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An Ode to a Wonder Drug: “The Placebo”

In the practice of medicine it has long been understood that, (and as Ambroise Paré expressed it), the physician’s duty was to “Cure Occasionally, Relieve Often, Console Always”. (“Guerir quelquefois, Soulager souvent, Consoler toujours”).

With the passage of the 18th Century, the practice of medicine gradually moved away from the patient having a considerable interaction with the physician, towards a stage where the patient was the recipient of a far more standard form of therapy or intervention determined by the prevailing opinions of the medical profession of the day. This transition moved all the way from “Bedside medicine” through “Hospital medicine” to “Laboratory medicine”!!: which is the most pertinent aspect of the present day medical practice.

From this point of view, the last vestiges of the “Consoling approach” to treatment was restricted to the prescription of morale-boosting and pleasing remedies which have no known pharmacodynamic action. These prescriptions served to reassure the patient whilst the “vis medicatrix naturae”, ie., the healing power of nature” performed its normalizing task of restoring the patient back to health.

Thus a ‘Placebo’ is a medicine or preparation which has no inherent pertinent pharmacological activity but is effective only by virtue of the ‘factor of suggestion’, attendant upon its administration. The placebo effect exerted by the drug is a subject centered response, due to the patient expecting or believing that this drug will work wonders for him.

When a placebo is administered to mimic a previously administered drug, it may incur the same side effects as the authentic drug. A placebo that involves ingestion, or injection is often more powerful than a non invasive sham procedure. Similarly the ‘placebo response’ is also dependent on the person who prescribes it. Placebos prescribed by a figure of authority, an expert in his field, exerts a more profound psychological effect. In fact the opposite effect can be created with prescriptions given by juniors in the medical field. This effect termed the ‘Nocebo effect’ (“noceb”= “I will harm” in Latin) prompts a disbelieving patient to experience a worsening of symptoms!.

Sometimes senior colleagues may prescribe placebos to a hypochondriac as T.Obecalp. Do not be surprised when you learn that it is PLACEBO spelt backwards!

In modern clinical application typically ‘Placebos’ are used in the context of clinical trials in which the ‘test group’ of patients receive the therapy being tested and a ‘control group’ receives the placebo.

The outcomes in the Natural History group, who receives no treatment of any kind, and, in whom the condition therefore, is allowed to run its natural course is also compared with the test and control groups.
There has been instances where, in clinical trials, the placebo treatment was just as effective as the active drug. To quote a well cited example is the placebo controlled trial of the gastric acid secretion inhibitor drug Cimetidine in the treatment of gastric and duodenal ulcer. A meta analysis of 31 placebo controlled trials on Cimetidine showed that the rate of relapses amongst those ‘healed’ by the active drug treatment was 5 times that of those ‘healed’ by the placebo treatment, prompting the remark that the active drug ‘heals’ ulcers while the placebo treatment “cures” them.

The placebo effect can alleviate pain in patients (producing objectively quantifiable analgesia), alleviate depression, (Khan.2000) and produce withdrawal symptoms which are largely subjective (hormone replacement therapy for menopause). Thus a placebo can work wonders if a high level of expectancy, proper conditioning and adequate motivation is present in the patient who takes the prescribed placebo.

Ethical challenges and concerns regarding the use of placebo in controlled clinical trials are clearly dealt with in the declaration of Helsinki- “ The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude use of placebo, or no treatment in studies where no proven prophylactic, diagnostic or therapeutic method exists. Even if proven therapy is available placebo controlled trials are ethically acceptable if the patient receiving the placebo is at no additional risk of serious or irreversible harm from proper therapy being withheld to him during the study period, especially when therapy is being investigated for a minor condition.

In conclusion to this “ode to a wonder drug” : it is wise to remember that as physicians we can cure sometimes, relieve often and console always! We don't have to feel bad when we prescribe nonspecific remedies to our patients. Remember that placebo exert a powerful psychotherapeutic effect, and that we are upholding the last vestiges of “the consoling approach” to therapy.
Angle Closure Glaucoma

Dr. Devindra Sood

The current understanding of glaucoma has undergone a significant change over the last few years. Epidemiological data, newer diagnostic procedures, collaborative planned trials, basic research, better documentation and analysis of clinical data, long term follow up of patients and a better understanding of ocular behavior and newer drugs have all contributed to the current understanding of the glaucomas.

A shift in understanding has logically lead to a change in the approach and strategy in glaucoma management. Raised intraocular pressure (IOP) has been a carlinal sign of glaucoma. The relevance of a raised intraocular pressure has to be understood in its proper perspective. In essence a raised IOP does not always need treatment. The ability to distinguish and decide when to treat and how much to treat is today a more scientific step than in yesteryears.

IOP no longer defines glaucoma. Both pressure dependent and pressure independent factors are responsible for the pathogenesis of the glauomatous damage. Even though factors other than IOP are involved, IOP is the most important risk factor because it is the only risk factor which we can pharmacomodulate todate. The primary aim in glaucoma management is to preserve visual function. Lowering of IOP is only a secondary goal.

