease like diabetes mellitus was found to be significantly associated with progression of cataract on. Chi-square test (P=0.01). There was no significant association between sex and cataract. Multi variant logistic regression analysis was done and odds ratio was calculated. One year increase in age causes 1.1 times risk of cataract development and it is statistically significant (P=0.05). Compared to 2mg Triamcinolone dosage 2.24 times risk of getting cataract which is statistically significant (P=0.01) and compared non-diabetic cases diabetic patients had 14.92% risk of getting cataract when adjusted other variables which was statistically significant

Independent sample t test showed there was significant relation of cataract progression and age (P=0.04)

Mann – Whitney u test showed there is no significant relation between follow up period and cataract progression (P0.15)

Chi square test

	Cataract	No Cataract	Chi square value	P value
IVTA Dose				
2 mg	7 (58.3%)	5 (41.7%)	4.21	0.04
4mg	31 (86.1%)	5 (13.9%)		
Systemic Disease				
DM	31 (88.6%)	4 (11.4%)	6.93	0.01
Nil	7 (53.8%)	6 (46.2%)		

There is a significant association between IVTA Dose and cataract.

There is a significant association between Systemic Disease and cataract.

Multivariate Logistic Regression

Characteristics	Odds Ratio	P-value	95% Confidence Interval	
			Lower	Upper
Age	1.15	0.05	0.999	1.339
IVTA Dose	29.12	0.01	2.242	378.27
Systemic Disease	14.92	0.02	1.425	156.15

One year increase in age they are 1.15 times risk of getting cataract, which is statistically significant (P=0.05).

Compared to 2 mg, 4 mg IVTA Dose had 2.24 times risk of getting cataract, which is statistically significant (P= 0.01). Compared to the Non-diabetic, diabetic mellitus has 14.92 times risk of getting cataract adjusted for the other variables, which is statistically significant(P=0.02).

Combined Analysis

Injected eyes were compared with the other eye, which was used as a control using Chi Square test. In Group 1 cataract progression was found to be significant with a P=0.05. In-group 2 with Lucentis arm it was not significant (P=0.415). In-group 3 it was highly significant with a P value of 0.001.

The cataract progression of other eye was subtracted from the cataract progression of injected eye to find the actual progression of cataract due to injection. This was compared among the groups.

Proportion Test

Group	Cataract	Proportion	P value
IVTA	23	47.91%	
Avastin	9	23.07%	0.001
Lucentis	3	10.71%	

Compared to Avastin and Lucentis, IVTA had more number of cataracts, which is statistically significant. Chance of cataract progression was 2 times in Avastin group and nearly five times in Triamcinolone group compared to Lucentis group.

Discussion

It is well known from different studies that triamcinolone injection increases the risk of progression of cataract. But the rate of cataract development and comparison between the other commonly used intravitreal injections like Lucentis Or Avastin were not available in literature. The need for long follow up was mandatory for this study. Here we have evaluated the eyes for a very long duration. Strict inclusion criteria have ensured that other causes of cataract and bias are removed. Also it can be argued that cataract can be progressing naturally since most of the patients are aged. That is the reason why we have taken the other eye as controls. There is significant association between cataract and age in groups 1 and 3. In Lucentis group it was not significant. We could not find a relation between sex and etiology or follow up duration with cataract. In-group 3 there was significant association between dosage of IVTA and Diabetes mellitus with cataract. One-year increase in age they are 1.15 times risk of getting cataract. Compared to 2 mg, 4 mg IVTA Dose had 2.24 times risk of getting cataract. Compared to the Non-diabetic, diabetic mellitus has 14.92 times risk of getting cataract adjusted for the other variables. In the Group 2 where Lucentis was used cataract progression was the lowest. There was no significant relation between age, etiology or systemic diseases and cataract. Compared to this group Avastin had more cataract progression. There was almost 2 times the chance of getting lens opacities compared to Group 2. In both Group 1 and 2 there was no relation between cataract and the number of injections. Comparison of injected eyes and control eyes also showed the significant increase in cataract in groups 1 and 3. Lucentis was the safest drug in thee settings. Probably the cataract in Avastin group was more because of the preservatives present in this off label preparation. This result has to be considered when deciding which drug to use. In our knowledge this is the only study of cataract progression comparing three most commonly used intravitreal drugs. The long follow up was the main

plus point of this study. Probably more numbers would have made the statistical outcome more assertive.

Conclusion

Cataract progression after intravitreous injection is maximum after triamcinolone, which is also dose dependent and almost 80% eyes requiring intervention within 2 years. Lucentis has been the safest in terms of lens changes while Off Label Avastin with preservatives caused progression in almost double that of Lucentis. Age and Diabetes mellitus are factors influencing cataract progression.

References

1. Leo T Chylack Jr, John K Wolf, David M Singer, Cristine Leske, Mark A Baltimore, Ian Bailey et al. The Lens Opacity Clasification System III. Arch Ophthalmol, 1993,111:831-6.
2. Cekic O,Chang S,Tseng JJ,Akar Y, Barile GR,Schiff WM. Cataract Progression after intravitreal triamcinolone injection.Am J Ophthalmol. 2005;139(6):993-8.
3. Thomson JT. Cataract progression and other complications of intravitreal triamcinolone for macular edema. Am J Ophthalmol. 2006:141(4);629-37.
4. Chu YK,Chung EJ,Kwon OW, Lee JH, Koh HY. Objective evaluation of cataract progression after high dose intravitreal triamcinolone injection. EyE.2008:22(7);895-9.
5. Iwami H, Kohno T, Yamamoto M, Kaida M, Miki N, Ataka S, Shiraki K. progression of cataract following photodynamic therapy combined with intravitreous triamcinolone injection in cases of age related macular degeneration. Osak City Med J. 2011;57(2): 49-57.
6. Gilles MC,Islam FM, Larsson J,Passadhika S,Gaston C,Zhu m,Wong TY. Triamcinolone indiced cataract in eyes with diabetic macular edema:3 year old prospective data froma randomized clinical trial.Clin Experiment Ophthalmol.2010.38(6);605-12.
7. Gillis MC, Kuzniarz M, Craig J, Ball M, LuoW, Simpson JM. Intravitreal triamcinolone indiced elevated intraocular pressure is assoiciated with the development of posterior subcapsular cataract. Ophthalmology. 2005:112(1);139-43.

Original Article

Real World Dosing of Anti Vegf Therapy in ARMD - Patient Compliance, Efficacy and Complications

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Abstract

Aim: To study patient compliance, real world dosing, efficacy and complications of antiVEGF therapy in AMD.

Methods: 240 eyes of 220 patients who underwent antiVEGF treatment for AMD between 2010 and 2013 were analyzed retrospectively. Patients who were diagnosed to have typical wet AMD and variants like PCV, RAP lesions were included. All patients had received 3 loading doses of antiVEGF at 4 weekly intervals and followed up monthly. Retreatment was based on vision and OCT characteristics in accordance with the PRONTO recommendations. Analysis included number of injections, vision change, OCT features and complications as noted during follow up. Reasons for poor compliance if observed were elucidated.

Results: 104 patients (47.3%) completed 2 years and 109 (45%) had < 1 year follow up. Only 76 patients (34.6%) strictly followed the advised monthly follow up schedule. 60 (78.9%) of these had medical claim benefits. 54.9% eyes that received Ranibizumab initially switched over to Bevacizumab. The mean number of injections was 4.77 at 1year, 3.83 at 2years and 5.81 at 3years. The mean pretreatment vision improved from 0.91 to 0.76 log units post-treatment. Overall 216 eyes showed stable/improved vision after antiVEGF therapy. Complications included uveitis(3 eyes), endophthalmitis(1 eye), accelerated hypertension(4 patients), angina(1 patient), minor stroke(1 patient).

Conclusion: Patient compliance to antiVEGF therapy is poor mainly due to cost of therapy involved. However treated patients maintain vision inspite of irregular follow up and antiVEGF therapy remains a safe treatment option in AMD. Tachyphylaxis may occur with irregular therapy.

Aim of Study

Neovascular or wet age-related macular degeneration (AMD), a leading cause of blindness[1], is responsible for 80% of significant visual loss related to AMD[2]. Vascular endothelial growth factor (VEGF) stimulates angiogenesis and increases vascular permeability, and appears to be the main mediator in the pathogenesis of neovascular AMD[3]. Anti-VEGF drugs has been demonstrated to be an effective treatment of AMD.Ranibizumab is currently the only FDA approved anti-VEGF drug available in India, for intravitreal treatment of choroidal neovascularization(CNV) that has shown improvement in visual acuity (VA)[4,5]. Bevacizumab another agent when injected intravitreal is an effective treatment for neovascular AMD.[6,7] However most of the major trials have ascertained the need for monthly injections for as long as 2 years for best results[4,5] which may not be feasible in real practice. Studies have demonstrated the efficacy of a variable dose PRN schedule [8,9,10,11]. However most of these studies focused predominantly on optimizing visual acuity. In reality, additional therapeutic goals come into play, including minimizing treatment burden and cost, ensuring patient compliance and minimizing ocular and systemic complications. The aim of this study is to look at patient compliance with a PrONTO akin variable dose schedule in our population and to study the efficacy and complications of such a regimen and elucidate causes for poor compliance.

Materials and Methods

This was a retrospective study involving eyes that were diagnosed as having wet AMD and treated with anti VEGF monotherapy at Chaithanya Eye Hospital and Research Institute, Trivandrum between June 2010 and May 2013. The diagnosis of wet AMD was made by 78 D examination, indirect ophthalmoscopy, OCT and fundus fluorescein angiography. All eyes were treated similar to the PRONTO

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schedule with 3 loading doses of pan VEGF blockade at 4 weekly intervals and followed up at monthly intervals for 1 year. Best corrected visual acuity and reading ability at baseline and at each follow-up examination were recorded. A note of systemic complications if any was also recorded. Patients who had OCT or FFA evidence of persistant activity or recurrence were treated with the same anti VEGF drug or changed to another drug under certain circumstances. OCT (Heidelberg Retina Angiogram and Zeiss STRATUS and CIRRUS) was used to detect macular oedema, subretinal fluid and pigment epithelial detachment. OCT criteria for retreatment was based on the PRONTO study5. Indocyanine green angiography and autofluorescence were done whenever necessary as decided by the treating surgeon. The diagnosis of PCV was confirmed with ICG angiography. Eyes primarily diagnosed as wet AMD or variants including PCV, RAP etc and initiated on anti VEGF monotherapy were included in the study.Those who did not complete the 3 loading dose schedule, eyes with other retinal diseases, those that had undergone laser treatment, PDT or anti VEGF therapy in the past were excluded from the study. Thus all the patients in this study were treatment naïve patients.All patients signed an informed consent for off label use of bevacizumab whenever used .The data was entered into a Microsoft excel sheet and statistical analysis done.

Patients after completion of 3 loading doses of anti VEGF were followed up at monthly intervals. Patients who completed atleast 7 out of the 9 scheduled follow ups in a year were considered to have regular follow up while those unable were grouped under poor follow up. Patients with poor follow up were questioned regarding their poor compliance and the causes elucidated. This included telephonic enquiry for those who did not follow up at the hospital.

Results

240 eyes of 220 patients were part of this analysis. In 20 patients both eyes had active CNVM and required anti VEGF therapy. In bilateral cases, the worse eye got the injection first followed 1 week later by other eye. The mean age of the study population was 65.79 yrs (Range 52-81 yrs). There were 142 males (64.5%) and 78 females (35.5%). The study included 129 eyes (53.8%) diagnosed with wet AMD, 105 eyes (43.8%) with polypoidal choroidal vasculopathy (PCV) and 6 eyes (2.5%) with Retinal angiomatous proliferation (RAP). 158 eyes (65.8%) received intravitreal bevacizumab primarily. 82 eyes (34.2%) received intravitreal ranibizumab, of which 42 eyes (52.1%) converted to intravitreal bevacizumab.

Patients after completion of 3 loading doses of anti VEGF were followed up at monthly intervals thereafter. Patients who completed at least 7 of 9 scheduled follow ups in a year were considered to have regular follow up while those unable were grouped under poor follow up. 109 patients (45.4%) had less than 1 year follow up(Group A), 111 patients (46.3%) had atleast 1 year follow up(Group B) including 104 patients with 2 years follow up(Group C). Only 56 patients (51.4%) in group A, 76 patients (68.5%) in group B and 69 patients (66.4%) in group C had regular follow up. The remaining had poor follow up- 48.6%, 31.5% and 33.7% respectively (mean 37.9%).

The causes of poor follow up are tabulated below.

Table: 1 -Causes of poor follow up.

Causes	<1 year follow up (n-53)	1 year follow up (n-35)	2 years follow up (n-35)
Financial implications	49	30	30
No bystander to accompany	23	11	13
Other systemic morbidity	15	10	12
Waiting time at hospital	8	3	3
Vision drop	12	16	14
Expired	2	0	1
Ocular complications	4	2	2
Unable to assess	4	5	5

Fig: 1 Patient with regular follow up showing improvement in vision after intravitreal bevacizumab. This patient received 4 injections in first year, 3 injections in the second year and 4 injections in the third year. Visual improvement was seen after the loading dose in this patient.

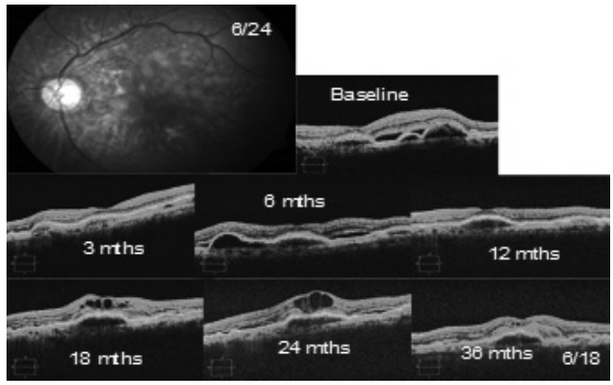


Fig: 2 Patient with irregular follow up showing persistence of fluid and poor visual outcome after intravitreal ranibizumab. This patient received 4 injections in the first year and 1 injection in the second year and was lost to follow up. Visual improvement was not seen after loading dose.

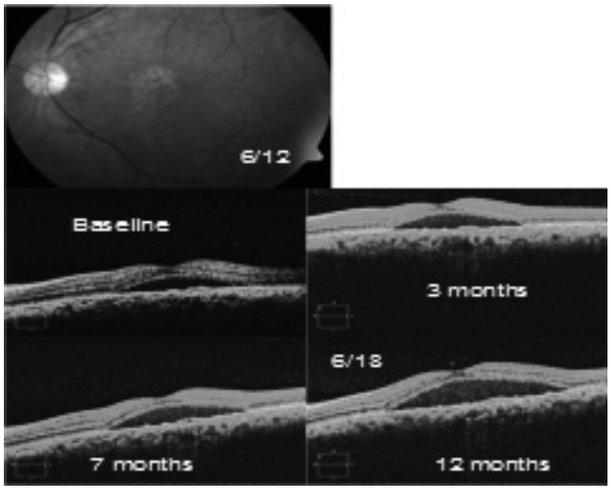
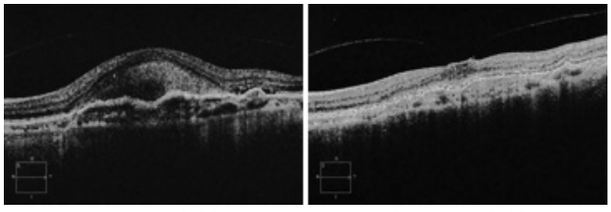


Fig: 3 Patient who resolved with 3 injections of intravitreal bevacizumab with no recurrence after 18 months of follow up with maintainence of vision.



Baseline 6/60 **3 months 6/12**

The mean pre-treatment visual acuity was 0.91 which improved to 0.76 log units post-treatment. At 3 months 116/240 eyes (48.3%) showed an improvement in vision by atleast 1 line from baseline, 24/240 eyes (10%) showed a drop in vision by atleast 1 line from baseline while in 100/240 eyes (41.7%) visual acuity remained status quo. Among the 127 eyes which had atleast 1 year follow up, visual acuity improved by more than 1 line in 22 eyes, remained stable in 80 eyes and worsened by more than 1 line in 9 eyes. At 2 years follow up visual acuity improved by more than 1 line in 19 eyes, remained stable in 78 eyes and worsened by more than 1 line in 7 eyes. Overall 216 eyes (90%) showed stable/improved vision after antiVEGF therapy at last follow up (range; 7 mths- 49 mths). The mean number of injections was 4.77 at year 1, 3.83 at year 2 and 5.81 at year 3.

Ocular complications included uveitis(3 eyes), endophthalmitis(1 eye) , retinal holes (2 eyes) and ocular hypertension (3 eyes). All 3 eyes with uveitis were following intravitreal bevacizumab and occurred during additional antiVEGF therapy for recurrence. All these patients had anterior nongranulomatous uveitis with minimal anterior vitritis and resolved well with topical steroids. 1 patient who developed anterior uveitis during first injection of bevacizumab during loading dose schedule was excluded from the analysis. One eye which developed endophthalmitis during the 4th injection of intravitreal bevacizumab was successfully treated with intravitreal vancomycin and ceftazidime. Culture was negative and a diagnosis of sterile endophthalmitis was made. 3 eyes developed elevated intraocular pressure (2 bevacizumab,1 ranibizumab) and was controlled with topical antiglaucoma drugs. 2 eyes were detected to have retinal holes that required barrage laser photocoagulation. Systemic complications included accelerated hypertension (4 patients), angina(1 patient), minor stroke(1 patient) and worsening of nephropathy in 1 patient. All the 4 patients with hypertension had preexisting disease and were on therapy. Out of these 1 patient had accelerated hypertension on day 1 and needed hospitalization while 3 patients developed accelerated hypertension 1-2 weeks after antiVEGF therapy (2 bevacizumab, 2 ranibizumab). 1 patient who received additional bevacizumab developed angina and required hospitalization and management. 1 patient who received additional bevacizumab developed a minor stroke 2 weeks after injection which resolved in 3 weeks. 1 patient who received additional ranibizumab developed worsening of diabetic nephropathy and required dialysis. 3 patients expired during the study period but cause of death could not be attributed to anti VEGF therapy as they had other significant systemic morbidity and the event occurred atleast 6 weeks after last injection.

Discussion

Determining the optimal dosing schedule for anti-VEGF therapy in neovascular AMD remains a challenge because neither the effect of drugs in human eyes nor the nature of the disease itself is fully understood. The MARINA and ANCHOR trials so far reported the best functional outcome results by using monthly injections of ranibizumab[4,5]. However monthly injections may not be a feasible option in real life practice. PRN treatment regimens aim to decrease the number of injections per year. Studies using PRN treatment regime[8,9] have reported a lower injection rate per year compared to monthly schedule with visual stabilisation. The PrONTO results showed a great inter-patient variability in the number of injections needed, ranging from 3 to 23 throughout a 2-year period[9]. Similar results have been reported in various studies[10,11] involving intravitreal bevacizumab. Though monthly injections may be required in some patients, many patients do well with less frequent injections. It is reported that 17- 20% of patients did not require further treatments

after the initial 3 monthly injections[9,12]. No statistically significant correlation was found between the need for more frequent injections and visual acuity outcomes in various studies[9,10,]. The PRN treatment schedule is the only feasible approach of treating patients with wet AMD in our clinical practice.

32-43% patients gained 15 or more letters from baseline in the ABC and PRONTO trials respectively at 24 months follow up[11,9]. However in our study percentage of people who showed vision improvement from baseline was 17.3% at 1 year and 15% at 2 years. The lesser percentage of people demonstrating visual improvement and lesser number of injections used in year 1 and 2 and the poor follow up, in a way indicates under-treatment. This may also be the reason for tachyphylaxis as found in our study by third year. The mean number of injections in our study was 4.77 at 1year which decreased to 3.83 at 2years but increased to 5.81 at 3years. However mean pretreatment vision improved from 0.91 to 0.76 log units post-treatment in our study. Bashshur et al had reported that the mean number of injections was 3.4 at 1 year and additional 1.5 at the end of 2 years[10]. The PRONTO study however required 5.6 injections at 1 year and additional 4.3 injections at 2years9. The variability in the number of injections may be due to the different agents used (bevacizumab has a longer half-life and so lesser number of injections), baseline lesion characteristics, eligibility criteria, geographic variations in the lesion and response.

Considering the cost of therapy involved, ranibizumab , per dose costs 30,000 rupees which is four times the cost of bevacizumab. Intravitreal bevacizumab is the commonly preferred drug among the participants (66%) even when both the drugs were offered and the status of ranibizumab being an eye specific agent and the fact that it is FDA approved was explained to the patients. Also 55% of patients who were initiated on ranibizumab therapy converted to bevacizumab when retreatment was required. Considering the average Indian monthly income as 3645 Rs (PTI news april, 2010) and considering the fact that many of these patients require multiple injections, this is a huge financial burden. Unlike in the west, most of our patients do not have a medical insurance and many insurance companies donot give full coverage so that expenses may become significant over time during treatment. Patient assistance programs exist in the west that may partially or totally offset the cost of these medicines. Such programs hardly exist in our country. Although the expense and risks may be reduced by the PRN dosing schedule, the time burden on patients and practitioners remain due to monthly follow up. In real-life scenario, patient adherence issues matter, considering their age, dependency and other systemic morbidity. The cost involved in travel and OCT examination adds up. Even in patients with financial assistance motivation for follow up is difficult due to the poor vision status. Most patients expect visual gains and find it difficult to comprehend the concept of vision stabilization. Even in the sponsored PRN trials ,drop outs ranged from 6-50%[4,5,11,13]. In our study 37% patients had poor follow up attributable to lack of awareness or due to other modifiable factors which was analysed in this study.

A metaanalysis on ranibizumab published revealed that serious adverse ocular events including retinal detachment and endophthalmitis occurred in< 0.1% of intravitreal injections. Less serious adverse ocular reactions occurring in < 2% of patients included intraocular inflammation and increased intraocular pressure[13,14,15]. In patients who received bevacizumab ocular adverse events were seen in 3%[11,16]. In our study serious ocular events included endophthalmitis which was seen in 0.4%. Other ocular problems included transient uveitis (1.25%), transient ocular hypertension (1.25%) and retinal holes (0.8%).The SAILOR study found that the incidence of vascular and nonvascular deaths during the 12-month study was 0.7- 0.9% and 0.7-1.5%[13]. The trials which involved bevacizumab found that 4.6 % of patients developed systemic problems including myocardial infarction but did not report any significant mortality[11,16]. In our study 0.9% of patients developed a significant thromboembolic event (minor stroke 1, angina 1). 1.8% developed accelerated hypertension and 0.5% patients developed worsening of nephropathy.

Conclusion

Patient compliance to even the less ideal variable dose antiVEGF therapy is poor mainly due to cost of therapy involved and the need for frequent follow ups. Patients who demonstrate significant visual improvement after the loading dose, patients who have medical claim facilities and those with bilateral disease have the best follow up rates. Intravitreal bevacizumab is the commonly preferred drug. However treated patients on the overall maintain/gain vision in spite of irregular follow up and antiVEGF therapy remains a safe treatment option in AMD. Poor response due to tachyphylaxis may occur with irregular therapy.

Notes: The authors declare no conflict of interest or financial disclosure.

References

1. Augood C, Fletcher A, Bentham G, et al. Methods for a population-based study of the prevalence of

and risk factors for age-related maculopathy and macular degeneration: the EUREYE study. Ophthalmic Epidemiol. 2004;11:117–129.
2. Bressler NM. Age-related macular degeneration is the leading cause of blindness. JAMA. 2004;291:1900–1901. doi: 10.1001/jama.291.15.1900.
3. Ferrara N: Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004;25: 581–611.
4. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1432–1444.
5. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1419–1431.
6. Arevalo JF, Fromow GJ, Sanchez JG, et al. Primary intravitreal bevacizumab for subfoveal choroidal neovascularization in age-related macular degeneration: results of the Pan-American Collaborative Retina Study Group. Retina 2008; 28: 1387–1394.
7. Martin DF, Maguire MG, Fine SL, et al;(CATT Research Group). Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two year results. Ophthalmology. 2012; 119: 1388-1398.
8. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol. 2008;145:239–248.
9. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol. 2009;148;43–58.
10. Bashshur ZF, Haddad ZA, Schakal AR, et al. Intravitreal bevacizumab for treatment of neovascular age-related macular degeneration: the second year of a prospective study. Am J Ophthalmol. 2009;148; 59–65.
11. Tufail A, Patel PJ, Egan C, et al. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. BMJ 2010;340:c2459.
12. Holz FG, Amoaku W, Donate J, et al. SUSTAIN Study Group. Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. Ophthalmology. 2011 Apr;118(4):663-71
13. Boyer DS, Heier JS, Brown DM, et al, A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. Ophthalmology. 2009 Sep;116(9):1731-9.
14. Burbee BG, Ho AC, Brown DM, et al;(HARBOR Study Group). Twelve-month efficacy and safety of 0.5mg or 2.0mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2013;120:1046-1056.
15. Kourlas H, Abrams P. Ranibizumab for the treatment of neovascular age-related macular degeneration: a review. Clin Ther. 2007 Sep;29(9):1850-61.
16. Fung AE, Rosenfeld PJ , Reichel E: The international intravitreal bevacizumab safety survey: using the internet to assess drug safety worldwide. Br J Ophthalmol 2006; 90: 1344–1349.

Original Article

Diagnostic Accuracy of Spectral Domain Optical Coherence Tomography in detecting RPE leak in Central Serous Chorioretinopathy

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Dr Bindu Rajesh MS, FVRS

Abstract

Diagnostic Accuracy of Spectral domain Optical Coherence Tomography in detecting RPE leak in Central Serous Chorioretinopathy

To study the accuracy of spectral domain optical coherence tomography (SD-OCT) in detecting retinal pigment epithelial (RPE) leak in central serous chorioretinopathy (CSCR) by comparing the leakage site with fundus fluorescien angiography(FFA).

Methods

A prospective interventional case series of 116 eyes. Cases were divided into 3 groups based on the duration of CSCR. Group 1 had CSCR less than 3 months. Group 2 with 3 to 6 months and Group 3 had eyes with more than 6 months duration. All eyes underwent comprehensive examination, FFA and SD-OCT evaluation.RPE leakage in FFA and SD-OCT was identified and documented by two independent investigators blinded to each other. A third investigator evaluated images from FFA AND SD-OCT in MS Paint software and compared leakage point in SD-OCT with FFA leakage. Overall diagnostic accuracy as well as group wise accuracy was statistically analyzed.

Results

There were 79% males and 21% females in the study. The mean age was 37.4 ± 7.3 years. There was no statistical difference in demographic characteristics among groups. Group1 had 39 eyes and group2 and group3 had 42 and 35 eyes respectively. The overall diagnostic accuracy of detecting RPE leak by SD- OCT was 60% (p-0.002). In group1, the accuracy was found to be 98% (p-0.001), Group2, SD-OCT showed 59% accuracy (p-0.12) and Group3 showed only 20% accuracy (p-0.001) in detecting the RPE leak when compared to FFA. In Group 1 SD-OCT showed an accuracy of 98%.Out of 39 eyes, it detected RPE leak accurately in 38.

Conclusion

SD-OCT can replace FFA in detecting RPE leak in acute CSCR (less than 3 months duration). It is useful in cases where FFA is contraindicated. All cases of acute CSCR should be subjected to SD-OCT. FFA is still the gold-standard diagnostic tool to detect RPE leak in chronic CSCR

Introduction

Central serous chorioretinopathy (CSCR) is characterized by idiopathic detachment of the neurosensory retina in the macular area, secondary to one or more retinal pigment epithelium (RPE). The ocular manifestations in CSCR have been thought to arise primarily from an abnormality of the RPE[1]. The gold standard investigation to demonstrate the RPE leak is Fundus Fluorescien Angiography(FA). FA of classic CSCR shows one or more focal leaks at the level of the RPE. The classic "smokestack" appearance of the fluorescein leak is seen only in 10-15% of cases. Ink blot pattern is the second type of presentation. FA of diffuse retinal pigment epitheliopathy demonstrates focal granular hyperfluorescence corresponding to window defects and blockage caused by RPE atrophy and clumping with one or more areas of subtle continued leakage. A newer classification scheme based on the status of the retinal pigment epithelium employs the terms classic CSCR and diffuse retinal pigment epitheliopathy(DRPE). Classic cases have minimal focal RPE damage and discrete leaks at the level of the RPE, and DRPE cases have extensive RPE damage and diffuse leakage[2]. CSCR can occur in an acute or chronic form. The designation of chronicity in CSC is

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somewhat arbitrary. Some authors have defined chronicity as persistent fluid for at least six months,[3] whereas recent clinical trials have used three months with persistent fluid[4].

Objective

To study the accuracy of spectral domain optical coherence tomography (SD-OCT) in detecting retinal pigment epithelial (RPE) leak in central serous chorioretinopathy (CSCR) by comparing the leakage site with fundus fluorescien angiography (FA).

Materials and Methods

A prospective interventional case series of 116 eyes of 116 patients clinically diagnosed with CSCR was included in the study. CSCR was diagnosed as either classic form, a circumscribed area of serous detachment of the neurosensory layer of retina with or without PED in the macular region associated with solitary or few leaks seen in FFA, or a diffuse retinal pigment epitheliopathy(DRPE) which was indicated by a widespread area of RPE changes associated with many angiographic leaks

Eyes were divided into 3 groups based on the duration of CSCR. Group 1 had CSCR less than 3 months. Group 2 with 3 to 6 months and Group 3 had eyes with more than 6 months duration of CSCR. All patients had undergone a complete ophthalmic examination, including measurement of best-corrected visual acuity (BCVA) using the Snellen visual acuity chart converted to logarithm of the mini¬mum angle of resolution (logMAR) visual acuity, slit-lamp biomicroscopy with a noncontact fundus lens. fundus colour photo, fundus fluorescien angiography (FA) and SD-OCT (Heidelberg Engineering, Heidelberg, Germany). The light source of SDOCT is a super luminescent diode of average wavelength 870nm. It uses an ultra high scan speed of 40,000 Ascans per second. Both eyes were dilated and line scans comprising 16 frames equally spread in a rectangular area of 8.6 x 7.2 x 1.9 mm (lateral x lateral x depth) were taken in both eyes in central 30^{o} of macula. An increase in the scanning area was done according to the size of the serous detachment. (3 frames more than the size of the serous detachment) 61 B-scans were acquired and each B-scan is 768 A scans per frame. The distance between each B scan was 120μ and the scan acquisition time was 35 seconds.

Eyes with any other ocular problems or past history of surgery were excluded. Eyes with bilateral CSCR also excluded from the study.

Patient Demography

Total no of eyes (n)	116
Group 1 (<3 months duration)	39
Group 2 (3 months – 6 months duration)	42
Group 3 (> 6 months duration)	35
Mean age	37.4 ± 7.3 years
Male : female ratio	3:1

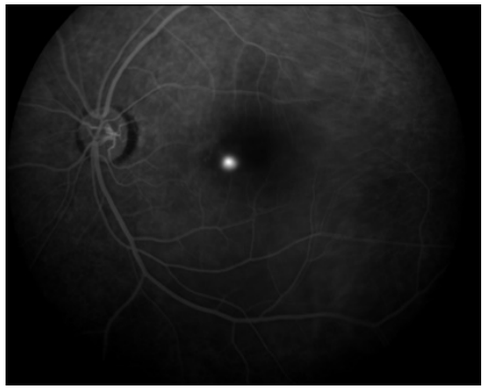
RPE leakage in FFA and SD-OCT was identified and documented by two independent investigators blinded to each other. RPE leak from SD-OCT was identified by a RPE micro rip (focal discontinuity in the RPE layer in dense scan mode) and RPE protrusion described by RPE protrusion. A third investigator evaluated images from FFA AND SD-OCT in MS Paint software and compared leakage point in SD-OCT with FFA leakage point.

INVESTIGATOR – 1 FFA evaluation	INVESTIGATOR – 2 SD-OCT evaluation	INVESTIGATOR -3 Comparative evaluation of FFA and SD-OCT

3 Independent investigators (blinded to each other)

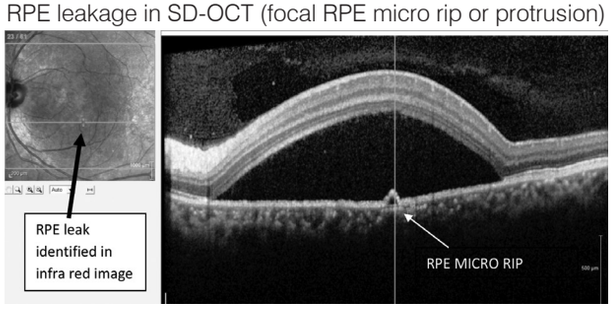
INVESTIGATOR – 1

RPE leakage in FFA as ink blot or smoke stack or DRPE



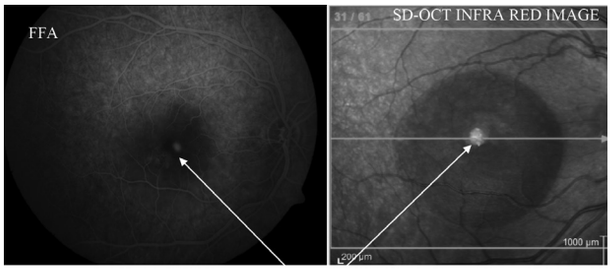
INVESTIGATOR – 2

RPE leakage in SD-OCT (focal RPE micro rip or protrusion)



INVESTIGATOR – 3

Comparison of RPE leakage points in FFA and SD-OCT INFRA RED IMAGE (pictures in MS paint software for comparison of leakage points)



RPE LEAK IN FFA AND SD-OCT INFRA RED IMAGE COMPARED

The third investigator compared the leakage points in FFA and SD OCT (marked in the red free image) and recorded accuracy. Overall diagnostic accuracy was statistically analyzed and also with in each group. Proportion test is used for the analysis. Statistical software R is used for finding proportion and SPSS Ver.19 is used for finding frequencies

Results

There were 79% males and 21% females in the study. The mean age was 37.4 ± 7.3 years. There was no statistical difference in demographic characteristics among groups. Group1 had 39 eyes and group2 and group3 had 42 and 35 eyes respectively. The overall diagnostic accuracy of detecting RPE leak by SD- OCT was 60% (p-0.002). In group1, the accuracy was found to be 98% (p-0.001), Group2, SD-OCT showed 59% accuracy (p-0.12) and Group3 showed only 20% accuracy (p-0.001) in detecting the RPE leak when compared to FFA. In Group 1 SD-OCT showed an accuracy of 98%.Out of 39 eyes, it detected RPE leak accurately in 38.

Group	Eyes (n)	Diagnostic Accuracy	Statistical significance (P value)
Group 1	39	98%	0.001
Group 2	42	59%	0.12
Group 3	35	20%	0.001
Overall	116	60%	0.002

Discussion

Previous studies using TD-OCT have reported on the morphologic changes of RPE5. However, it was difficult to confirm that such RPE changes corresponded precisely to the leakage sites on FA. SD-OCT allows us to identify the configurations of morphologic RPE changes at the leakage sites in eyes with CSC. Using Spectralis HRA+OCT, RPE microrips cor¬responding to leakage sites were precisely demonstrated in 38 cases out of 39. The one case which was not detected was a case of multiple leak CSCR where the second leak area was out of the scan frame. If the scan area would have been increased by 10%, then the second leakage site would also have been identified. The second group (duration of CSCR 3 to 6 months) showed multiple RPE irregularities which made it difficult to distinguish the micro rip and RPE protrusion from the RPE irregularities and disruptions. The presence of fibrin also hindered the process of identification of the RPE rip. The third group (duration of CSCR more than 6 months) showed extensive RPE alterations and atrophic changes. The accuracy of detecting the leak was only 20%.

Imaging of acute CSCR (< 3 months) with SD-OCT dense scan mode will enable us to identify the micro rip corresponding to the leakage site in FFA. This means that, SD-OCT can replace FFA in acute cases of CSCR especially in cases with contraindication. But FFA remains the gold standard for identifying the RPE leak in chronic CSCR. The cases with no leakage and only DRPE in FFA showed extensive RPE damage and mottling.

Conclusion

SD-OCT can replace FFA in detecting RPE leak in acute CSCR (less than 3 months duration). It is useful in cases where FFA is contraindicated. All cases of acute CSCR should be subjected to SD-OCT. FFA is still the gold-standard diagnostic tool to detect RPE leak in chronic CSCR

References

1. Gass JD. Pathogenesis of disciform detachment of the neu¬roepithelium. Am J Ophthalmol 1967;63 Suppl:1-139.
2. Spaide RF, Campeas L, Haas A, et al. Central serous chorioretinopathy in younger and older adults. Ophthalmology. 1996;103:2070–2079.
3. Yannuzzi LA. Central serous chorioretinopathy: a personal perspective. Am J Ophthalmol.2010;149:361–363
4. Chan WM, Lai TY, Lai RY, Tang EW, Liu DT, Lam DS. Safety enhanced photodynamic therapy for chronic central serous chorioretinopathy: one-year results of a prospective study. Retina 2008;28:85–93
5. Hussain N, Baskar A, Ram LM, Das T. Optical coherence tomographic pattern of fluorescein angiographic leakage site in acute central serous chorioretinopathy. Clin Experi¬ment Ophthalmol 2006;34:137-40.

Original Article

Cornea Changes After Corneal Collagen Crosslinking Using Riboflavin and Ultraviolet - A Light

Dr. Teena Elizabeth George MBBS, Dr. Meenu C Jacob DO, Dr. David Pudukadan MS, Dr. Lilan Bhat MS

Abstract

Aim: To study the visual & corneal topographic changes after corneal collagen cross-linking with riboflavin using ultraviolet-A light in keratoconus.

Materials and methods:
Prospective analytic study
25 eyes of 23patients,with the below mentioned inclusion criteria are identified at the outpatient clinic at little flower hospital,Angamaly from Jan 2013 to Jan 2014. Ocular examinations including refraction, best corrected visual acuity (BCVA),slit lamp examintion, dilated fundus examintion with 90D, corneal topography and pachymetry were recorded before C3R and at 6months follow up.

Inclusion criteria :
Progressive keratoconus.
Age less than 45 years

Exclusion criteria:
Corneal thickness less than400 μm
Slit-lamp evidence of corneal scarring
Steep K >60 D
History of herpes virus keratitis
Severe dry eye
Concurrent corneal infections
Women who are pregnant or nursing at the time of the initial treatment.

Results :
Male:female ratio 18:5
Mean age :18.33+/-4.35(range 13-29)
24/25 had subepithelial haze post C3R.
No complaints of glare/photophobia
This showed that BCVA improved at least one line in 36% (9/25) of eyes and improvement by half line in 28% (7/25) of eyes and stable in rest of the eyes .
Astigmatism decreased by a mean of 0.55Ddiopter (D). ($p<0.05$)
The steepest keratometry value decreased by a mean of 1.17 D($p<0.05$)

Conclusion:
Results indicate there is an improvement in BCVA and flattening of cornea after C3R in keratoconus .Thus, collagen crosslinking is an effective therapeutical option for progressive keratoconus.

Aim of the study

To evaluate the effect of collagen crosslinking (CXL) with riboflavin using ultraviolet-A light in eyes with progressive keratoconus and a minimum follow-up of 6 months.

The purposes of this study were
(1) To evaluate visual outcome (changes in best corrected visual acuity and corneal astigmatism) after C3R .
(2) To evaluate topographic changes (curvature of the anterior surface of the keratoconus cornea) after C3R.
(3) To study the side effects following collagen cross linking with riboflavin.

Methods and materials

25 eyes of 23 patients with progressive keratoconus were included in this study. All eyes had completed 6 months of follow-up .

Inclusion criteria :
Progressive keratoconus.
Age less than 45 years

Exclusion criteria:
Corneal thickness less than400 μm

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Slit-lamp evidence of corneal scarring
Steep K >60 D
History of herpes virus keratitis
Severe dry eye
Concurrent corneal infections
Women who are pregnant or nursing at the time of the initial treatment

All patients provided informed consent after receiving a detailed description of the nature of the treatment.

Procedure

After topical anesthesia of propracaine hydrochloride 0.5% eye drops was administered, the epithelium was removed using a blunt spatula in a 9.0 mm diameter area. This was to ensure that the riboflavin penetrated the stroma and that a high level of UVA absorption was achieved. As a photosensitizer, 0.1% riboflavin solution was applied to the cornea every 5 min for 30 min before the irradiation to allow sufficient saturation of the stroma. Next, an 8.0-mm diameter of central cornea was irradiated with UVA light with a wavelength of 370 nm and an irradiance of 3 mW/cm2 for 30 mins using radiators with UVA diode(IROC ,Zurish Switzerland)

After crosslinking, bandage contact lens was applied(which is removed on day 3). Topical antibiotic eye drops(Moxifloxacin) for 2 weeks and artificial tears for 1 month were prescribed. Topical steroids were also prescribed in tapering doses for 1 month after the epithelium has healed.

Follow-up examinations were performed on day 1 and six months. At 6months,ocular examinations including refraction, best corrected visual acuity (BCVA), corneal topography using visante OCT were recorded at each visit.

To quantify the cross-linking effect, maximum in the 3.0 mm zone topography, astigmatism, and BCVA were recorded.

Results

The mean age was 18.33+/-4.35(range 13-29).
The Male:female ratio 18:5.
24/25 had subepithelial haze 6 months after C3R.
But there were no complaints of glare/photophobia in any patients.

Moreover, no side effects such as persistent epithelial defects or cataracts were encountered.

The preoperative values on the day of treatment were compared with postoperative values of the 6-month examination.

The mean preoperative simulated K determined was 52.056+/- 2.97D, the mean astigmatism was 5.14± 1.855D (this obtained from the topography derived Keratometry). Preoperative maximum simulated K was 58.4 D and maximum astigmatism was 10.63D.

Pachymetry was done in all eyes preoperatively to assess suitability and was 429+/-31μm .
The mean postoperative simulated K determined at 6 months was 50.958+/- 2.632 , the mean astigmatism was 4.800± 1.849D.

The BCVA improved at least one line in 36% (9/25) of eyes(of which 3 eyes showed 2 line improvement) and improvement by half line in 28% (7/25) of eyes and stable in rest of the eyes .

After treatment, no eyes lost lines of best spectacle-corrected acuity (BCVA)
Astigmatism decreased by a mean of 0.588D dioptres (D). ($p<0.05$) Maximum decrease in astigmatism was by 4.11D.
The simulated keratometry value decreased by a mean of 1.17 D($p<0.05$) Maximum decrease in simulated keratometry was 3.67 D.

Discussion

Keratoconus is a disorder characterized by progressive corneal steepening, most typically inferior to the centre of the cornea, with eventual corneal thinning, induced myopia, and both regular and irregular astigmatism[1,2]

The etiology and pathogenesis of these disorders are unknown but may be associated with a variety of factors, including contact lens wear, eye rubbing, Down's syndrome, atopic disease, connective tissue disease, tapetoretinal degeneration and inheritance. [3,4,5]

Manifestations of keratoconus are limited to the cornea. They include steepening of the cornea, especially inferiorly, thinning of the corneal apex, scarring at the level of Bowman's layer, and deep stromal stress lines that clear when pressure is applied to the globe. A ring of iron deposition accumulates in the epithelium at the base of the cone (Fleischer ring). The steepening of the cornea leads to clinical signs, which include protrusion of the lower eyelid on downgaze (Munson's sign), focusing of a light beam shown from temporally across the cornea in an arrowhead pattern at the nasal limbus (Rizutti's sign), and a dark reflex in the area of the cone on observation of the cornea with the

pupil dilated using a direct ophthalmoscope set on plano (Charleaux's sign). Other signs have been described, such as pulsation of the mires on applanation tonometry and pulsation of the reflected images on standard keratometry because the thinned cornea readily transmits the ocular pulse. In addition, a scissoring reflex can be found on retinoscopy[1]

A long-term study of a well-evaluated population in Minnesota found a prevalence of 54.5 cases per 100 000.[6] Treatment consists of spectacles for myopic astigmatism and then rigid contact lenses once spectacle-corrected acuity becomes inadequate. When contact lenses fail, surgical treatment is indicated. In one series, the most frequent reason for contact lens failure that resulted in the need for keratoplasty was inadequate acuity (43%), followed by inadequate lens tolerance (32%), frequent lens displacement (13%), and peripheral thinning (12%).[7]

Intracorneal ring segments have achieved some success in patients without corneal scarring in reducing the myopia and astigmatism and improving spectacle-corrected visual acuity[8]

CXL is an effective treatment for limiting the progression of keratoconus, thus reducing the need for penetrating keratoplasty[9]

It increases corneal rigidity by almost 300% and enhances its resistance to proteolytic enzymes.[11]

C3R process increases rigidity of corneal collagen and thus reduces the likelihood of further ectasia. Wollensak G et al in a recent study of 60 eyes treated with collagen cross-linking, 31 eyes had a reversal and flattening of the keratoconus up to 2.87 D. With follow-up at 3 and 5 years, all 60 eyes did not show any progression of the keratoconus.[10]

Caporossi et alreported mean reduction of 2.10 D in maximum K values after 6 months[12]

Raiskup-Wolf et al described reduced curvature of 2.68 D in the first year, 2.21 D in the second year, and 4.84 D in the third year[13].

Raiskup-Wolf et al followed up patients up to six years and reported on a larger cohort of patients concluded that the improvement in vision after collagen cross-linking is caused by a decrease in astigmatism and corneal curvature as well as by topographical homogenization of the cornea as a result of the increased rigidity in the cross-linked cornea.[13]

Agrawal et al showed a stabilization and improvement in keratoconus after collagen cross-linking in Indian eyes. Thus suggesting that it is an effective treatment for progressive keratoconus[14].

Conclusions

Results indicate there is an improvement in best corrected visual acuity after collagen crosslinking with riboflavin. Visual improvement could have been due to the decrease in corneal steepness and astigmatism(hence a decrease in refractive error).

Decrease in keratometry after C3R in keratoconus shows that collagen crosslinking with riboflavin does not just halt progression but also has a flattening effect on keratoconus. Thus, collagen crosslinking may have a therapeutical effect on progressive keratoconus.

References

1. Yanoff And Duker Textbook Of Ophthalmology 3rd Edition
2. Cornea, 3rd Edition: Krachmer, Mannis & Holland
3. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. Surv Ophthalmol. 1984;28:293–322
4. Karseras A.G., Ruben M.: Aetiology of keratoconus. Br J Ophthalmol 1976; 60:522-525.
5. Macsai M.S., Varley G.A., Krachmer J.H.: Development of keratoconus after contact lens wear: patient characteristics. Arch Ophthalmol 1990; 108:534-538.
6. Kennedy R.H., Bourne W.M., Dyer J.A.: A 48-year clinical and epidemiologic study of keratoconus. Am J Ophthalmol 1986; 101:267-273
7. Dana M.R., Putz J.S., Viana M.A.G., et al: Contact lens failure in keratoconus management. Ophthalmology 1992; 99:1187-1192.
8. Colin J., Cochenee B., Savary G., et al: Intacs inserts for treating keratoconus: one-year results. Ophthalmology 2001; 108:1409-1414
9. Corneal collagen cross-linking: An introduction and literature review Original Research Article Optometry - Journal of the American Optometric Association, Volume 83, Issue 1, January 2012, Pages 33-42 Brandon J. Dahl, Eric Spotts, James Q. Truong
10. Wollensak G.: Crosslinking treatment of progressive keratoconus: new hope. Curr Opin Ophthalmol 2006; 17:356-360.
11. Spoerl E, Wollensak G, Dittert DD, Seiler T. Thermomechanical behavior of collagen-cross-linked porcine cornea. Ophthalmologica. 2004;218:136–140
12. Caporossi A, Baiocchi S, Mazzotta C, Traversi C,

Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen: preliminary refractive results in an Italian study. J Cataract Refract Surg. 2006;32:837–845.

13. Raiskup-Wolf F, Hoyer A, Spoerl E. Pillunat LE: Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: Long-term results. J Cataract Refract Surg. 2008;34:796–801.
14. Corneal collagen cross-linking with riboflavin and ultraviolet-A light for keratoconus: Results in Indian eyes:Vinay B Agrawal-Indian journal of ophthalmology, 2009 march-apr,57(2):111-114.

No Suture No Glue: Autologous Blood For Graft Adhesion in Pterygium surgery

Dr. Soumya S. MS, Dr. Padmaja Krishnan MS, Dr. Anup Menon MS

Introduction

A pterygium is a degenerative condition of the conjunctiva, characterized by a wing shaped overgrowth of bulbar conjunctiva on to the cornea, in the interpalpebral area. It is common in India where the risk of ultra-violet exposure is high[1]. It can induce visually significant astigmatic changes or grow over the cornea to occlude the visual axis.

The mainstay of management of pterygium is surgical excision. One of the major concerns in the surgical management is the high rate of recurrence[2].

Aim of the Study

To study the efficacy and complications of limbal conjunctival autograft using autologous blood for graft adhesion after pterygium excision.

Materials And Methods

This prospective case study was conducted in the Department of Ophthalmology, at MES Medical College, Perinthalmanna, for a period of 1.5 years from January 2013 to June 2014. The study was conducted according to the principles of the declaration of Helsinki and was approved by the hospital ethics committee. Informed consent was obtained from all patients included in the study.

A total of 12 eyes of 10 patients who underwent limbal conjunctival autografting using autologous blood for graft adhesion were studied. Patients unable to come for regular follow-up were excluded.

All surgeries were performed by a single surgeon to reduce operator bias. After subtenons block, the apex of the pterygium was scraped off from the cornea and the entire pterygium excised. Oozing at the excision site was neither cauterised nor washed off with saline. After measuring the extent of the raw area, a graft 1 mm larger than this was harvested from the superior limbal conjunctiva of the same eye and moved to the raw area. The autograft was secured in place while maintaining proper limbal orientation using the blood over the raw area. Using a non-toothed forceps direct pressure was applied over the graft and with the edges apposed a pad and bandage was applied. The time taken for the surgery and any intra-operative complications were noted.

Post operatively all patients were put on Moxifloxacin, Nepafenac and Dexamethasone eye drops. The corticosteroid drops were tapered over a period of 1 month. Patients were followed up on the 1st postoperative day, and at the end of 1st week, 1st, 2nd and 6th months. At each follow-up patients were asked about their symptoms, examined at the slit lamp and visual acuity tested.

Results

A total of 12 nasal pterygia in the eyes of 10 patients underwent pterygium excision with autograft using autologous blood for graft adhesion. There were 2 female and 8 male patients, with a mean age 59.1 years (SD: 13.4) in this study. The other preoperative parameters studied are shown in table 1.

Table 1: Preoperative evaluation

No. of eyes	12
No. of patients	10
OD	5
OS	7
Location	12 Nasal
Mean age (years)	59.1 (SD: 13.14)
Mean corneal extension (mm)	2.125 (SD: 0.962)

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Table 2: Intraoperative evaluation

Operation time, mean (min)	27.58 (SD: 6.05)
Intraoperative complications	none

Of the 10 patients, 2 patients had pterygia in both eyes. No intraoperative complications were noted.

Table 3: Postoperative evaluation

Postoperative pain	4 patients
Watering	2 eyes
SCH	3 eyes
Graft displacement	1 eye
Recurrence	nil

Postoperative pain in the 1st week was rated less than or equal to 2 out of 10 on visual analogue scale by 4 patients. There was just one case of mild graft displacement but this did not cause recurrence. No recurrences were noted in any patient during the 6 month follow-up period.

Discussion

Pterygium surgery has evolved over time, to meet the challenge of the high recurrence rates associated with earlier techniques like the bare-sclera technique[3], which is now obsolete. Recurrence following pterygium excision is now prevented by methods like limbal conjunctival autografting[4], amniotic membrane transplantation[5], application of mitomicin-C[6], 5FU[7] or ß irradiation[8] to the site of excision. Among these, limbal conjunctival autografting is one of the most frequently used methods, for both primary and recurrent pterygium management[9]. Apart from the low cost, fewer complications and low recurrence rates[16], it also ensures better postoperative comfort and cosmesis10.

Various methods of fixing the limbal conjunctival autograft include use of sutures[11] and fibrin glue[12] for graft adhesion. Conjunctival graft adhesion using sutures is associated with complications like suture abscess, suture granuloma, tissue necrosis and giant papillary conjunctivitis[14]. The major concern while using fibrin glue for graft adhesion is its cost and the potential risk of transmission of infection[15]. A new method of securing the graft in the raw area is using autologous blood[13], with the fibrin in the blood clot causing graft adhesion.

Our findings are similar to the study on conjunctival autografting using autologous blood by D de Wit et al[17]. In their study of 15 eyes with a mean follow-up period of 9.2 (SD: 2.2) months, the mean surgical time was 14 (SD: 1.4) minutes, there were no intraoperative or postoperative complications including recurrence.

However a prospective interventional case series in 40 eyes with primary nasal pterygium over a 12 month follow-up period by Malik KP et al[13] showed graft dehiscence in 2 eyes, graft retraction in 3 eyes and recurrence in 1 eye.

A prospective randomized case control study by Singh PK et al[18] compared the outcomes of conjunctival autograft adhesion after pterygium excision using fibrin glue to that using blood clot in two groups of 10 patients each who were followed up for 12 months. The latter group showed mean duration of surgery of 17.45(SD: 2.89) min. However the recurrence rates were identical (10%) in both groups. The longer duration of surgery in our study could be due to our noting the time of surgery from draping rather than from the start of the actual surgical procedure.

M Fernandez et al[19] studied the outcomes of different methods of pterygium surgery over 14 years and observed that recurrences after surgery were noted on an average of 6.0 (SD: 8.2) months for primary pterygia and an average of 3.1 (SD: 3.1) months for recurrent pterygia. In our study the absence of recurrence for the first six months after surgery could be a significant finding. However this study has found recurrences as late as 59.9 months.

The sutureless and glue free method of conjunctival autografting using autologous blood is therefore an easy and effective method with shorter learning curve. It has all advantages of the fibrin glue without its drawbacks. It is cheaper and needs no additional raw materials. It is associated with less postoperative pain, foreign body sensation and inflammation compared to sutures.

Conclusion

The outcomes of this study demonstrated that conjunctival autografting using autologous blood is less time consuming and is associated with less chance of recurrence. It is an effective method and the graft was stable in almost all cases. There were no intraoperative complications and postoperative complications were mild and few.

The limitations of this study are that it is not a randomized study, does not compare with the other methods of graft adhesion and is on a small study population. The follow up period of 6 months is also inadequate to know the long-term recurrence rate. Therefore future randomised studies with long-term follow-up in larger case series are required to substantiate the findings of this study.

References

1. D J Moran, F C Hollows. Pterygium and ultraviolet radiation: a positive correlation. Br J Ophthalmol 1984; 68:343-346
2. Sebban A et al. Pterygium recurrence rate at the Princess Alexandra Hospital. Australian and New Zealand Journal of Ophthalmology, 1991:19(3): 203-206
3. Donald T. H et al. Effect of Pterygium Morphology on Pterygium Recurrence in a Controlled Trial Comparing Conjunctival Autografting with Bare Sclera Excision. Arch Ophthalmol. 1997; 115(10):1235-1240.
4. Starck, Tomy M.D; Kenyon KR, Kenneth R, Serrano, Federico M.D. Conjunctival Autograft for Primary and Recurrent Pterygia: Surgical Technique and Problem Management. Cornea 10:196-202
5. P Luanratanakorn, T Ratanapakorn, O Suwan-apichon, R S Chuck. Randomised controlled study of conjunctival autograft versus amniotic membrane graft in pterygium excision. Br J Ophthalmol 2006; 90: 1476-1480
6. Chen PP et al. A randomized trial comparing mitomycin C and conjunctival autograft after excision of primary pterygium. American Journal of Ophthalmology .1995, 120(2):151-160
7. Akarsu, Cengiz; Taner, Pelin ; Ergin, Ahmet. 5-Fluorouracil as Chemoadjuvant for Primary Pterygium Surgery: Preliminary Report. Cornea: 2003 - Volume 22(6): 522-526
8. C.O. Bekibele, A.M. Baiyeroju , B.G.K. Ajayi. 5-fluorouracil vs. beta-irradiation in the prevention of pterygium recurrence. International Journal of Clinical Practice, 2004. 58 (10): 920-923
9. KR Kenyon, MD Wagoner, ME Hettinger. Conjunctival autograft transplantation or advanced and recurrent pterygium. Ophthalmology 1985; 92: 1461-1470
10. B D Allan, P Short, G J Crawford, G D Barrett, I J Constable. Pterygium excision with conjunctival autografting: an effective and safe technique. Br J Ophthalmol 1993;77: 698-701
11. S Srinivasan, M Dollin, P McAllum, Y Berger, D S Rootman, A R Slomovic. Fibrin glue versus sutures for attaching the conjunctival autograft in pterygium surgery: a prospective observer masked clinical trialBr J Ophthalmol 2009;93: 215-218
12. Koranyi G, Seregard S, Kopp ED. Cut and paste: a no suture, small incision approach to pterygium surgery. Br J Ophthalmol 2004; 88: 911-914
13. Malik KP et al. Efficacy of sutureless and glue free limbal conjunctival autograft for primary pterygium surgery. Nepal J Ophthalmology; 2012:4(8):230-5
14. Victoria W, Y. Wong, Srinivas K. Rao, Dennis S. C. Lam. Polyglactin sutures versus nylon sutures for suturing of conjunctival autograft in pterygium surgery: a randomized, controlled trial. Acta Ophthalmologica Scandinavica 2007, 85(6): 658-661
15. Masayuki Hino, Osamu Ishiko et al. Transmission of symptomatic parvovirus B19 infection by fibrin sealant used during surgery. British Journal of Haematology, 2000: 108(1): 194-195
16. Albert and Jakobiec Principle and Practice of Ophthalmology, 2nd edition, Newyork, Raven press;1993: pg.748
17. D de Wit, I Athanasiadis, A Sharma and J Moore. Sutureless and glue-free conjunctival autograft in pterygium surgery: a case series; Eye (2010) 24, 1474-1477.
18. Singh PK, Singh S, Vyas C, Singh M. Conjunctival autografting without fibrin glue or sutures for pterygium surgery. Cornea, 2013 Jan; 32(1):104-7
19. M Fernandes et al. Outcomes of pterygium surgery: analysis over 14 years. Eye 2005: 19: 1182-1190

Pregnancy and Its Spectrum of Changes in Eye

Dr. Ranjakumar T C MS.DO.MBA, Dr. Lalith Sundaram MS, Dr. Sruthi Swaminathan MBBS, Dr.Rahana Ashraf MBBS

Pregnancy and its changes are vivid. Intraocular changes both physiological and pathological changes are noted during the course of pregnancy. Significant changes in eye has been supported by various studies from early 1970s. It can occur for the first time in pregnancy itself[1-6].Ocular changes can thus be a determining factor of pre-existing ocular disease or as a manifestation of systemic disease or even a factor for the development of a new pathology during the course of pregnancy.[2]

Corneal changes

• Corneal sensitivity is decreased in late trimester in pregnancy and returns to normal by early weeks of postpartum. Corneal thickness variation is another manifestation with various mechanisms due to oedema which may result in a change in refractive index in cornea mostly increasing towards the last trimester [1-6]. Contact lens users may find it difficult to continue wearing contact lens during pregnancy due to these changes. [6-7]

• Statistically significant increase in corneal curvature during second and third trimester can occur and may resolve after delivery or cessation of breast feeding. [1]

• Corneal front steep keratometry value is statistically higher in the pregnant group.[9]

• Corneal biomechanical parameters during pregnancy may not affect corneal biomechanics. This may be due to the balanced effect of the various hormones on the cornea during pregnancy.[10]

Intraocular Pressure (IOP) & Pregnancy

• IOP may affect women of childbearing age. A decrease in intraocular pressure has been observed during pregnancy and often persists for few months after delivery. The decrease in IOP can lead to changes in women with pre-existing glaucoma which can improve during this period however medications have to be continued.

• Possible mechanisms include : increase in outflow as a result of hormone levels modification, a decrease in systemic vascular resistance, decrease in episcleral venous pressure, increased tissue elasticity ,generalised acidemia and physiological changes in late pregnancy may reduce corneoscleral rigidity, making the results of applanation tonometry falsely low. Likewise an increase in corneal thickness could also affect the measured values of IOP.[1-12]

• Aqueous humour formation & its production remained stable, whereas IOP decreased throughout the trimesters and returned to normal levels at 3 months postpartum. Proposed mechanisms underlying the decrease in IOP during pregnancy indicate an association between female hormones and increased outflow.[15]

• A marked increase in aqueous outflow facility can be associated with progesterone levels in pregnancy. The decrease in IOP with the use of progesterone or the combination of progesterone and estrogen at pharmacologic doses is also reported. Another hypothesis suggests that excess progesterone during pregnancy acts as a glucocorticoid receptor antagonist and that it blocks the ocular hypertensive effect of endogenous steroids. [12]

• Glucocorticoid receptors are known to exist in the outflow apparatus; their inhibition would thus have an IOP-lowering effect.

• Intramuscularly administered relaxin, which is pregnancy-associated hormone, IS shown to decrease IOP via increased outflow facility in both male and female patients with glaucoma. The effect of relaxin on outflow facility is thought to be mediated by collagen changes, which in turn affect the rigidity of Schlemm's canal and the trabecular meshwork.[11-12]

• Episcleral venous pressure has been reported to decrease in pregnant women could be associated with a decrease in general peripheral vascular resistance during pregnancy and might contribute to a decrease in IOP. [14-15]

Refractive Errors

• Visual disturbances are found to have experienced a myopic shift from pre-pregnancy levels with a return to near pre-pregnancy levels post partum.[6]

• Tendency of fluid retention during pregnancy affects

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refraction. Hence spectacles or contact lenses may be temporarily either too weak or too strong depending upon patient's specific refractive errors.

Pre-Existing Diabetic Retinopathy

• Progression of diabetic retinopathy (DR) occurs at least temporarily during pregnancy. More recently there is growing evidence suggesting that in the progression of retinopathy activation and adaptation of the immune system during gestation could also have certain role. It is established that during pregnancy, certain components of the immune system that are knowingly implicated in the pathogenesis of DR are activated.[(2),(9)]

Pregnancy and Preeclampsia

A pregnant woman should be evaluated for blurring of vision, photopsias and diplopia. Conjunctival vascular anomalies to fundus changes like exudative retinal detachment, vitreous and pre-retinal haemorrhages, hypertensive retinopathy and ischemic optic neuropathy could be a spectrum in patients with PIH.

Hormonal changes & tumours

• Major hormonal changes emerge during pregnancy. Pituitary adenomas may cause problems by their hormone secretion that affects the mother and fetus as well as causing an increased risk of tumour growth. [(2),(7)]

• Progressive visual field loss during pregnancy can result in changes in the visual field such as bitemporal loss, concentric constriction, and enlarged blind spots can be observed. It could be asymptomatic and seen to be completely reversible, usually 10 days after delivery.[(1-5)]

• Magnetic resonance imaging studies show that the size of the pituitary gland increases even during a normal pregnancy and thus damage the optic chiasm causing bitemporal visual field changes. Likewise, another cause of visual field damage could be of glaucoma or tumour[(7)]

Uveitis & Posterior segment changes

• Non-infectious uveitis an increase in disease activity within the first four months of pregnancy occurs. The disease appears to be relatively inactive in later pregnancy with a rebound within six months of delivery. Inflammatory eye diseases such as uveitis can affect females during their reproductive period. [(16)]

• Pathologic conditions reported to develop during pregnancy include hypertensive and vascular disorders, central serous chorioretinopathy, uveal melanoma and others. The most significant modified pre-existing condition is diabetes mellitus.

Autoimmune diseases and pregnancy

• Many autoimmune diseases in females are known to improve during pregnancy but worsen in the postpartum period, since pregnancy induces immune deviation promoting anti-inflammatory cytokines that prevent immunological rejection of the allogenic fetus.[(8)(16)]

Reactivation of prexisting conditions :

• Pregnant state may provoke the recurrence of ocular toxoplasmosis. Acute toxoplasmic retinochoroiditis in pregnancy could be a risk of trans placental transmission due to potential parasitemia with detrimental effects on the developing foetus[(2),(16)]

• Pregnancy is associated with improvement of some autoimmune diseases including rheumatoid arthritis and multiple sclerosis and with exacerbation of other autoimmune conditions such as systemic lupus erythematosis.

Thyroid disease and pregnancy

• Pregnancy causes a number of physiological alterations in thyroid hormone metabolism. Graves' disease often shows a characteristic course in pregnancy with amelioration of thyrotoxicosis in the second half of pregnancy[(1-5)(16)]

Demylineating disease and pregnancy

• Multiple sclerosis, on the contrary has been known to stabilise during pregnancy especially in the final trimester, and then relapse usually in the first three months postpartum may be linked to pattern with estrogen levels.[(1-6)]

Ophthalmic Medications in Pregnancy

• Glaucoma medications (beta blockers) are to be avoided or at least used in the lowest possible dose especially in the first trimester when the risk of teratogenesis is highest and should be discontinued several days prior to delivery to avoid beta-blockade in the infant. Carbonic anhydrase inhibitors are known to have teratogenic effects and should be avoided during pregnancy. [(13-15)]

• Miotics appear to be safe during pregnancy whilst their toxicity during lactation is unknown. One exception is demecarium.

• Prostaglandine analogues have insufficient active ingredients to cause adverse effects on the fetus whilst other reports consider that the use of prostaglandin is generally contraindicated in pregnant women.

• Mydriatic drops for the purposes of ocular examination is considered to be safe; however repeated use should be avoided due to potential teratogenic effects of both parasympatholytics (eg, atropine) and sympatho- mimetics (eg, epinephrine) but contraindicated in mothers who are breastfeeding because of anticholinergic or hypertensive

effects on the child.

• Corticosteroids are considered to be contraindicated even though there are no known teratogenic effects of topical steroids.

• Antibiotics that are considered safe during pregnancy include erythromicin,tobramycin, gentamicin, polymyxin B and the quinolones with the latter two showing to be safe even during breastfeeding.

• The list of antibiotics that should be avoided during pregnancy include: chloram- phenicol, systemic gentamycin, neomycin, rifampin. Acyclovir is generally well tolerated in pregnant women. No known side effects of fluorescein and topical anaesthetics drops if used during pregnancy. [15]

References

1. Khwala Abu Samra,.The eye and visual system in pregnant eye. What to expect? An in-depth review. Oman J Ophthalmol 2013; 6:87-91
2. Gotovac M, Kastelan S, Lukenda ,A. Eye and Pregnancy,Coll Antropol. 2013 Apr;37 Suppl 1:189-93.
3. Efe, YaseminKozluca et al. "The course of corneal and intraocular pressure changes during pregnancy." Canadian journal of ophthalmology. Journal canadiend' ophtalmologie 47.2 2012 : 150-4.
4. Razeghinejad MR, Tania Tai TY et al "Pregnancy and glaucoma ." Surv Ophtlhalmol 2011 Jul-Aug;56(4):324-35
5. D. Pizzarello Louis. Refractive changes in pregnancy, Graefe's Arch ClinExp Ophthalmology.2003; 241:484-48
6. Garg P, Aggarwal P, Ocular changes in pregnancy, Nepal J Ophthalmol 2012;4:150-161
7. Afekhide E. Omoti, Joseph M.Waziri Erameh and Valentina W.Okeigbemen, A review of the changes in ophthalmic and visual system in pregnancy, Afr J Reprod Health 2008;2:185-196
8. Kuczkowski Km, Looking into the pregnant woman's eye, Hong Kong Med J 2004,10:365
9. Goldich Y, Cooper M, Barkana Y, Tovbin J, Lee Ovadia K, Avni I et al.Ocular Anterior Segment Changes in Pregnancy,J Cataract Refract Surg. 2014 Nov;40(11):1868-71
10. Sen, Emine et al. "Corneal biomechanical parameters during pregnancy."European Journal of Ophthalmology 24.3 (2013) : 314-319
11. Green K,Phillips CI,Cheeks L. The aqueous humor flow rate and intraocular pressure during an Garg P, Aggarwal P, Ocular changes in pregnancy, Nepal J Ophthalmol 2012;4:150-161
12. Paterson GL, Miller SJH: Hormonal influences in simple glaucoma. Br J Ophthalmol.1963; 47:129
13. Frishman WH, Chesner M. Beta-adrenergic blockers in pregnancy. Am Heart J 1988;115:147-52.
14. Ozawa H, Azuma E, Shindo K, Higashigawa M, Mukouhara R, Komada Y. Transient renal tubular acidosis in a neonate following transplacental acetazolamide. Eur J Pediatr 2001;160:321-2
15. Bhatia Jagdish, Sadiq Naqaish Mohammed et al, Eye changes and risk of Ocular Medication during pregnancy and their Management; Pak J Ophthalmol 2007; 23:1
16. Nathalie P. Y. Chiam , Lyndell L. P. Lim. Uveitis and Gender: The Course of Uveitis in Pregnancy J Ophthalmol. 2014:: 401915.

Keratoconus

Dr Jayaram V R MS

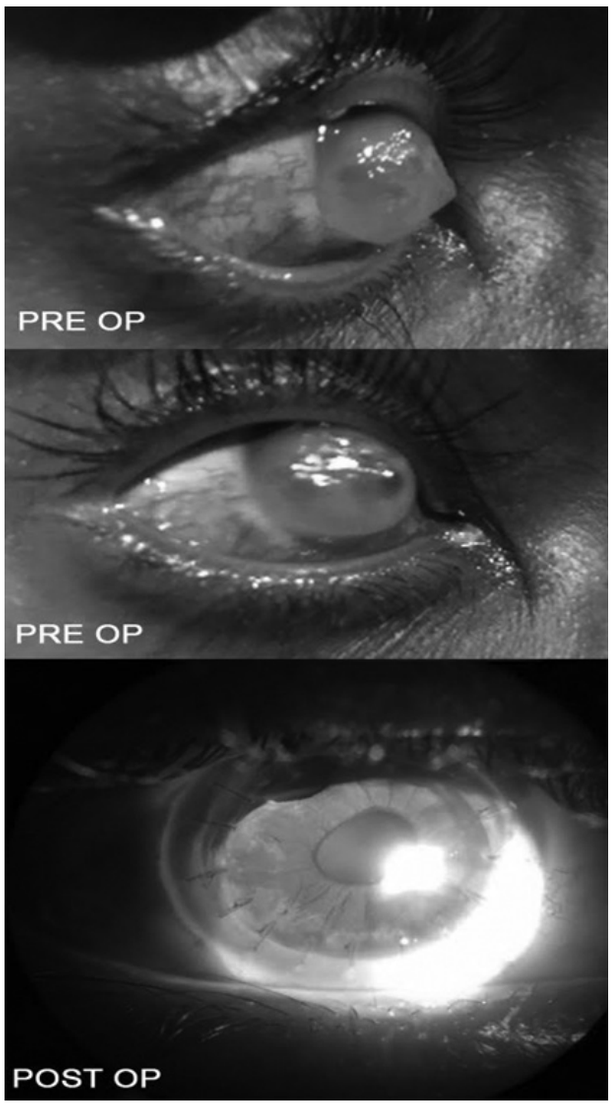
*16*yr old boy having cerebral palsy presented to the OP department c/o discoloration and swelling of cornea, watering right eye since past few weeks. He was on treatment from elsewhere on e/d antibiotic steroid 4 times, hypertonic saline 5 e/d 4 times,cycloplegic e/d 3 times. He was a known case of keratoconus and was using glasses. His best-corrected visual acuity was HMCF (PR accurate) NIF in right eye and 6/36p improving to 6/18 with -7 D sph/-2.5 D cyl @70o left eye. Intraocular pressure was normal digitally both eyes. Examination showed severely edematous and ectatic cornea in right eye, thin central cornea with vogt's striae ,fleishers ring left eye.Fundi by Binocular indirect not visible in right eye and was normal in left eye.Usg bscan was wnl right eye

How would you like to manage this case?

Dr Sujith nayanar
Cornea and Refractive Surgeon
Vasan Eye Care Hospital,Calicut

Thank you for including me in the discussion of this interesting case. This young boy, who is physically and mentally challenged, is suffering from acute corneal hydrops in his right eye secondary to advanced keratoconus. From the details provided, we understand that the fellow eye is also showing signs of keratoconus. The acute hydrops results from rupture in Descemets membrane (DM) resulting in leakage of aqueous humor into the corneal stroma. This condition is associated with acute inflammation causing pain, discolouration of cornea, photophobia and rapid fall in visual acuity.

The immediate line of management is conservative with measures to control pain, inflammation and edema. The boy should be immediately put on cycloplegics, hypertonic saline and steroid eye drops with an antibiotic coverage. If the facility is available and the child is cooperative, Anterior Segment OCT(AS-OCT) may be recorded to document the DM rupture and baseline stromal edema before the start of treatment (Fig 1). This will help in serial monitoring of response of edema to treatment. The child should then



be evaluated weekly or fortnightly to assess the response to medical management. The natural course is slow and spontaneous resolution of edema followed by scarring of the area of DM rupture.

Alternate option is to try intracameral gas (SF6 or C3F8) injection to tamponade the DM which helps to facilitate the response to topical medication. In this difficult child I prefer

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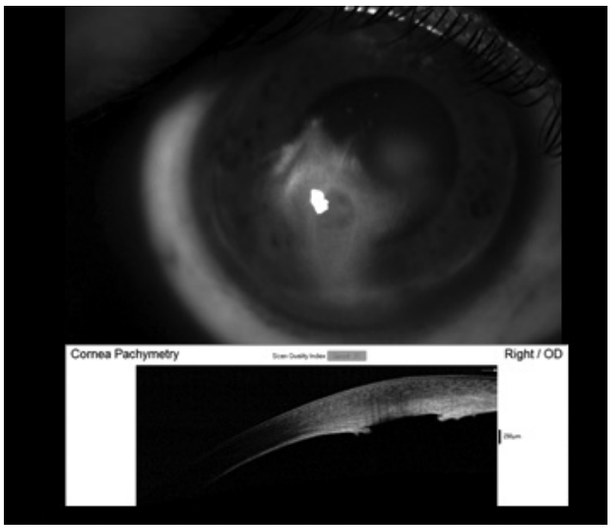


Fig 1: AS OCT image showing DM break and the corresponding clinical picture

not to attempt that to avoid risk of general anaesthesia. Also in post procedural period, the IOP monitoring may be difficult in this child and IOP spike may be missed out. Other options of compression sutures and AS-OCT guided stromal fluid drainage with air tamponade as available in literature are viable but difficult options in this particular case.

The aim of the conservative treatment initially is to control symptoms and also to buy time to plan an optical keratoplasty for a later date. The definitive correction lies in replacing the damaged cornea with a donor cornea and aim for better refractive surface to achieve visual recovery. Better results from keratoplasty are always achieved if it is done as a well-planned elective procedure in a non-inflamed eye. In acute stage mostly the whole cornea is swollen from limbus to limbus and hence it is difficult to identify the location and extent of cone. This will lead to large diameter graft and thus increasing the risk of rejection. The natural course of scarring and resolution incidentally leads to a central depression of the cone which will slightly improve the visual acuity and may allow a better RGP fitting in the healed stage. In this stage we can identify the cone location and extent and plan optical keratoplasty involving the cone completely.

To summarize, I would suggest conservative line of management using topical medication only, in this case to avoid repeated exposure to general anesthesia. As it heals and scars, an optical keratoplasty can be planned to achieve better best corrected visual acuity. In the meantime the fellow eye should be taken care of to avoid a similar situation because such patients do vigorously rub their eyes which can put the fellow eye also at risk of hydrops.

Comment by

Dr Anil Radhakrishnan
Senior Consultant Cornea and Refractive Surgery
Amritha Institute of Medical Sciences,Cochin

This rather macabre presentation of hydrops in a corneal ectasia with possibility of perforation indeed poses a therapeutic challenge. The options would be [1] Conservative management [2] Intracameral injection of C3F8 or SF6 and [3] Tectonic keratoplasty.

Tectonic keratoplasty, though can immediately bring back vision, I would consider it my last option as [1] it would require a full thickness limbus to limbus graft, which is bound to get rejected in a young patient [2] the chances of sutures getting loose early in the postoperative period is high as the cornea is very oedematous, usually 3 or 4 times the normal thickness due to fluid clefts in the stroma.

Intracameral injection of isoexpansile gas though successful in early resolution of hydrops would not be my preferred choice in this mentally subnormal patient as [1] it requires general anesthesia and performing peripheral iridectomy through such an opaque cornea would be difficult [2] it carries the risk of elevated IOP in the immediate postoperative period, which in a normal case can easily be tackled by 'burping the AC' [letting some of the expansile gas out of anterior chamber by gently pressing on the side port, with the patient sitting in front of slit-lamp] [3] more than 2 weeks have elapsed after the onset of hydrops [or breach in Descemet's membrane] and so it is likely that the Descemet's membrane scroll would have receded significantly and chances of it getting permanent is high and [4]small risk of anterior subcapsular cataract after the procedure

I would prefer to manage it conservatively as much as possible. Pressure patching the eye, I feel is indeed helpful in such cases with a high degree of ectasia with severe corneal edema and corneal bullae [the comment is purely based on my limited experience of managing a few similar cases, which means it can be a biased point of view and not peer-reviewed information].

Comment by

Dr Ilan Bhatt
Senior Consultant Cornea and Refractive Surgery
Little Flower Hospital, Angamaly

In current times, acute corneal hydrops is uncommon, (2 to 3 %); the predisposing factors being a young patient with a history of atopy or VKC and perhaps a background of developmental delay as in this case. Trivial trauma like eye rubbing is the usual precipitating incident.

In this patient, it would be ideal to perform an anterior segment OCT to assess the extent of the stromal edema, the size of DM tear and intra stromal clefts.

Clinically the case appears to be a severe form of corneal hydrops with little or no response to conservative treatment.

Option 1: Continue conservative therapy and wait for resolution which may take upto 3 or 4 months whether medical therapy actually helps is also doubtful and the condition may even be self-limiting.

This may not be advisable as the corneal edema appears to be extreme and there has been no response till date.

Option 2: The second option may be to go ahead with intra cameral gas or air injection to shorten the duration of corneal oedema and hasten the resolution of vision.

Air injection has to be repeated several times, so also SF6; hence C3F8 injection is probably the better choice. Pilocarpine 2% every 15 minutes for an hour and paracentesis to remove 0.1ml aqueous followed by injection of gas to fill 2/3rd AC using 26/27-gauge needle may be done. Postoperative supine position is to be maintained and anti glaucoma agents are given. In this patient the procedure may be performed under intravenous sedation.

Option 3: Yet another relatively new option may be to perform 'intra stromal fluid drainage with air tamponade ' guided by anterior segment OCT to locate intra stromal fluid pockets. This is combined with multiple corneal venting incisions. This procedure further reduces the duration and morbidity and avoids potential complications due to repeated gas injections.

Outcome: Once corneal hydrops reduces, a residual corneal scar is usually seen with flattening of the cone. This may actually improve and facilitate CL fitting. A large percentage of patients (18-67%) require penetrating keratoplasty to improve vision following corneal hydrops.

In this particular patient, with a history of cerebral palsy, contact lenses may pose to be a problem. Likewise, surgical intervention in the form of penetrating keratoplasty with its inherent problems is further complicated by the developmental delay in the patient unless the care providers are willing to play an active role.

Discussion

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Thanks to Dr Sujith, Dr Anil and Dr Lilan for giving their valuable veiws on the management this unusual case

Acute corneal hydrops, usually a self-limiting complication of keratoconus with clinical signs of edema usually resolves after 3 months of onset [1]. This case was suggested for discussion due to the clinical dilemma of non-resolution and progression of the condition after usual time period of resolution in this mentally and physically challenged boy.

Initially as all the panelist suggested medical therapy was attempted, with topical steroids, hypertonic saline,cycloplegics and lubricants with out effect, gradual progression was noticed on follow ups.since the patient was mentally challenged and had involuntary movements investigations like OCT could not be performed.

The second option suggested by the panelists, Intracameral isoexpansile c3 f8 injection and supine positioning was attempted after 3 months of ineffective medical therapy. Simultaneous drainage of fluid from intrastromal clefts although described was not attempted, in view of possible leak and shallow AC in this particular patient. Gas was noticed inside the stroma after 2 days of the procedure [2], possibly due to larger decemets membrane rupture and intra stromal clefts. Edema and ectasia progressed further in the ensuing weeks making it difficult for the patient to close his eyes.

Considering this situation and the possibility of rupture due to eye rubbing or minor trauma [3] and progression of the condition inspite of medical therapy and gas injection, it was decided to perform a penetrating keratoplasty even though the classical approach is to continue medical therapy till the hydrops resolves before performing keratoplasty.The challenges in performing keratoplasty in this case was[1] total cornea was involved demanding a limbus to limbus graft [2]apex of the cornea was protruding around 10 mm anteriorly [3]periphery was bulging sideways [4] judging diameter and depth upto which trephination has to be done was unclear[5] post operative care in a mentally challenged child

Penetrating keratoplasty was performed under general anesthesia. 9 mm trephine was used with slow gradual rotating movements, the edematous cornea was remarkably tougher than expected and could be safely trephined down till entering the anterior chamber. a same sized graft was used. Tight sutures where applied, host edges even though edematous, rapidly decreased in thickness during the procedure and satisfactory graft host apposition could be obtained. Patient eventually gained 6/9 vision with -4 D sph/1 D cyl @ 120o.

To conclude Penetrating keratoplasty in active acute corneal hydrops although not described in literature could be considered in refractory cases with good results. Lesser diameter grafts can be performed even when total cornea is involved. Peripheral corneal edema resolves as the graft replaces ruptured decemets membrane, which caused hydrops.

References

1. Acute corneal hydrops in keratoconus - new perspectives. Fan Gaskin JC1, Patel DV1, McGhee CN Am J Ophthalmol. 2014 May;157(5):921-8. doi: 10.1016/j.ajo.2014.01.017. Epub 2014 Jan 31.
2. Nonresolution of acute hydrops because of intrastromal migration of perfluoropropane gas.Sharma N1, Mannan R, Titiyal JS. Cornea. 2010 Aug; 29(8): 944-6. doi: 10.1097/ICO.0b013e3181ca6353.
3. Spontaneous bilateral corneal perforation of acute hydrops in keratoconus.Dantas PE1, Nishiwaki-Dantas MC.Eye Contact Lens. 2004 Jan; 30(1):40-1.

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Brief Report

Anatomical and Functional Outcome of Autologous Transplantation of the Internal Limiting Membrane in a Case of Persistent Macular Hole

Dr. Rameez N Hussain MS, Dr. Prisca Bernardin, Dr. Rakesh Seenappa

Case Report

Internal Limiting Membrane (ILM) peeling is the standard surgical procedure which provides good anatomic and functional results in cases with macular hole by releasing the tractional forces on the macula[1]. However, removal of the ILM alone may be ineffective for large, chronic refractory macular holes and results in failed anatomical closure. For large macular holes, Michalewska and associates reported the efficacy of a modified surgical procedure, called the inverted ILM flap technique[2]. Ho and associates and Shimada and associates reported an ILM peeling technique that left the epifoveal ILM in situ to avoid postoperative development of macular holes in myopic foveoschisis[3,4]. These techniques cannot be applied to eyes with idiopathic macular holes, in which the initial vitrectomies with ILM peeling fail to achieve closure, or to eyes with secondary macular holes, in which the ILM already has been removed in previous vitrectomies. In this case report, we are describing a technique for achieving anatomical closure in a case of failed macular hole surgery.

A 56 year old Austronesian female presented to us with history of macular hole surgery in the form of vitrectomy and ILM peeling in the right eye 5 months back. On examination, she was found to have a persistent macular hole in the right eye with a pseudophakic lens status. Visual acuity was Snellen's 6/60 <N36 in the right eye. Optical coherence examination (OCT) confirmed the same with a base diameter of 998 microns. (Fig.1)

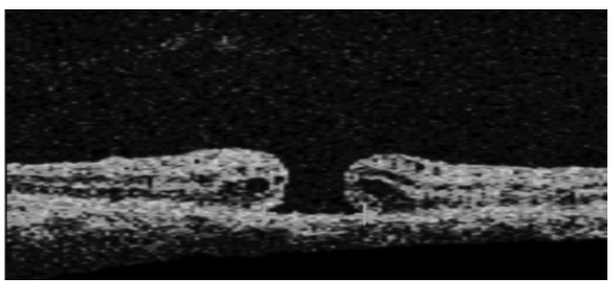


Fig.1 OCT image showing persistent macular hole of base diameter 998 microns with minimal cystoid changes at its edges.

We decided to do a surgical intervention in the right eye aiming at anatomical closure of the macular hole under guarded visual prognosis. The same was done on 20/08/2015 at Orbit health, Antananarivo, Madagascar. A 25G re vitrectomy was done and visualization of the residual ILM using 0.25 mg/mL brilliant blue G solution to identify the area where the ILM already had been peeled off during the initial surgery (Fig.2). A bit of ILM (Approximately 1/2 disc diameter in size) was gently peeled from the nasal margin of the previously peeled area and was placed in the macular hole filling up the crater (Fig.3). The free flap of ILM was stabilized by placing low molecular weight viscoelastic material over it. To avoid losing sight of the free flap of ILM, the infusion line was turned off and placed the free flap inside the macular hole. Fluid air exchange was done carefully keeping the extrusion needle away from the macula and C3F8 gas was injected for tamponade. Strict prone positioning for 5 days was advised post operatively.

Post operatively, the transplanted ILM flaps were visible as highly reflective areas on OCT within seven days of autologous transplantation of the ILM. Three weeks postoperative examination with OCT showed anatomical closure of the hole in the right eye with residual C3F8 gas insitu (Fig.4). Twelve weeks later, the visual acuity was Snellen's 6/24 N12 (with minimal metamorphopsia).

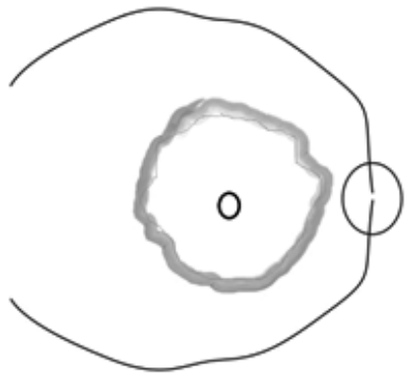


Fig2. Schematic diagram showing persistent macular hole (Black arrowhead) and the Brilliant blue stained Previously peeled ILM margins (Blue arrowhead)

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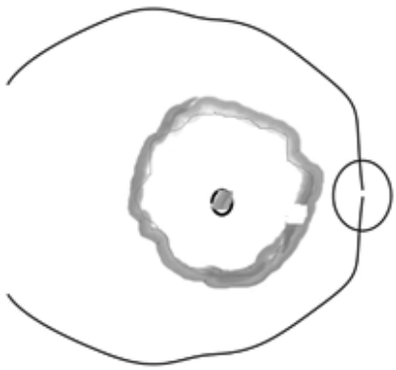


Fig3. Schematic diagram showing ILM being transplanted (Blue dotted arrow) from the nasal margin of the peeled area to the macular hole.

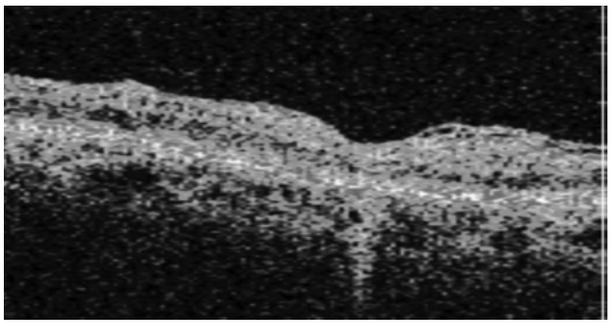


Fig.4 Three weeks post-operative OCT showing anatomical closure of the hole.

Large and traumatic macular holes may be conditions in which removing the ILM is sometimes ineffective. After vitrectomy with ILM removal, up to 44% of large macular holes have been reported to remain open[2]. A number of surgical procedures like inverted flap technique and 'epi foveal ILM sparing' was described by various authors for large and chronic macular holes. Although these procedures can be options for the initial vitrectomy, they cannot be the solution for eyes with macular holes from which the ILMs already have been removed in previous surgeries. The visual outcomes for large macular holes usually are limited even after hole closure because, although large macular holes frequently close with flat borders with the retina (Type 2 closure), the retinal pigment epithelium (RPE) may be bare (flat-open macular holes)[5].

The case which we are describing is an example for overcoming this issue by transplanting the ILM to the macular hole and preventing formation of bare RPE area and thereby achieving anatomical closure and improvement in the visual acuity. The results of this case imply that the flap of ILM placed inside a macular hole has the ability to repair the foveal contour. Recent in vivo studies using OCT to detect glial tissue reflectivity suggested that Muller cell gliosis is essential for macular hole healing[7,8]. In animal models, Muller cells have been reported to have the potential to proliferate, dedifferentiate, and produce photoreceptors under cytotoxic conditions[9,10]. Muller cell proliferation is thought to play an important role in filling macular holes and in producing an environment conducive to the repositioning of photoreceptors by moving photoreceptors to new locations[2]. Our OCT results after autologous transplantation of the ILM, which indicate that filling macular holes with new tissue occurs around the ILM flap support the above mentioned hypothesis.

Lack of SD OCT imaging is a limitation of this report as this would have helped us to understand the micro morphological changes happening across the healing process. This simple procedure might help the surgeons to tackle the failed macular hole cases and to achieve improvement in visual acuity as well.

References

1. Almony A, Nudleman E, Shah GK, et al. Techniques, rationale, and outcomes of internal limiting membrane peeling.Retina 2012;32(5):877–891
2. Michalewska Z, Michalewski J, Adelman RA, Nawrocki J. Inverted internal limiting membrane flap technique for large macular holes. Ophthalmology 2010;117(10):2018–2025.
3. Shimada N, Sugamoto Y, Ogawa M, Takase H, Ohno-Matsui K. Fovea-sparing internal limiting membrane peeling for myopic traction maculopathy. Am J Ophthalmol 2012; 154(4):1–9.
4. Ho T-C, Chen M-S, Huang J-S, Shih Y-F, Ho H, Huang Y-H. Foveola nonpeeling technique in internal limiting membrane peeling of myopic foveoschisis surgery. Retina 2012;32(3): 631–634.
5. Cho HY, Kim YT, Kang SW. Laser photocoagulation as adjuvant therapy to surgery for large macular holes. Korean J Ophthalmol 2006;20(2):93–98
6. Michalewska Z, Michalewski J, Cisiecki S, Adelman R, Nawrocki J. Correlation between foveal structure and visual outcome following macular hole surgery: a spectral optical coherence tomography study. Graefes Arch Clin Exp Ophthalmol 2008;246(6):823–830.
7. Oh J, Yang SM, Choi YM, Kim S-W, Huh K. Glial proliferation after vitrectomy for a macular hole: a spectral domain optical coherence tomography study. Graefes Arch Clin Exp Ophthalmol 2013;251(2):477–484
8. Madreperla SA, Geiger GL, Funata M, la Cruz de Z, Green WR. Clinicopathologic correlation of a macular hole treated by cortical vitreous peeling and gas tamponade. Ophthalmology 1994;101(4):682–686
9. Ooto S, Akagi T, Kageyama R, et al. Potential for neural regeneration after neurotoxic injury in the adult mammalian retina. Proc Natl Acad Sci U S A 2004;101(37):13654–13659.
10. Osakada F, Ooto S, Akagi T, Mandai M, Akaike A, Takahashi M. Wnt signaling promotes regeneration in the retina of adult mammals. J Neurosci 2007;27(15):4210–4219.

Brief Report

Sympathetic Ophthalmia- A Rare But Existing Possibility

Dr. Reena Rasheed MS

Summary

We hereby report a case of bilateral granulomatous panuveitis in a young male patient with history of penetrating trauma in one eye. The diagnosis of SO should be suspected in patients with recent history of penetrating trauma or intra ocular surgery and bilateral panuveitis. Also discussed are the newer concepts, changing trends in epidemiology and management of sympathetic ophthalmia in 21 st century.

Case Report

A forty three year old male diabetic patient, painting artist by profession, presented to us with acute painful defective vision in his only seeing left eye(OS). He had lost vision in his right eye (OD) following a penetrating trauma two years ago.

On examination, his best corrected visual acuity(BCVA) in OD was no perception of light and OS was 20/40. He had features of granulomatous anterior uveitis with large mutton fat keratic precipitates(KP) and retrolental vitreous haze in OS. His injured right eye was deformed, pre phthisical with a sutured limbal wound from 4 to 6 o clock position. Loose limbal sutures were in situ with iris pulled up to wound. Ciliary congestion and active iritis were present with plenty of fine and medium sized keratic precipitates in that eye. A dense fibrovascular membrane was seen occluding the pupillary area with seclusio pupillae. Intraocular pressure in OD was 7 mm of Hg and OS was 12 mm of Hg by applanation. Retinal examination was difficult at the time of presentation due to severe media haze and non dilating pupil in left eye and occlusio pupillae in OD. B scan ultrasonography showed irregular thickening of RCS complex in OS and total RD with vitreous opacities and bands in OD(fig:)

Clinical diagnosis of Sympathetic Ophthalmia was made and the patient was started immediately on intravenous methyl prednisolone (IVMP) therapy 1 gm/ day as a slow infusion along with other supportive treatment with intensive topical corticosteroids(CS) and mydriatics.

Meanwhile his old medical records were retrieved and verified for the details of previous injury. The patient was treated at our institute on 9th November 2013 for penetrating inferior corneoscleral wound with total intraocular hemorrhage, uveal and lens prolapse following injury with a metal piece while at work. BCVA recorded was no perception of light (PL) at admission on the affected eye and he underwent emergency wound repair for the same. CT scan imaging detected no intraocular foreign body but confirmed the presence of vitreous hemorrhage and total retinal detachment. The patient developed re bleed with secondary glaucoma for which paracentesis and hyphema evacuation was done as a second procedure after 10 days of conservative management. He was treated with intravenous antibiotics, systemic corticosteroids and anti glaucoma measures. Systemic corticosteroids were tapered and stopped over a period of 6 weeks. The patient was lost for follow up till he developed symptoms in other eye after and was asymptomatic since then.

The patient responded well to IVMP therapy which then tapered to injection dexamethasone and continued with very slow tapering with oral CS. His BCVA improved to 20/20 in OS. Posterior segment examination at this stage showed normal attached retina. Fundus fluorescein angiography was done during recovery phase, demonstrated few late staining areas in posterior pole suggestive of choroidal involvement. OCT imaging could not reveal any choroidal thickening, nodules or serous detachment.

The clinical diagnosis, possibility of recurrence of disease and the guarded visual outcome explained to the patient and family. The option of enucleation of exciting eye with no useful vision and histopathological confirmation of diagnosis Vs starting long term immunomodulatory treatment(IMT) with present clinical diagnosis was given to patient after appropriate counseling explaining pros and cons. The patient and family opted for enucleation with orbital implant, the same was performed and a customized prosthesis was

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given in OD. Histopathology examination of enucleated eye demonstrated heavy lymphocytic infiltration in choroids confirming our clinical diagnosis.

Patient was started on IMT with oral methotrexate while on slow tapering of oral corticosteroids and is kept under monitoring and follow up. He is tolerating his medications well and is currently maintained on MTX 15 mg/ week with no recurrences and BCVA 20/20 at 12 months follow up.

Discussion

Sympathetic ophthalmitis (SO) is a bilateral diffuse uveitis occurring as a consequence of ocular trauma or intraocular surgery in one eye. The eye sustaining the injury or undergoing surgery is called the "inciting" or the "exciting" eye while the contralateral normal eye is called the "sympathizing" eye. Mackenzie in 1840 and Fuchs in 1905 provided the earliest description of SO [1,2,3]. The possibility of an autoimmune inflammatory response against uveal antigens as the etiology was proposed by Elschnig in 1910. [3]

With improvements in ocular trauma management, SO has become a rare, though still a feared blinding uveitic disease. The onset of SO may be insidious with symptoms manifesting a few weeks to several months or years after the inciting injury. The vast majority (90%) of cases reported within a year of injury.

Prior penetrating injury has been the most common precipitating factor for SO till recent times. However, recent studies have reported an etiologic shift from accidental trauma to surgical trauma for SO,mostly following multiple vitreoretinal (VR) procedures. The reported incidence range from 0.2% to 0.5% following injury and 0.01% following intraocular surgery [9,10]. Multiple surgical interventions are reported as an important risk factor for inciting SO and this could be explained by the additional insults and trigger imposed by the recurrent surgical manipulations in a vulnerable eye. Rishi et al from Chennai reported that SO following VR surgery for antecedent trauma presents early and may have atypical central serous choroids patchy like features with better visual outcome compared to those following VR procedures for retinal diseases[5,16]

Over the years many classic concepts on SO has also been reported differently in addition to changing trends in etiology. It is classically described that the retina and choriocapillaries are spared in the inflammatory process in SO. Many studies, however, have implicated the choriocapillaries in disease progression, with one study reporting 40% of sympathetic ophthalmia patients with choriocapillary involvement and another noting chorioretinal scarring in 25% of cases.

Dalen-Fuchs nodules are a well-known feature of sympathetic ophthalmia that appears in 25% to 35% of cases. They are primarily located in the choroid beneath the

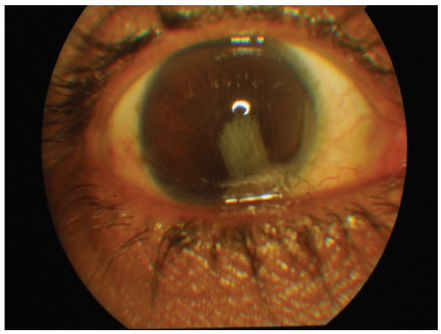


Fig-1 (injured exciting right eye)

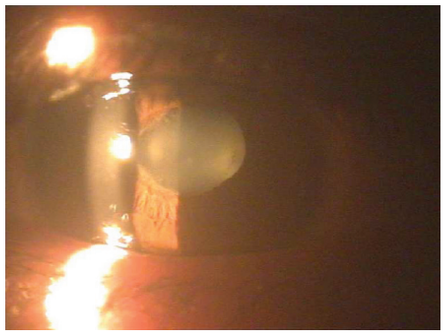


Fig -2 (OD loose sutures insitu)



Fig -3 (Bscan OD Total RD)



Fig -4 (B scan OS thickened RCS complex - active disease)

RPE or under the neuroretina and are primarily composed of macrophages in early stages but later on may be composed of depigmented or degenerated RPE and a small number of lymphocytes. While these nodules were initially characterized in sympathetic ophthalmia cases, they are not pathognomonic and may appear only in approximately one-third of enucleated eyes with sympathetic ophthalmia. [11]

It is always believed that penetrating trauma allows ocular antigens to gain access to lymphatics and be presented to the systemic immune system, producing self-destructive, autoimmune, ocular sequelae. The most convincing recent theory on SO immunology points more to the role of cell-mediated immune response to antigens from the retinal photoreceptor layer. While the particular antigen is yet to be determined, putative retinal antigens studied include retinal soluble antigen (S-antigen), rhodopsin, interphotoreceptor retinoid-binding protein, and recoverin. Retinal S-antigen has been the most extensively studied. In the intact eye, the intraocular antigens bypass local lymph nodes and circulate directly to the blood and spleen. Following injury, however, uveal tissue is exposed to conjunctival lymphatics, and antigens move to the regional lymph nodes, resulting in a cell-mediated immune response. Rao et al. showed induction of uveitis through injection of retinal antigens with adjuvant under the conjunctive but not into the eye. They also suggest the concurrent presence of an infectious agent with an antigen, necessary to incite immune response, to serve as adjuvants in this mechanism of sensitization.[4,11]

Genetic predisposition to the development of sympathetic ophthalmia has also been proposed, with particular focus on human leukocyte antigen (HLA) HLA-A1, as well as HLA-DRB1*04, DQA103,and DQB104 have been recognized in association with SO. [11] In a recent study, Furusato et al. demonstrated elevated CXCL11, CCL19, IL-18,and IL-23, as well as high IL-17, within granulomatous infiltrates of sympathetic ophthalmia, suggesting the possible cytokine milieu of the disease and characterization of cytokine and chemokines involved in pathogenesis of SO [4]. Another study reports nitration of photoreceptors mitochondrial proteins prior to macrophage infiltration and inflammatory cell recruitment , suggesting an initiating role of mitochondrial oxidative stress, photoreceptors cell death and visual loss in SO. [4]

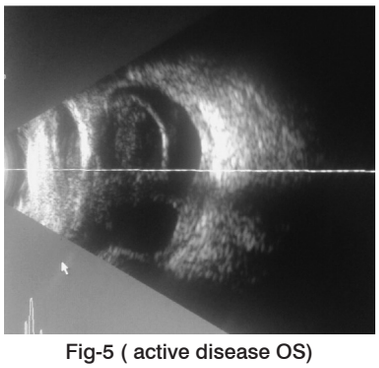


Fig-5 (active disease OS)

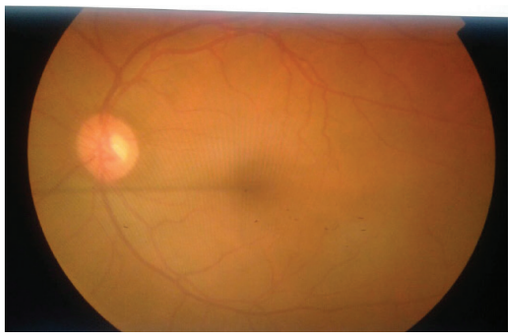


Fig 6 (mutton fat KPs OS)

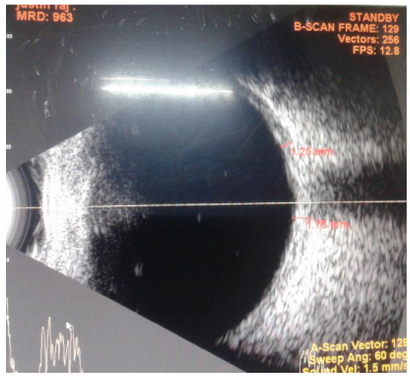


Fig -7 (OS Retina attached and normal after Rx)

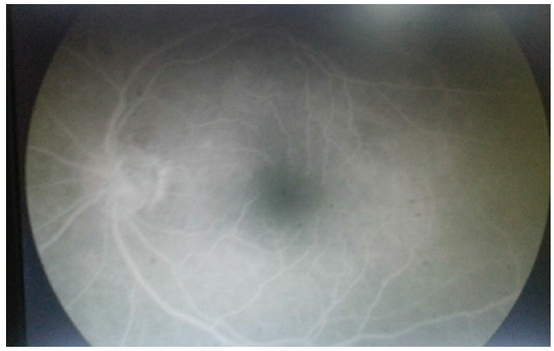


Fig -8 (FFA showing few areas of late leakage OS)

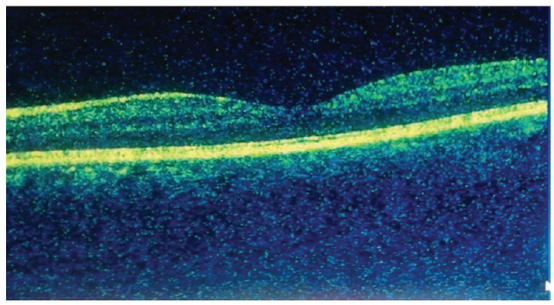


Fig -9(OS - OCT normal macula)

Our patient had a very bad penetrating trauma with complete loss of vision involving the ciliary body region, and recurrent intraocular hemorrhage in OD. He had to undergo a second procedure after initial wound repair to control re bleed and secondary glaucoma which might have triggered the insult on to the already "excited" traumatized eye.

Enucleation of exciting eye (as we did in this case) after onset of SO still remains a controversy. While some authors have suggested that early enucleation of the exciting eye (within 10 -14 days) led to improved visual prognosis, Kilmartin et al and associates suggested that enucleation of the inciting eye following onset of SO did not lead to a better visual outcome in the sympathizing eye nor lessened the need for immunosuppressive therapy, although there are no clinical trials to support this approach. However, most authors agreed on enucleation of a disfigured blind painful exciting eye as in these cases, enucleation with customized prosthesis gives better cosmesis and pain relief in addition to histopathological confirmation of diagnosis [11]

Sympathetic ophthalmia is a concern following multiple intraocular surgeries such as cataract extraction, paracentesis, and iridectomy, and is of particular concern following vitreoretinal surgery. Additionally, non-perforating procedures such as cyclophotocoagulation, irradiation for choroidal melanoma has also been documented to incite sympathetic ophthalmia. To conclude, although incidence of sympathetic ophthalmia has declined in the recent past, prevalence of ocular surgery is on the rise and this necessitates alert and careful prevalence monitoring of changing disease incidence and pattern in this era of modern ophthalmic surgery practice.

References

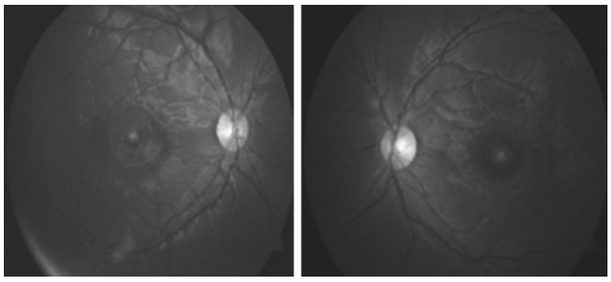
1. Mackenzie W. Treatise on the Diseases of the Eye. 3rd ed. London: Longmans; 1840. p. 523-34.
2. Fuchs E. About sympathetic inflammation (first remarks about serous traumatic iritis). Arch ClinExp Ophthalmol Graefe 1905;61:365-456.
3. Elschnig A. Studies on sympathetic ophthalmitis, II: The antigenic effects of eye pigments. Graefes Arch Clin Exp Ophthalmol 1910;76:509-46.
4. Chu and Chan Sympathetic ophthalmia: to the twenty-first century and beyond Journal of Ophthalmic Inflammation and Infectionhttp://www.joii-journal.com/content/3/1/49
5. Rishi P, Appukuttan B, Walinjkar J, Biswas J, Sharma T. Sympathetic ophthalmitis following vitreoretinal surgery: Does antecedent trauma make a difference?. Indian J Ophthalmol 2015;63:692-8
6. Chan CC, Roberge RG, Whitcup SM, Nussenblatt RB. 32 cases of sympathetic ophthalmia. A retrospective study at the National Eye Institute, Bethesda, Md. from 1982 to 1992. Arch Ophthalmol 1995;113:597-600.
7. Su DH, Chee SP. Sympathetic ophthalmia in Singapore: New trends in an old disease. Graefes Arch Clin Exp Ophthalmol 2006;244:243-7.
8. Pollack AL, McDonald HR, Ai E, Green WR, Halpern LS, Jampol LM, et al. Sympathetic ophthalmia associated with pars plana vitrectomy without antecedent penetrating trauma. Retina 2001;21:146-54.
9. Vote BJ, Hall A, Cairns J, Buttery R. Changing trends in sympathetic ophthalmia. Clin Experiment Ophthalmol 2004;32:542-5. [PUBMED]
10. Maisel JM, Vorwerk PA. Sympathetic uveitis after giant tear repair. Retina 1989;9:122-6.
11. Ozbek Z, Arikan G, Yaman A, Oner H, Bajin MS, Saatci AO. Sympathetic ophthalmia following vitreoretinal surgery. Int Ophthalmol 2010;30:221-7.
12. Middle East Afr J Ophthalmol. 2012 Jan-Mar; 19(1): 13–21.Update on Sympathetic Ophthalmia J. Fernando Arevalo,1,2 Reinaldo A. Garcia,3 Hassan A. Al-Dhibi,2 Juan G. Sanchez,4 and Luis Suarez-Tata3
13. Lewis ML, Gass DM, Spencer WH. Sympathetic uveitis after trauma and vitrectomy. Arch Ophthalmol 1978;96:263-7. [PUBMED]
14. Tamai M, Obara J, Mizuno K, Koisumi A. Sympathetic ophthalmia: Induced by vitrectomy not by trauma. Jpn J Ophthalmol 1984;28:75-9. [PUBMED]
15. Galor A, Davis JL, Flynn HW Jr, Feuer WJ, Dubovy SR, Setlur V, et al. Sympathetic ophthalmia: Incidence of ocular complications and vision loss in the sympathizing eye. Am J Ophthalmol 2009;148:704-10.
16. Gupta V, Gupta A, Dogra MR. Posterior sympathetic ophthalmia: A single centre long-term study of 40 patients from North India. Eye (Lond) 2008;22:1459-64.
17. Tandon R, Vanathi M, Verma L, Bharadwaj A. Central serous retinopathy masquerading as sympathetic ophthalmia. Eye (Lond) 2003;17:666-7. [PUBMED]
18. Ganesh SK, Sundaram PM, Biswas J, Babu K. Cataract surgery in sympathetic ophthalmia. J Cataract Refract Surg 2004;30:2371-6.
19. Croxatto JO, Rao NA, McLean IW, Marak GE. Atypical histopathologic features in sympathetic ophthalmia. A study of a hundred cases. Int Ophthalmol 1982;4:129-35. [PUBMED]
20. Kilmartin DJ, Dick AD, Forrester JV. Prospective surveillance of sympathetic ophthalmia in the UK and Republic of Ireland. Br J Ophthalmol 2000;84:

Brief Report

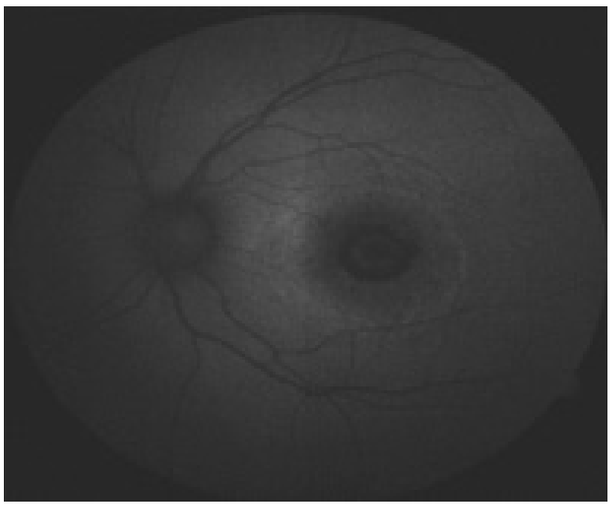
Best Disease

Dr Vidhu Anna Chacko DO, Dr. Ashok Nataraj MS

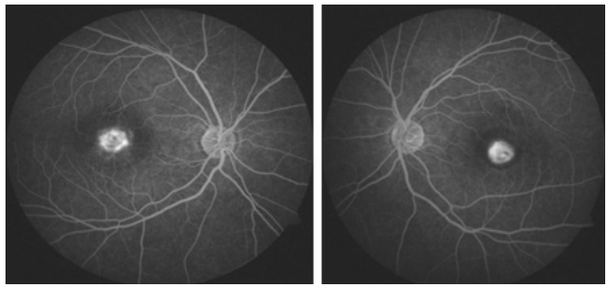
An 11 year old boy presented to us with defective vision both eyes since one year. It was painless and progressive in nature. No relevant family history present. On examination, his best corrected visual acuity was 6/9 P both eyes, near vision was J2 right eye, J6 left eye. Anterior segment with slit lamp was normal for both eyes. Fundus examination with indirect ophthalmoscopy showed yellowish round elevated vitelliform lesions in the central macula of both eyes, rest fundus examination was within normal limits.



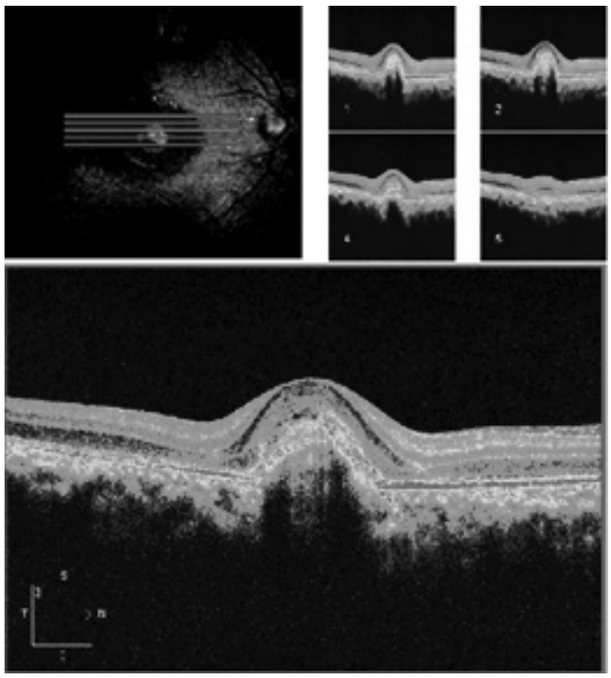
Autofluroscence is as shown below



Fluroscein angiography revealed marked hypofluorescence in the zone covered by the lesion surrounded by hyperflourescence(window defects) due to RPE changes.

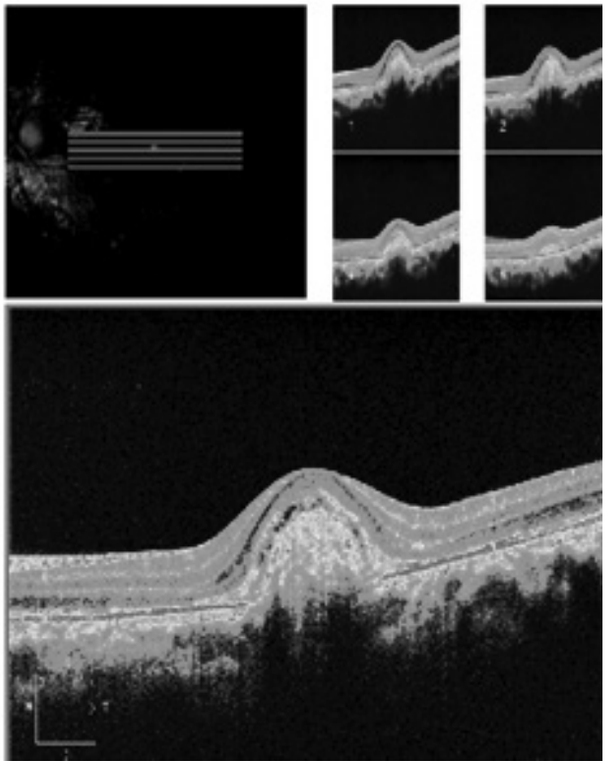


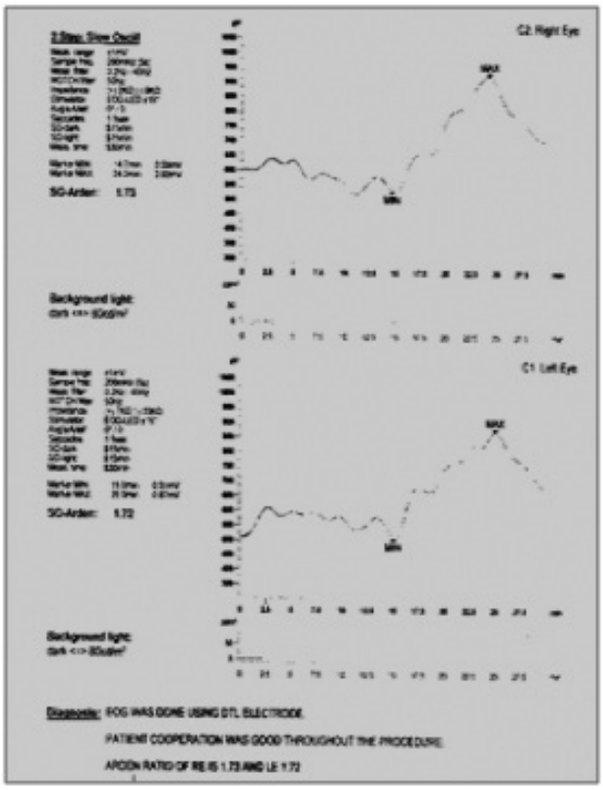
SD- OCT showed splitting and elevation at the outer retina-retinal pigment epithelium complex and a hyperreflective lesion located between the hyporeflective outer nuclear layer and the hyperreflective RPE layer.



ELECROOCULOGRAM – SUBNORMAL (ARDENS RATIO 1.73 & 1.72 for right and left eye respectively)

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DIAGNOSIS - Vitelliform dystrophy or Best disease

Discussion

Vitelliform dystrophy or Best disease, is a hereditary retinal dystrophy involving the retinal pigment epithelium (RPE). It leads to a characteristic bilateral yellow"egg-yolk" appearance of the macula. Autosomal dominant inherited disease with variable clinical expression and diminished penetrance. Some individuals who carry the defective gene have completely normal vision and fundus examination findings but with EOG abnormalities (and are referred to as carriers of Best's Disease which is a misnomer). This disease presents itself in childhood or early adulthood having good prognosis. The first pedigree was presented by Best in 1905, hence is often called 'Best disease'.

Pathophysiology

The causative gene is VMD2 on chromosome 11q 13 and this gene encodes bestrophin. Bestrophin protein has been localized to the basolateral plasma membrane of RPE cells and is important in the formation of oligomeric chloride channels. Abnormal chloride conductance caused by mutations in VMD2 gene might disturb the fluid transport across the RPE which could result in accumulation of debris between the outer retina and the retinal pigment epithelium. This build up leads to the appearance of the typical subretinal vitelliform lesion often described as an "egg-yolk" lesion, alter the EOGs. Breakdown of RPE/ Bruchs membrane can allow choroidal neovascularization to develop as a late complication.

Ocular Manifestation

Visual acuity often is only minimally affected and gradual diminution in visual acuity occurs over a period of years. Choroidal neovascularization (CNV) is the most significant potential sequelae and can cause rapid, significant visual loss. The appearance of the vitelliform lesion usually occurs in the ages of 3-15 years, but can be seen in the later decades of life. It can evolve over time, and is classically grouped into the following stages:

Stage I (Previtelliform): normal vision, normal or only subtle RPE changes (small round yellow dot at site of foveola or a tiny honeycomb structure centrally) with abnormal EOG. Fluorescein angiogram (FA) shows window defects.

Stage II (Vitelliform): classic "egg-yolk" lesion. 30% have ectopic lesions. Normal vision or mild vision loss. A yellow, yolk like slightly elevated lesion (disc like) 1-5 mm (0.5-3 DD) surrounded by somewhat dark border is seen. FA reveals marked hypofluorescence in the zone covered by the lesion.

Stage II a. Vitelliform lesion contents become less

homogenous to develop a "scrambled-egg" appearance. FA shows partial blockage of fluorescence with a non-homogenous hyperfluorescence.

Stage III (Pseudohypopyon): layering of lipufuscein. The lesion develops a fluid level of a yellow-colored vitelline substance. FA shows inferior hypofluorescence from the blockage by the vitelline material, along with superior hyperfluorescent defects. Vision similar to stage II.

Stage IVa Orange-red lesion with atrophic RPE and visibility of the choroid. FA shows hyperfluorescence without leakage.

Stage IVb. Fibrous scarring of the macula. FA shows hyperfluorescence without leakage

Stage IVc. Choroidal neovascularization with new vessels on the fibrous scar or appearance of subretinal hemorrhage. FA shows hyperfluorescence as a result of neovascularization and leakage.

The atrophic stage usually occurs after age 40 years.

Investigations

Fundus Autofluorescense (FAF): During the earlier vitelliform stages, hyperautofluorescence predominates. This hyperfluoresecence settles with the pseduohypopyon stage, and becomes mottled with areas of hypoautofluorescence during the vitelleruptive stage, and eventually becomes hypofluorescent during the atrophic stage. Changes seen with FAF may precede or appear more striking than with ophthalmoscopy.

FFA: shows hypoflourescence at the site of macula in the vitelliform stage as the yellowish material doesn't transmit the choroidal fluorescence. As soon as the lesion disintegrates hyperflourescence areas indicating atrophic pigment epithelium become visible and ultimately one may see a hyperflourescent circle at macula.

OCT : In vitelliform stage, HDOCT shows material as a hyperreflective lesion located between the hyporeflective outer nuclear layer and the hyperreflective RPE layer.

EOG : It is affected even early in the stage of disease and is almost always subnormal. A normal light peak/dark trough ratio (Arden ratio) is greater than 1.8. In Best vitelliform macular dystrophy, the EOG is abnormal with a reduced light peak/dark trough ratio usually less than 1.5, typically between 1.0 and 1.3.

ERG : The full-field electroretinogram (ERG) is normal. Foveal ERG or multifocal ERG reveals reduced central amplitudes.

Follow Up & Management

Examination of visual acuity and fundus lesions should be performed on a schedule dictated by the current stage of the disease. If visual changes occur at any stage, then an earlier visit should be scheduled.

- Previtelliform stage - Yearly
- Vitelliform/pseudohypopyon stage - Every 6 months
- Scrambled egg stage - Every 6 months
- Atrophic stage - Every 6 months to yearly

Patients in the atrophic stage should routinely use an Amsler grid. Changes in the central visual field should prompt an early visit to evaluate for choroidal neovascularization.

The electrophysiology test is usually only necessary once to establish the diagnosis. Initial results remain fairly stable during disease progression.

Fluorescein angiography should be performed at any visit if choroidal neovascularization is suspected. No treatment exists for vitelliform macular dystrophy (Best disease).

Management may include genetic counselling, as well as support concerning school or professional activities of patients. In case of visual acuity loss, magnifying low vision can be applied for optimal use of remaining visual functions. Secondary choroidal neovascularization can be managed with direct laser treatment or photodynamic therapy. Treatment with intravitreal injection of bevacizumab has also been described.

Evaluation of family members (clinical and genetic examination) is important to identify carriers and individuals with vitelliform macular dystrophy. Both genetic counseling and career counseling are provided.

Diferential Diagnosis

1) Adult vitelliform macular dystrophy (AVMD). This autosomal dominant disorder, characterized by the presence of bilateral, small, circular, yellow, symmetrical, subretinal lesions with drusen-like deposits, affects mainly middle-aged individuals. The funduscopic findings can easily be mistaken for Best vitelliform macular dystrophy, but the EOG is normal or only slightly reduced in these individuals. Mutations in PRPH2 (RDS) (which encodes the protein peripherin) and BEST1 have been found in a small number of individuals with AVMD, demonstrating the genetic

heterogeneity of the disorder. AVMD shows significant phenotypic overlap with Best vitelliform macular dystrophy. Using OCT the structure of the vitelliform lesions in the two disorders were similar.

2) Age-related macular degeneration (AMD). This common disorder is characterized by drusen, RPE disruption, and choroidal neovascularization. Multiple lines of evidence indicate that AMD has a familialcomponent. Mutations in a number of genes (including CFH, CFB, ABCA4, TIMP3, and EFEMP1) have been associated with AMD. Mutations in BEST1 are rare in cases of AMD

3) Bull's-eye maculopathy. This descriptive clinical diagnosis is typified by an annular region with depigmentation of central RPE in the macula]. The phenotype can be seen in individuals with cone dystrophy, cone-rod dystrophy, Stargardt disease, chloroquine maculopathy, and other maculopathies.

References

1. Ryan SJ. Retina, 4th edition. Volume II; Medical Retina, editor Schachat AP. Elsevier Inc, 2006.
2. Retina and Vitreous, Section 12. Basic and Clinical Science Course, AAO, 2012-2013.
3. Myron Yanoff & Jay S Duker ophthalmology,3rd edition
4. Postgraduate ophthalmology Zia Chaudhari,M Vanathi,Volume 2
5. Best's vitelliform dystrophy. Blodi CF, Stone EM. Ophthalmic Paediatr Genet. 1990 Mar;11(1):49-59
6. Duncker T, Greenberg JP, Ramachandran R et al., Quantitative fundus autofluorescence and optical coherence tomography in best vitelliform macular dystrophy. Invest Ophthalmol Vis Sci. 2014;55:1471-1282.
7. Hartzell HC, Qu Z, Yu K, Xiao Q, Chien LT. Molecular physiology of bestrophins: multifunctional membrane proteins linked to best disease and other retinopathies. Physiol Rev. 2008 Apr. 88(2):639-72.
8. Querques G, Regenbogen M, Quijano C, Delphin N, Soubrane G, Souied EH. High-definition optical coherence tomography features in vitelliform macular dystrophy. Am J Ophthalmol. 2008 Oct. 146(4):501-507
9. Kay DB, Land ME, Cooper RF, Dubis AM, Godara P, Dubra A, et al. Outer retinal structure in best vitelliform macular dystrophy. JAMA Ophthalmol. 2013 Sep. 131(9):1207-15
10. Glybina IV, Frank RN. Localization of multifocal electroretinogram abnormalities to the lesion site: findings in a family with Best disease. Arch Ophthalmol. 2006 Nov. 124(11):1593-600.
11. Kay CN, Abramoff MD, Mullins RF, et al. Three-dimensional distribution of the vitelliform lesion, photoreceptors, and retinal pigment epithelium in the macula of patients with best vitelliform macular dystrophy. Arch Ophthalmol. 2012 Mar. 130(3):357-64.

PG Tear Sheet

A Ray of Hope for the Blind - Bionic Eye

Dr. Ranjakumar T C : MBBS, DO, MBA; Dr. LalithSundaram : MBBS,MS (AFMC, Pune); Dr. Rahana Ashraf : MBBS

Abstract

Among all the senses we possess, Eye has a major role to play. However, there are many people in the world denied of this invaluable sense. Some are blind by birth, and some become eventually blind due to vision threatening diseases like Retinitis Pigmentosa (RP) and Age Related Macular Degeneration (ARMD). These diseases were incurable, until recently when a special type of prosthesis has been designed to be placed in the inner eye/ retina (IRP- Intra Retinal Prosthesis) to impart vision to these unfortunate individuals.

Keywords

Vision, Night blindness, Retinitis Pigmentosa, Macular Degeneration, Visual prosthesis, Bionic Eye.

Introduction

In the normal visual system, light travels via the tear film, cornea, aqueous, pupil, lens, then through the vitreous to activate the light sensitive photoreceptors and set up trans-synaptic connections of retina. The study and advances in the field of bionic eye is very rapid. It has been quite successful and it restores vision to the people who have lost their vision for their lifetime. The bionic eye mimics the original functioning of the human eye by stimulating the optic nerve, which is activated by the electrical impulse. A small retinal implant is implanted into the human eye and a device is attached to the human body. This implant receives the radio signal and transfers it to the brain through the optic nerve. (1,2)

The device is implanted at any location in the visual pathway to set up a neuronal electrical stimulation. This device is called an Artificial Eye or a Bionic Eye. The vision imparted by the device is called Artificial Vision. (3,4)This has been of great importance for patients with blinding diseases like Retinitis Pigmentosa affecting around 1.5 million people around the world, and patients with Age Related Macular Degeneration (ARMD), 10% of these turn blind each year. 4

History

The pioneer in this field was a German Neurosurgeon Foerster. In 1929, he demonstrated that electrical stimulation of the visual cortex lead to the perception of light spot (phosphene) by subject. 5 However, the first prototype was deviced by Brindley in 1960s, who improvised a device on to the cerebral cortex. Depending upon location along the visual pathway this prosthetic device could be placed in the visual cortex, on the optic nerve or at the retina. The following are the type of prosthesis available.

Cortical Prosthesis (Figure- 1)

Brindley and Dobelle did remarkable work in the development of the visual prosthesis. They demonstrated that phosphenes and patterned perceptions could be evoked, by electrically stimulating the occipital cortex by implanted electrodes. They implanted arrays with 50 electrodes subdurally over the occipital pole. Current models of the intracortical prosthesis include the Utah and Illianos type processor.

a) Utah type prosthesis - muliple silicon spikes arranged in a square grid measuring 4.2 x 4.2 mm with a platinum electrode at the tip of each spike

b) IllianosIntracotical Visual Prosthesis Project - consisting of 152 intracortical microelectrodes, has been implanted in an animal model and the model for human implantation is under discussion. 6

The advantage of the prosthesis is that it bypasses all diseased visual pathway neurons rostral to the primary visual cortex. There are many disadvantages of this type of prosthesis too.

i. Various histological changes induced by this prosthesis.

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ii. The organisation of the visual field at the level of the primary cortex is very complicated.
iii. Prosthesis related complications which causes significant morbidity and mortality in these patients.



Figure – 1 (Cortical Prosthesis)

Optic Nerve Prosthesis (Figure – 2)

An electrode cuff is surgically placed, circumferentially on external surface of Optic Nerve. This was done by Veerart et al. 7 It does not penetrate the Optic nerve sheath. It is based on the principle of retinoptic organisation within the optic nerve. It offers the advantage of representation of the entire visual field on a small area and that it is accessible. However there are many disadvantages like surgical manipulation of this region involves dissection of dura which makes it highly prone for infections.

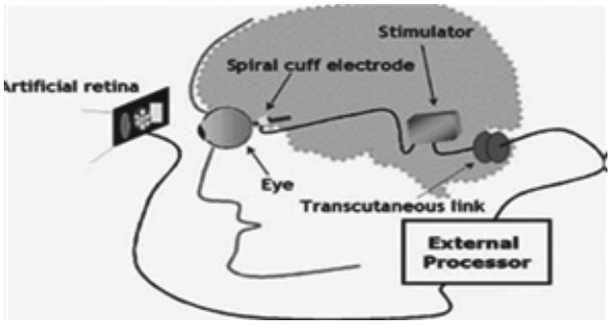


Figure 2 – Optic Nerve Prosthesis

Retinal Prosthesis (Figure -3)

This is based on the fact that the electrical impulse stimulates remaining intact retinal neurons to elicit visual perceptions. There are two main types of retinal prosthesis – Epiretinal and Subretinal. 5

(a) Epiretinal Prosthesis -
Here the device is implanted into vitreous cavity and attached to the inner retinal surface. Epiretinal implants rely on imaging devices such as a camera and then transform this visual information to patterns of electrical stimulation to excite remaining viable retinal neurons. Humayun et al, developed a device called the Intra retinal Prosthesis (IRP). This prosthesis has two components – External or a wearable component with spectacle, incorporated with a light weight camera, pocket batteries & visual processing unit wherein power and data is sent by a wireless link from external unit to internal portion of the prosthesis. The other component is an Implantable or intraocular component with a reciever stimulating chip & microelectrode array including 16 platinum electrodes. The major advantage of this type of prosthesis is that the wearable portion of electronics allows for easy upgrades without requiring subsequent surgery. It has drawbacks like technical difficulty in holding the device on to the inner retina. 5

(b) Subretinal Prosthesis - The subretinal approach to the retinal prosthesis involves implanting a microphotodiode array (MPDA) bipolar cell layer and retinal pigment epithelium. This is accomplished surgically either via an intraocular approach through a retinotomy site (abinterno) or a transscleral approach (abexterno). It uses microphotodiodes (solar cells) as a powering mechanism. According to Chow et al, the low level of current delivered by the implant has a therapeutic and neuroprotective effect on the dying photoreceptors. 8 Zrenner et al, have also concluded that a subretinal implant may act as a replacement for lost photoreceptors. 9 However it offers many advantages like closer proximity to rest of the surviving neurons to the visual pathway (i.e; bipolar cell) and therefore less current requirement, also lack of mechanical means of fixation. Limitations are that there is limited subretinal space to place electronics close proximity of the retina to the electronics which would increase the risk of thermal injury to the neurons. 5

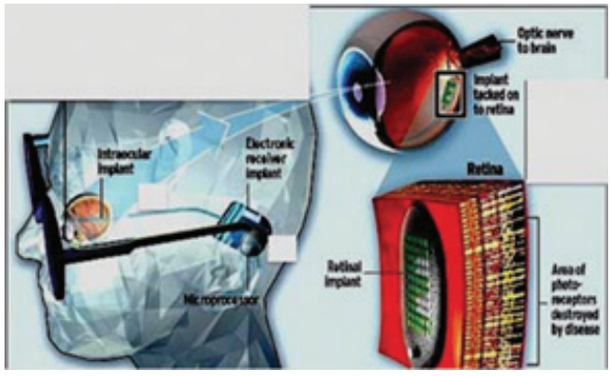


Figure 3 – Epiretinal Prosthesis

The ARGUS II Epiretinal Prosthesis (Figure – 4)

It belongs to the second generation epiretinal implant designed for the treatment of RP induced blindness. It is an

epiretinal stimulating device to improve visual functioning in the visually disabled. The devices are electrically conducting and has potential to be used in patients to detect light or even differentiate various objects. The device contains 16 electrodes, which aids in providing images with better resolution. It received the CE mark of Europe back in 2011. However, the FDA approved it for the treatment of RP in 2013. This is currently in use in United States of America.

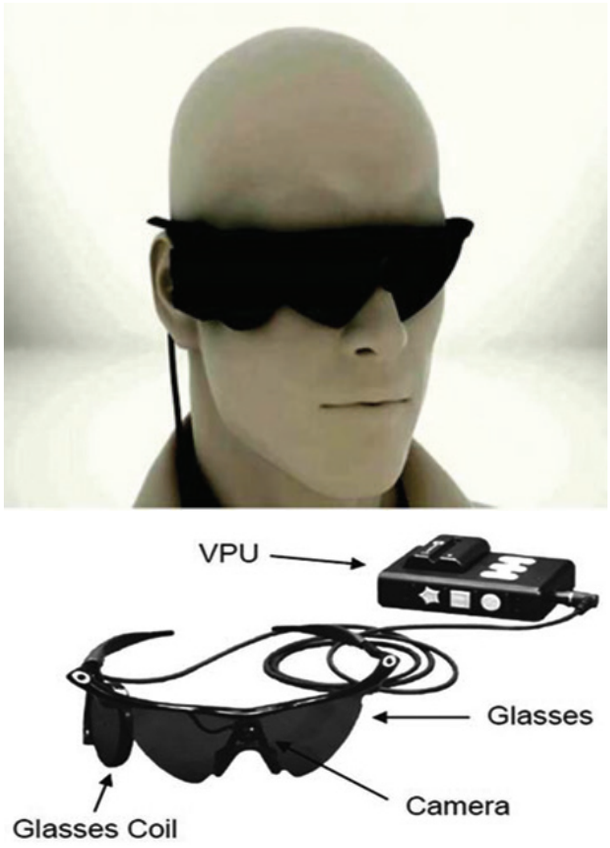


Figure 4 - ARGUS II Prosthesis

The ALPHA IMS Prosthesis

Its being manufactured in the Retina Implant AG at Germany. 10This is the only retinal prosthesis that has undergone long term testing in humans. In July 2013, it received the CE mark in Europe. Unlike the ARGUS, it does not require an external eyeglass mounted camera. Also, it has a wireless subretinal chip, which moves with the eye, containing 1,500 electrodes, which transform the incoming light into electric signals. After passing via an amplified circuit, these signals will stimulate the remaining intact retinal cells to induce visual perceptions. From the various trials conducted recently, authors have mentioned ALPHA IMS as a "reliable and luminance dependent signal generation".

Conclusion

The advancement of science and technology has enabled the immobile brindley type of prosthesis to be replaced by the portable and hassle free Epiretinal prosthesis. This has been of great advantage especially to the RP and the AMD pateints. The micro technology have allowed for the development of high end circuit systems to be placed in the epiretinal or the subretinal spaces. These devices are very similar to the Cochlear Implants, but the viual system is much more complex than the auditory system and hence more challenging.

Inspite of these advances, there are several ill effects of these implants. Biocompatibility is one such issue due to the various kinds of chemical, biophysical, and immunological reactions to the implanted materials. Encapsulation of the implant due to fibrosis could lead to miscommunication between the implant and the target tissue. Also, the potential effects of heat generation and transfer of electrical energy have not been completely understood by majority of the investigating groups. Hence continued research is required for other modalities of treatment of RP like drug therapy and gene therapy.

References

1. Alice C. Parker and Adi N. Azar, "A Hierarchical Artificial Retina Architecture", Viterbi School of Engineering, University of Southern California Los Angles CA.
2. News Brief, "Argus IITM Retinal Prosthesis System for Peripheral Retinal Degradation" National HorizonTM Scanning Center, June 2011.
3. Weiland JD, Humayun MS. Past, Present and future of artificial vision. Artif Organs 2003; 27: 961-2.
4. Ajay Banarji, VS Gurunadh, S Patyal, TS Ahluwalia, DP Vats. Visual prosthesis Artificial vision. MAJFI 2009, Vol.65(4), 348- 352.
5. V.S. Gurunadh, Sandeep Gupta, M.A. Khan, Ajay BanarjiKhaleel M, Parth Patel, Shefali Joshi. Bionic Eye. DOS times 2014, September.
6. Margalit E, Maia M, Weiland JD, Greenberg RJ, Fujii GY, Torres G, et al. Retinal prosthesis for the blind. SurvOphthalmol 2002; 47: 335-6.
7. Veraart C, Raftopoulos C, Mortimer JT, Delbeke J, et al. Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode. Brain Res 1998;813:181-6.
8. Chow AY, Chow VY, Packo KH, Pollack JS, et al. The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. Arch Ophthalmol 2004; 122 :460-9.
9. Zrenner E. Restoring neuroretinal function: new potentials. The Emiko Adachi award lecture. Doc Ophthalmol 2007;115:56-9.
10. Elaine a. Richman. Retinal Prostheses: What Next After Argus Approval. www.eyenet.org: August 2013.

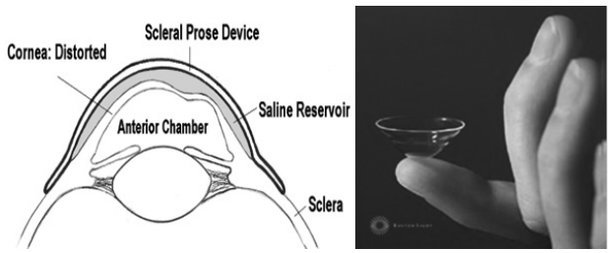
Prose - A Surrogate to Keratoplasty?

Dr Rahana Ashraf (MBBS), Dr Ranjakumar T C (MS, DO, MBA)

Introduction

Prosthetic Replacement of the Ocular Surface Ecosystem (PROSE) is a novel treatment approach to ocular surface disease. It is a prosthetic device to replace & enhance the function of ocular surface ecosystem, thereby improving vision, providing comfort & supporting ocular surface. The device used in PROSE was approved by the FDA in 1994 for daily wear in the treatment for irregular astigmatism & ocular surface disorders. Over the past 20 years it has been referred as Boston Scleral Contact lens, Boston Scleral lens, Boston Scleral lens device, Boston Scleral lens prosthetic device and Boston Ocular surface prosthesis (BOS-P).[1]

Design



The prosthetic devices created by Boston Foundation for Sight are transparent domes, about the size of a nickel. They look similar to an oversized hard contact lens and resemble in shape a margarita glass without the stem. PROSE devices fit under the eyelids, vaulting the damaged cornea and resting on the sclera. Worn during waking hours, patients are trained in daily application, removal and cleaning, as part of the treatment process.[1,2]

PROSE devices are made out of a highly gas-permeable hard plastic that allows oxygen to reach the cornea. They are designed to create a space between the prosthetic device and the eye that is filled with sterile saline. The liquid remains in the reservoir, providing constant lubrication by bathing the eye in a pool of artificial tears.[2]

Lack of corneal touch and positional stability eliminate all sources of frictional microtrauma. The high oxygen permeability constant (Dk) of the material allows oxygen to readily diffuse through the lens matrix. PROSE treatment also overcomes the drawbacks of other modalities such as surgical risk and temporary effect of amniotic membrane grafting, the cosmetic and vision concerns of tarsorraphy, the contamination risk and the potential inconsistencies in preparation & storage of autologous serum eye drops.[3]

Prosthetic devices are customized by specially trained PROSE doctors and made on-site at the Boston Foundation for Sight PROSE Manufacturing Lab.

PROSE creates

- A new transparent, smooth optical surface over the irregular, damaged or diseased cornea.
- An expanded artificial tear reservoir that provides constant lubrication while maintaining the necessary oxygen supply.

Indications

1. Corneal Ectasia- Eyes with advanced corneal ectasia can be successfully fitted with the PROSE device, and the Visual Acuity outcome for stage 4 ectasia was better and more rapid compared to keratoplasty.[4]
2. Most popular indication is for ocular surface disease like Persistent Epithelial Defect (PED).The mechanism by which PROSE supports re-epithelization in refractory persistent epithelial defect may include continuous lubrication, ocular surface protection and maintenance of oxygenation.[3,5,6]
3. Steven Johnson Syndrome (SJS) & Toxic Epidermal Necrolysis - with remarkable improvement in photophobia & surface breakdown, it also helps in healing of persistent epithelial defects associated with SJS when used on a daily wear basis.[5,7,8]
4. Limbal stem cell deficiency - Grover et al reports 2 patients with persistent epitheliopathy following treatment of conjunctival melanoma who were rehabilitated with PROSE. The authors finally concluded that “PROSE device can be an useful non-surgical option for these patients”.[5,9]

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5. Neurotrophic keratopathy- Gumus et al published a case repot on the use of PROSE device in management of persistent corneal epithelial defect from Herpes Zoster Opthalmicus. Along with other modalities of treatment like Oral Doxycycline, autologous plasma, punctal plugs, multiple therapeutic lenses & double layer amniotic membrane transplantation, he combined PROSE therapy. A remarkable change in the epithelial defect was seen within 3 weeks of daily use.[5,10]

6. Atopic keratoconjunctivitis - PROSE device can be considered in these patients with PED, who are poor candidates for contact lens use. It promotes rapid healing of PED.[5]

7. As a pharmaceutical reservoir - With PROSE, fluid turnover is low, allowing for prolonged availability of drugs in the reservoir. Epithelial toxicity could be enhanced by sustained contact, hence care is taken to use only preservative-free solutions.[3]

Treatment providers

PROSE treatment is provided by a team that includes Cornea Specialist Ophthalmologists, Optometrists who have completed the PROSE Clinical Fellowship and Ophthalmic technicians.

Treatment takes an average of 4 to 12 day long visits to complete, with periodic follow-up visits as needed during the first six months.

Customization Process

PROSE doctors customize multiple trial prosthetic devices. Each step is followed by a trial wearing session to make sure each patient achieves the best customization possible. The final prosthetic device or devices is unique to each patient's eye condition and specific treatment goals.

Patient Training

Patients participate in three or more training sessions to learn how to apply, remove and care for their prosthetic devices. Family members and caregivers are often trained to assist patients as well.

Follow-up with Primary Eye Care Doctor

Patients are instructed to follow-up with their referring eye doctor within 2 to 3 weeks of finishing treatment. Ongoing care is provided by the primary eye care doctor and coordinated with the PROSE treatment providers.

Annual Evaluation

Patients are advised to come for follow up annually to their PROSE provider for detailed examination of their PROSE devices, make adjustments as needed and address any related issues.

According to the Boston Foundation for Sight

Following are the requirements for insertion

a. An application plunger
b. A removal plunger
c. Two alcohol wipes
d. A small mirror
e. Preservative-free saline



Plunger **Method of insertion**

Care and Handling of the PROSE Device

Following are the requirements:
- One PROSE disinfection case
- One unopened package of Clear Care™



Disinfection case **PROSE cleaning solution**

Centers in India providing PROSE treatment[2]

1. LV Prasad Eye Institute, Hyderabad.
2. Sankara Nethralaya, Chennai.
3. The Eye Super Specialities (TESS), Mumbai.

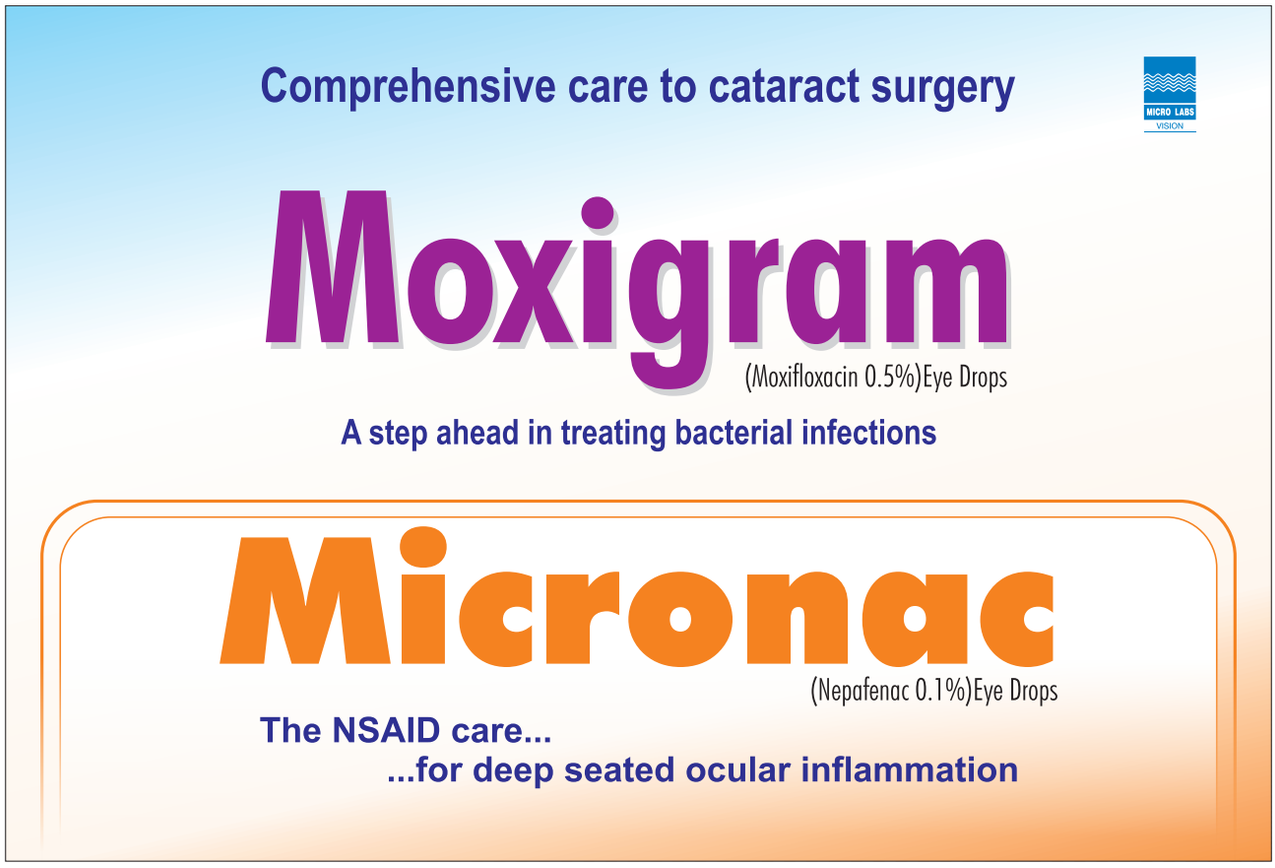
Limitations

Limitations to the wider adoption of PROSE treatment includes cost and availability at a limited number of tertiary eye care centers. An economic appraisal found that PROSE treatment is cost effective and cost beneficial in patients with severely compromised visual function attributable to ocular surface disease. Others have also reported that epithelial

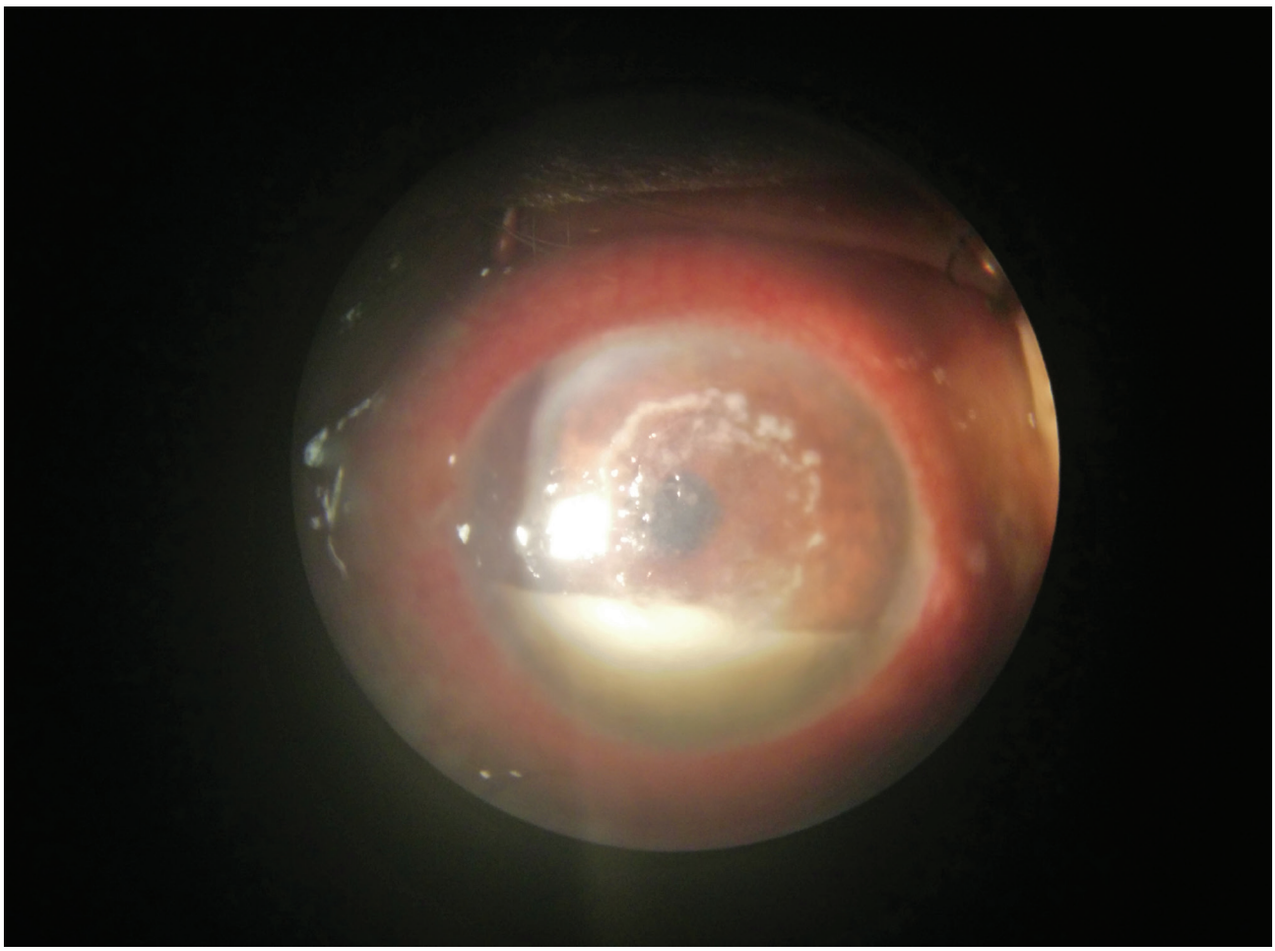
defects requiring PROSE for healing typically recur following cessation of therapy. In comparison to earlier series of cases, the rate of microbial keatitis as a complication of treatment has been reduced with the use of a non preserved topical fourth generation fluoroquinolone in the device reservoir. [3]

References

1. Holland J, Mannis J, Lee W. Ocular Surface Disease: Cornea, Conjunctiva & Tear film. Saunders Elseivier; 2013. p.286-288.
2. Boston Foundation for Sight [Internet]. Massachusetts: Boston Foundation for Sight; 2015 [cited 2014 September 20]. Available from: http://www.bostonsight.org/
3. Lim P, Ridges R, Jacobs S, Rosenthal P. Treatment Of Persistent Corneal Epithelial Defect With Overnight Wear Of A Prosthetic Device For The Ocular Surface. Am J Ophthalmol 2013 Dec; 156:1095-1101.
4. Deloss S, Fatteh H, Hood T. Prosthetic Replacement of the Ocular Surface Ecosystem (PROSE) Scleral Device Compared to Keratoplasty for the Treatment of Corneal Ectasia. Am J Ophthalmol 2014 Nov; 158:974-982.
5. Copeland A, Afshari A. Copeland and Afshari's principles and practice of Cornea. New Delhi: Jaypee Brothers Medical Publishers; p.857-862.
6. Stason WB, Razavi M, Jacob D S, et al. Clinical Benefits of the Boston Ocular Surface Prosthesis. Am J Ophthalmol. 2010;149(1):54-61.
7. Heur M, Bach D, Theophanous C, Chiu GB. Prosthetic replacement of the ocular surface ecosystem scleral lens therapy for patients with ocular symptoms of chronic Stevens-Johnson syndrome.Am J Ophthalmol. 2014 Jul;158(1):49-54.
8. Rathi V M, Mandathara PS, Dumpati S, et al. Boston ocular Surface Prosthesis: An Indian Experience. Indian J Ophthalmol.2011 Jul;59(4):279-81.
9. Grover S, Jacobs DS, Colby KA, et al. Boston Ocular Surface Prosthesis for persistent epitheliopathy after treatment of conjunctival melanoma. Cornea.2010 Apr;29(4):459-61
10. Gumus K, Gire A, Pflugfelder SC. The Successful use of boston ocular surface prosthesis in the treatment of persistent corneal epithelial defect after herpes zoster ophthalmicus. Cornea.2010 Dec;29(12):1465-8.



Identify the condition
What is the drug of choice?



Send your answers to: drashok.eye@gmail.com

Dr. Smitha Rani Syriac DO,DNB, Dr. Ashok Nataraj MS

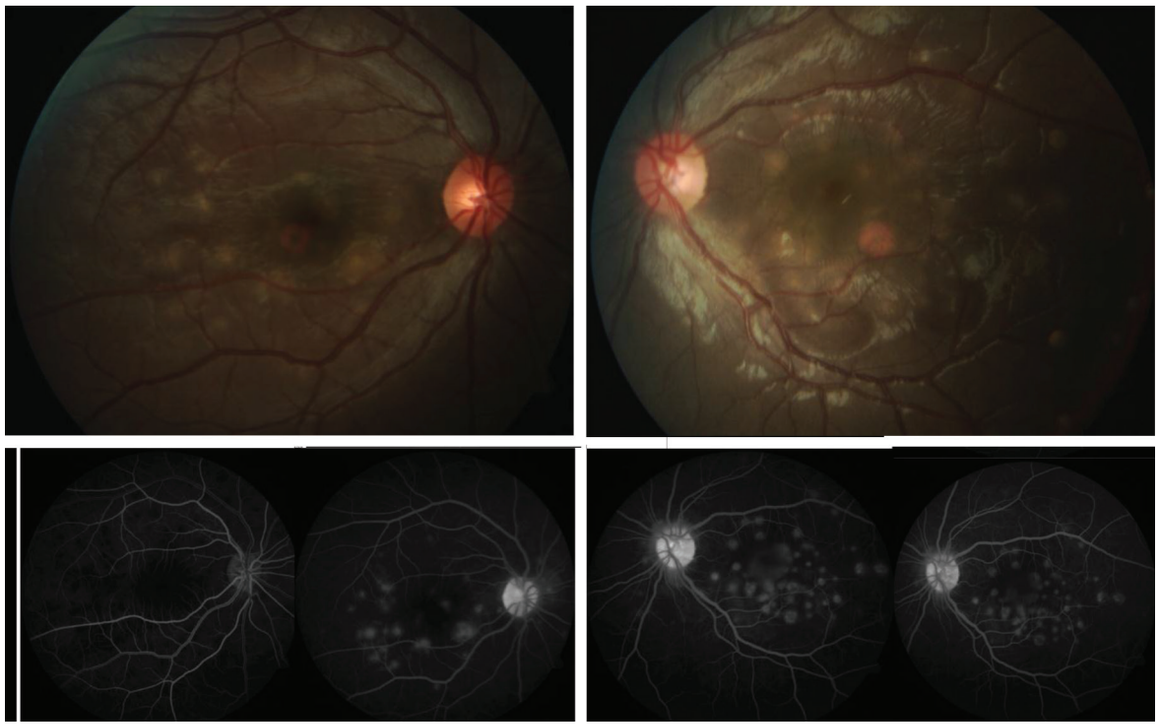
17 year old female came with complaints of sudden onset defective vision of LE since 2 days, associated with headache & vertigo of 1 week duration.Systemic &general examination was normal.

Fundus-Both eyes showed multiple solid subretinal white dots with serous detachments.

Her best visual acuity on presentation was RE-6/6; LE-CF 1mts

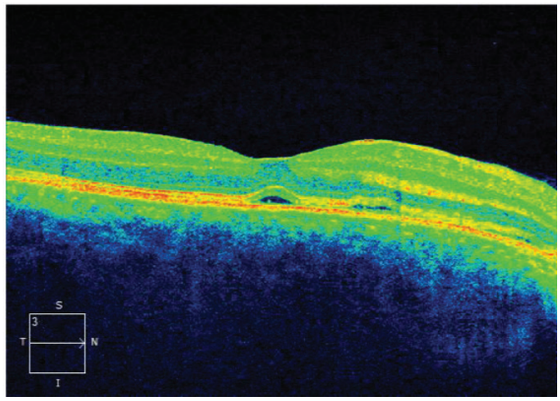
Anterior segment was within normal limits. Fundus examination -as shown below

RE LE



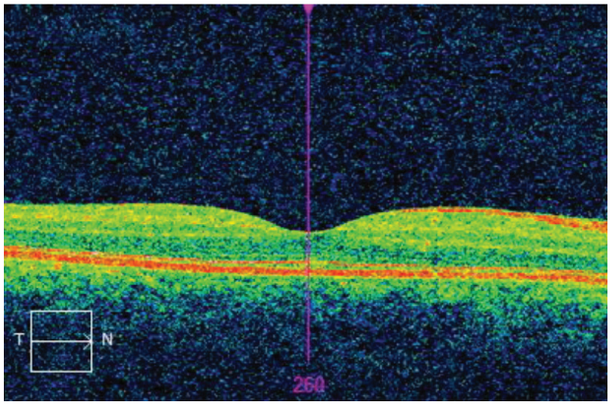
FFA-BE-multiple pinpoint leaks,areas of placoid hyperfluorescence,pooling of subretinal fluid.

OCT- RE showed multiple serous detachments& LE multiple serous detachments with large subfoveal detachment.



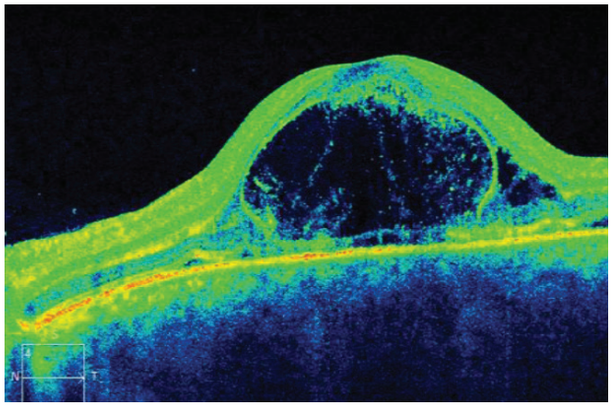
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Mob: 9446407781

RE



Diagnosis-Incomplete VKH Disease

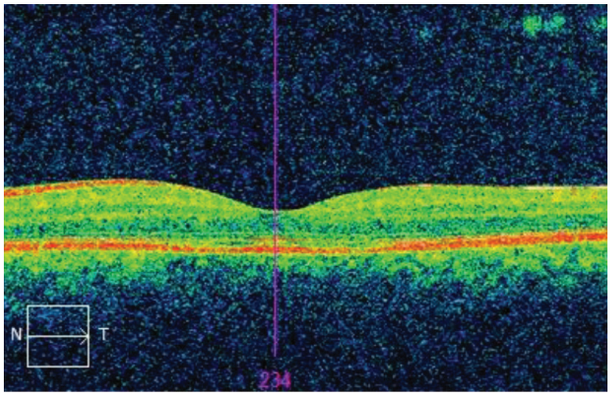
LE



B-scan LE showed choroidal thickness more than 2.4mm.

Treated with systemic and topical steroids- tapered over 6weeks with complete resolution.





Visual acuity after 4 weeks of treatment was both eyes:6/6. Experience shows that the stages of VKH are often indistinct. Moreover ,it is not clinically relevant to distinguish the stages for a treatment strategy.The critical aspects of treatment are to make the correct diagnosis without delay,to institute appropriate systemic anti-inflammatory therapy,&to taper therapy appropriate to disease activity and side effects.

Dr. Sheera K. R. MBBS

CORNEAL CROSSLINKING

J Bradley Randleman, MD; Sumitra S Khandelwal, MD; Farhad Hafezi MD phD

Survey of ophthalmology 2015, 60(6): 509-523

This article explains the history, fundamental concepts, clinical applications, optimizing cross linking success, cross linking controversies and future directions. Observational studies demonstrating decreased rate of keratoconus in patients with diabetes revealed that natural crosslinking occurs in these patients from the non-enzymatic glycosylation of proteins which result in the formation of advanced glycosylation end products. This combined with Theo Seiler's inspiration to use ultraviolet light to stimulate cross linking in the cornea, similar to the manner in which dentist use cross linking to strengthen gums, led to the advent of this revolutionary treatment. The basic requirement for corneal cross linking include a photoinducer, a light source with adequate intensity but safe parameters and the photochemical reaction which induces free radicals while creating a chemical bond between collagen fibrils.

In attempt to accelerate the treatment, variations in these parameters promoted use of shorter treatment time at higher intensities. This is based on Bunsen- Roscoe law of reciprocality. They have divided the complications of cross linking as related to the primary process, wound healing process, LASIK flap complications and to the limbal stem cells. The primary clinical indications for corneal cross linking include progressive keratoconus in adults and progressive ectasia after LASIK. Other indications are paediatric keratoconus, cross linking combined with refractive surgical procedures called CXL PLUS and cross linking for infectious keratitis.

Paediatric patients benefit more with CXL because of the progressive nature of the keratoconus. Studies shows that eyes with more advanced keratoconus shows more flattening during the first year. CXL PLUS include cross linking combined with intrastromal corneal ring segments, photorefractive keratectomy, phototherapeutic keratectomy, phakic intraocular lenses. Cross linking for infectious keratitis is called PACK CXL- photoactivated chromophore for keratitis. Studies showed better success rate in bacterial group than in the fungal group. CXL should be avoided in patients with herpetic keratitis since it may cause reactivation. Accelerated CXL means shorter treatment time and higher intensity UV exposure. Comparison of effect of standard and accelerated CXL shows varying outcome. These study results imply that accelerated CXL may have more rapid overall corneal recovery after CXL which could improve safety profiles. There is only limited evidence that prophylactic CXL will be efficacious as traditional cross linking can induce progressive continued flattening over time, it may be challenging to titrate the effect of CXL.

ADDITIVE EFFECT OF REPEATED CORNEAL COLLAGEN CROSS-LINKING IN KERATOCONUS

Farhad Hafezi, MD, PhD; David Tabibian, MD; Olivier Richoz, MD,

J Refract Surg. 2014 Oct; 30(10):716-8.

This is a case report from Switzerland which report the long term clinical outcome of repeat corneal cross linking in a case of keratoconus. This is an observational case report. Topographical changes were assessed by high-resolution Scheimpflug imaging. The right eye underwent a standard epithelium-off CXL procedure in Febru¬ary 2008, followed by the left eye 4 weeks later. In 2012, the left eye was treated with CXL for a second time. Irradiation was performed in all cases at a fluence of 5.4 J/cm2. Energy settings were 30 minutes @ 3 mW/cm2 for the CXL procedures performed in 2008, and 10 minutes @ 9 mW/cm2 for the second CXL pro¬cedure of the left eye that was performed in 2012.

The right eye that underwent a single CXL procedure showed a flattening of keratometry values between 2008 and 2012, followed by stabilization. The left eye showed a similar flat¬tening effect between 2008 and 2012, followed by another flat¬tening effect after the second CXL procedure and accompanied by a distinct increase in corrected distance visual acuity. Following repeated CXL, the corneal stroma and endothelium remained inconspicuous, and postoperative haze and visibility of the stromal demarcation line was similar to what is usually observed after a single CXL procedure. Between 2008 and 2012, the left eye showed distinct remodeling with central flattening of up to 4 D, but also an increase of maximum keratometry values from 46.6 to 47.8 D. In 2014 (2 years after the repeated CXL

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procedure), the left eye showed a further flattening effect of another 4 D, for a total flattening of 8 D between 2008 and 2014. Whether the addi¬tive flattening effect of the anterior surface observed in this single case goes along with an additive increase in biomechanical stiff¬ness remains to be seen.

PATTERNED CORNEAL COLLAGEN CROSSLINKING FOR ASTIGMATISM: COMPUTATIONAL MODELING STUDY

Ibrahim Seven, MS, Abhijit Sinha Roy, PhD, and William J. Dupps Jr, MD, PhD

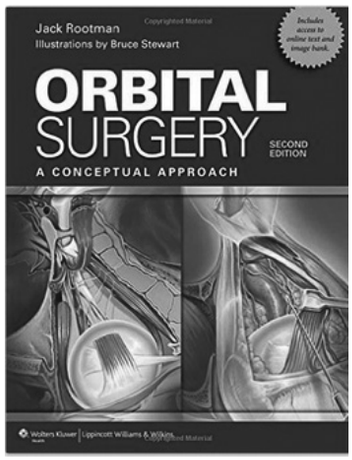
J Cataract Refract Surg. 2014 June; 40(6): 943–953

Study conducted in USA to test the hypothesis that spatially selective corneal stromal stiffening can alter corneal astigmatism and assess the effects of treatment orientation, pattern, and material model complexity in computational models using patient-specific geometries. Three-dimensional corneal geometries from 10 patients with corneal astigmatism were exported from a clinical tomography system (Pentacam). Corneoscleral finite element models of each eye were generated. Four candidate treatment patterns were simulated, and the effects of treatment orientation and magnitude of stiffening on anterior curvature and aberrations were studied. The effect of material model complexity on simulated outcomes was also assessed.

Pretreatment anterior corneal astigmatism ranged from 1.22 to 3.92 diopters (D) in a series that included regular and irregular astigmatic patterns. All simulated treatment patterns oriented on the flat axis resulted in mean reductions in corneal astigmatism and depended on the pattern geometry. The linear bow-tie pattern produced a greater mean reduction in astigmatism than other patterns tested under an assumed 2-times increase in corneal stiffness, and it had a nonlinear relationship to the degree of stiffening. The mean astigmatic effect did not change significantly with a fiber- or depth-dependent model.

They concluded that in silico simulations based on patient-specific geometries suggest that clinically significant reductions in astigmatism are possible with patterned collagen crosslinking. Effect magnitude was dependent on patient-specific geometry, effective stiffening pattern, and treatment orientation.

Dr. Meenu C Jacob MBBS, DO

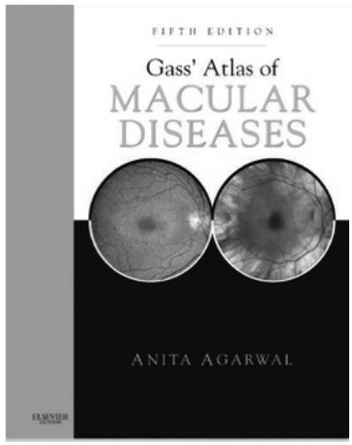


ORBITAL SURGERY – A CONCEPTUAL APPROACH
Author – Jack Rootman
Second edition – 2014
Lippincott Williams & Wilkins
Pages - 432

Book by Jack Rootman is a comprehensive reference guide to orbital diseases along with excellent anatomical and surgical illustrations. The book is divided into four sections and subdivided into fourteen chapters. Using a conceptual model, along with more than 800 photographic and hand-drawn illustrations this book provides the reader with a clear description of the factors to consider when deciding on the proper approach to lesions anywhere in and surrounding the orbit

First section gives an immense idea about the principles of analyses, planning and surgical management of orbital disorders. Orbital anatomy is illustrated in a three dimensional easy to reproduce artistic manner

Orbital approaches for specific disease entities are explained with examples of more than 70 case reports. Each case report is documented with clinical illustrations, surgical atlas and imaging studies. Last section gives a beautiful narration and illustration of individual procedures like exenteration, enucleation, evisceration and socket reconstruction etc.
Book is presented in an easy to follow format and decision making approach to orbital lesions. This book is an invaluable text for learning surgical techniques in orbital diseases



Gass' Atlas of Macular Diseases
Author – Anita Agarwal
Edition – Fifth 2012
Publisher – Elsievier Saunders
Pages - 1378

This is a unique book which gives a cocktail of macular disorders. Book is spread in two volumes covering the entire macular disorders in texts followed by clinical, schematic, histological and imaging photographs. Dr. Anita Agarwal has maintained the rich heritage of the hallmark of Dr. Gass' book, with great attention to clinical detail.
Books give a case descriptive format for retinal disorders encompassing history, clinical examination and follow up. Management of the diseases are minimally discussed. It helps the clinician to arrive at a diagnosis and to understand the pathogenesis of both common and uncommon diseases. Common retinal disorders are covered in detail. Multiple images are often available of the same entity demonstrating variability of the diseases.
Infections, inflammatory, heredo – dystrophic retinal disorders are described in detail. This updated comprehensive atlas is justly considered to be the bible of macular diseases affecting the retinal periphery, in addition to optic nerve head diseases that mimic macular diseases
The scope of the atlas is remarkable, covering everything from diseases seen in daily practice to those we've never heard of, like Bothnia dystrophy and Leigh syndrome. Gass' Atlas is most appropriate for highly ambitious residents, retina fellows and specialists, and general ophthalmologists who are looking for an excellent reference book with a proud lineage and impeccable reputation

Address for Correspondence: Little Flower Hospital, Angamaly. Email: meenucjacob@gmail.com

Dear Editor,

I would like to congratulate the authors for doing an excellent work on "Clinical outcome of Amniotic membrane grafting in acute chemical injuries" in the last issue of KJO. Usefulness of AMG in chemical injuries and its biological action is clearly enlightened in your article. I would like to know whether AMG can be done immediately after injuries or we can wait for a few days of medical treatment excepecting some normal epithelialisation ,in severe chemical injuries.

Dr Meenu C Jacob
Little Flower Hospital, Angamaly

Author's reply

We thank Dr.Meenu for the keen interest taken in our article.

The acute phase of chemical injuries is associated with severe ocular surface inflammation and epithelial interruption leading to tissue melting. The goals of treatment in the acute phase include reduction of inflammation, stimulation of epithelialization and prevention of tissue necrosis. Hence the emergency department should be familiar with the necessity of prompt evaluation and treatment of this emergency and it should be triaged appropriately.

AMT can facilitate healing of the corneal and conjunctival surfaces in mild and moderate chemical injuries and prevent symblepharon formation in severe cases. In severe chemical burns, diffuse inflammation in the ocular surface, deep stromal ischemia and near total destruction of limbal stem cells occur. Hence medical management may be sufficient in grades 1 and 2 chemical injuries (Dua's classification), but an immediate AMT is beneficial in grades 3-6. Repeat AMT may be needed later depending on the healing response. In the acute phase, even in an ICU set up , the membrane can be spread in the eye, stromal side down, fornix to fornix and secured with a symblepharon ring or a large diameter bandage contact lens. ProKera (available abroad) is a cryopreserved amniotic membrane, clipped to a dual polycarbonate ring system with an inner diameter of 16 mm and an outer diameter of 21 mm for use in the acute phase. ProKera is placed in the eye in a similar fashion to a large contact lens. Ocular surface restoration with AMT has the advantage of creating an environment with reduced perilimbal inflammation; promoting healthy epithelium with reduced corneal neovascularization and may set the patient up for successful future ALT and/or PKP if stromal scarring remains.

Further prospective randomized studies including a control group are required to determine the effectiveness of AMT in acute chemical injuries.

Dr. Seema
Malabar Eye Hospital
Kannur

Dear Editor,

It is with great interest that I read the article- 'Innovations in Strabismus Surgery: Closed Conjunctival, Fornix Approach, Delayed Adjustable Suture Technique in Strabismus Surgery.' I would like to congratulate the author for the novel method. This approach would obviate a second procedure in patients with orthotropia on postoperative day 1.

I would like to know whether there is any complication associated with this procedure.

Once again I thank the author for this beautiful technique.

Dr. Joseph John
Little Flower Hospital, Angamaly

Author's reply

Dear Dr Joseph John,

Thank you for the interest you have shown in the new technique of adjustable suture. The advantages of the new innovation is that it avoids a second procedure of post operative adjustment in patients who have achieved orthotropia and secondly since adjustment can be done as late as 2-3 weeks, post operative drift can be taken care of. There are no specific complication, but , since we are tucking a longer length of suture under the conjunctiva, post op inflamation will be slightly more than the conventional procedure where we trim off the extra long suture.

Yours Sincerely,

Dr Elizabeth
Little Flower Hospital, Angamaly

Dear Editor,

It is with great interest I read the article titled - correlation between DME & choroidal thickness using enhanced depth imaging OCT by Dr Joseph John et al. I would like to congratulate the authors for their research as we now know that choroidal vasculopathy does have a role in the pathogenesis of DME. As suggested by the authors, reduced choroidal thickness indicates overall decreased choroidal blood flow further causing retinal hypoxia .Similar to CSCR, IPCV, ARMD where choroidal thickness has prognostic values, similar prognostic values are expected in patients with DME. With the advent of enface imaging we would get better insight into pathology of DME and other diseases.

Dr. Awaneesh
Little Flower Hospital, Angamaly

Author's reply

Thank you Awaneesh for the encouraging words. The advent of enhanced depth imaging, image averaging, volume rendering, swept source modalities in the OCT helped us to better visualize the choroid and to recognize its significance.

In our clinical practice we see some patients responding very well to intravitreal anti- VEGF agents in the first injection itself. On the other hand some patients do not seem to respond at all. In our study we could clearly demonstrate the factors which discern the two. This study also showcased the disparate response of choroid to focal laser photocoagulation and anti-VEGF agents. As mentioned by Dr. Awaneesh, we can take into account the choroidal thickness too in the counselling of our patients.

Once again the authors thank Dr. Awaneesh for his valuable comments and the enthusiasm shown in our article.

Dr. Joseph John
Little Flower Hospital, Angamaly

The Kerala Journal of Ophthalmology (KJO) is a quarterly; peer reviewed one, devoted to dissemination of the latest in ophthalmology to the General Ophthalmologists as well as to specialists in the various subspecialties of this discipline. It invites submission of original work dealing with clinical and laboratory materials.

Authors submitting materials to this journal are requested to adhere STRICTLY to the norms laid down below. The matter must be typed on one side of the paper. A margin of 1" must be left all around and the material must be double spaced. A page should contain not more than 25 lines. Two copies of the text in paper and one copy in a CD must be submitted to the Editor and the corresponding author is advised to keep another copy with him. The corresponding author must give it in writing in his covering letter that the same matter will not be submitted elsewhere if accepted. He must also enclose the copyright transfer of his work to this journal. The papers sent will be subjected to peer review. The accepted manuscripts become the permanent property of this journal. The author is informed that, if his work is returned to him for correction / clarification after peer review, he should effect the same and send the manuscript back to the Editor within one month. Each manuscript component mentioned here under must begin with a new page and the pages are to be numbered at the right tip corner starting from the Title page.

1. TITLE: The title of the work must be brief and precise. It should not exceed two lines and 40 characters (including comma, period) Author(s) full name (s) must be given along with his (their) degree and the affiliations. Corresponding author's name, correct address (including e-mail and Fax, if available) and phone number must be mentioned at the bottom left hand corner of the first page.

2. ABSTRACT: The abstract is to be given in the beginning itself. It should not exceed 200 words. It must contain the aim, methodology, results and conclusion. For case report, summary / conclusion alone is to be given.
KEY WORDS: (maximum five) in capitals are to be included at the end of Abstract.

3. INTRODUCTION: Describe the aim of the study, along with the hypotheses that were tested. Only necessary references are to be given.

4. METHOD: Give in detail the materials used and the methods employed. Describe the type of study. Pharmacological names only must be mentioned for the drugs used and, if proprietary name is used, then the manufacturers name must be given in parentheses. Except for standard, well-accepted abbreviations (including SI Units), all others must be introduced in parentheses when the full term is used for the first time in the article.

5. RESULTS: Giver only the results obtained by the study under discussion. State the statistics in the correct scientific form (P value, mean etc). Results based on assumptions must not be given. Indicate in the text the place where the tables have to be inserted.

6. DISCUSSION: The discussion should be to the point and relevant to the subject under discussion. This section can be combined with the previous one if the author desires. Avoid speculations. Use only standard abbreviations or the abbreviations already introduced.

7. ACKNOWLEDGEMENT: This is to be made only to those who were directly and scientifically involved with the preparation of the paper. Permitting authorities, technicians, photographers who assisted in the work need not be mentioned.

8. REFERENCES: The references should be given in numerical order in which they first appear in text and not in alphabetical order (Citation Order System). It should be numbered consecutively in the text. The references will not be checked by the Editor or by the Peer reviewer and hence the author is solely responsible for its completeness and the accuracy. Period should not be employed anywhere in the references. Personal communications, unpublished data and poster references, if mentioned, should be in the text itself and the source mentioned in parentheses. References should be in the following form:

Journal reference: Author(s) full title, Journal name (as abbreviated in Index Medicus), volume number, pages and year. If there are more than three authors, then mention the first three authors and then 'et al'.
Book reference: Author(s) (& Editor, if any), title of book (and chapter), publisher, place of publication, page number (s) of the cited portion and year.

9. THE LEGEND: The legend for the illustrations (and

tables, if necessary) must be given in a separate sheet of paper and should be typed double-spaced.

Illustrations: The photos and figures should be prepared in glossy prints with good contrast and of the size 6" x 4". Only salient details should be included. On the back of the illustration, the figure number in text, title of the paper, the first author's name and the top side (marked with an arrow) must be specified. Except for arrows, no text is to be on the photos. It is the duty of the author(s) to get the patient's written permission when the subject is identifiable in the photo. Submit two sets of illustrations. Illustrations from other Journals and books are usually not accepted. If used, it rests with the author(s) to get the copy right permission from the original author / publisher and this permission letter must be sent to the Editor at the time of submitting the manuscript. For Histological figures the stain and magnification used should be noted e.g.: H & E Stain x 70.

10. TABLE: It should be in double space. Each table must have an Arabic numeral (except for single table) and a title both in a single line. Each column in the table must have a short heading. If a table is large, then it must be continued in a second page, which also must have the table number and the title. Avoid vertical lines in the tables. Two sets must be submitted.

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12. OTHER CATEGORIES OF MANUSCRIPT

a) Original Articles should generally not exceed 3,000 words or 12 double – spaced pages.

b) Review Articles: can be on topics of relevance to clinical practice, research methodology, community ophthalmology or investigative work, of relevance to visual science. These articles should include up to date review of existing literature, and summarize the current status / preferred practice for that particular topic.

Brief reports are short communication of new instruments, new laboratory techniques or surgical techniques as well as interesting case reports with unique findings. These should not exceed 1000 words with a maximum of 2 illustrations. They should follow the format – introduction, case, and discussion. No more than 8 references should be cited. Each brief report must begin with a 75-100 word summary that highlights the significance of the articles.

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