Primary glaucomas: Glaucoma is the second leading cause of blindness worldwide accounting for 67 million sufferers. Primary Open Angle Glaucoma (POAG) is estimated to affect 33 million people worldwide, majority of whom (about 26 million) reside in developing countries. 90-100% of those affected in developing countries are unaware that they have the disease. Visual impairment is also more severe. The estimated risk of blindness (over 12-20 years) from POAG ranges from 14.5% to 27% (unilateral) and from 7-9% (bilateral). With an expected increase in the population and longevity, POAG is likely to become a major cause of ocular morbidity in the developing world.

Prevalence in India

Population based studies: 12 million people in India are affected by glaucoma accounting for 12.8% of the blindness in the country. Early population based studies reported a prevalence of glaucoma between 2% and 13%.

Three population based surveys, with modern techniques have been recently conducted.

<table>
<thead>
<tr>
<th>Table 1. Comparison of results of Vellore Eye Survey (VES) and Andhra Pradesh Eye Disease Survey (APEDS).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VES</strong></td>
</tr>
<tr>
<td>Age (95% CI)</td>
</tr>
<tr>
<td>POAG (95% CI)</td>
</tr>
<tr>
<td>OHT (95% CI)</td>
</tr>
<tr>
<td>PACG (95% CI)</td>
</tr>
<tr>
<td>Occludable Angles (95% CI)</td>
</tr>
</tbody>
</table>

The Vellore Eye Survey (VES) reported a prevalence of POAG as 0.41%, OHT 3.08% and 4.32% for PACG. Occludable angles accounted for 10.3% in the population.

The Andhra Pradesh Eye Disease Survey (APEDS) reported a prevalence of 1.62% for POAG, 0.32% for
OHT. Primary ACG was 0.71% and occludable angles accounted for 1.41% of the study population. The difference in the prevalence of POAG, PACG and occludable angles in the above studies can be explained by the age groups sampled, definitions of POAG, PACG, occludable angles and also the methodology used.

The Aravind Comprehensive Eye Survey (ACES) reported a prevalence of 1.7% for POAG, (95% CI 1.3 - 2.1) and 0.5% PACG (95% CI 0.3 - 0.7). The reported prevalence of glaucoma in the ACES study is higher than that reported by the VES and lower than the APEDS although the CI's overlap. The VES and APEDS did not perform threshold perimetry on all participants. Another reason could be the difference in the age of the study participants, 40-90 years in the ACES study (VES did not include people more than 60 years of age). However prevalence of POAG even in the ACES study was 0.7% (95% CI 0.5 – 1.0) amongst 40 – 60 years, similar to the VES.

The VES criteria of occludable angles (inability to visualize 180 degree of the functional trabecular meshwork) and the use of indentation gonioscopy lead to higher prevalence of PACG and occludable angles. The APEDS used the epidemiological criteria for occludable angles.

Hospital based data from India reported POAG as common as PACG, with 45 to 55% of primary glaucomas being PACG. Aphakic glaucoma (37.7%) is the commonest type of secondary glaucoma reported in a hospital setting. Others include lens induced (12.5%), corneal pathology (12.2%), neovascular (9.6%) traumatic (8.4%) and chronic uveitis (8.2%). Steroid induced glaucoma and trauma are common causes for secondary glaucoma amongst young people. A prevalence (95% CI 5.3 – 6.6) of Pseudo exfoliation was 6.0%. The prevalence increased with age and was more in males. The prevalence of glaucoma among subjects with pseudo exfoliation was 7.5%. Pseudo exfoliation was present in 26.7% of these with POAG. A hospital based study in 1968 reported a prevalence of 34% pseudo exfoliation amongst glaucoma patients.

**Primary Angle Closure Glaucoma**

Primary Angle Closure Glaucoma (PACG) has not received the same level of attention as POAG. Amongst other reasons, is the preponderance of POAG in Caucasian eyes and also because gonioscopy has not become a routine in the workup of all glaucoma patients.

With damage to the optic nerve becoming the diagnostic hallmark of POAG, the definition for primary angle closure glaucoma has also undergone a change

**Primary Angle Closure (PAC):** there is a significant obstruction of the functional trabecular meshwork by the peripheral iris, in the absence of a secondary pathology. In **Primary Angle Closure Glaucoma (PACG)** this trabecular obstruction is present with glaucomatous damage to the optic nerve head. In this concept, people suffering from an acute rise in intraocular pressure are not considered to have glaucoma unless there is damage to the optic nerve head. This concept is able to explain why 60-75% of people with an acute symptomatic episode of angle closure, recover without optic disc or visual field damage.

The traditional classification of primary angle closure is based on symptomatology (acute, sub-acute and chronic) has its limitations. Estimating the prevalence of PACG and POAG in South Africa it was shown that people with chronic angle closure (white eyes and clear corneas) had intraocular pressure ‘s as high as 72 mmHg. They were unable to demonstrate an association between symptoms and development of visual deficit. Even in East Asia, asymptomatic angle closure is more common. Symptomology of angle closure does not specify the involved mechanism. Hence management strategies cannot be based on symptomology alone. Angle closure is a mechanical process and is best classified by physical signs.

**Primary angle closure glaucoma suspect (occludable angle):** Where on gonioscopy there is appositional contact between the peripheral iris and the posterior trabecular meshwork. For epidemiological studies an angle is considered occludable where more than 270 degrees of the trabecular meshwork cannot be seen.

**Primary angle closure:** An eye with an occludable angle on gonioscopy with peripheral anterior synechiae, will have elevated intraocular pressure, or excessive pigment deposition on the trabecular meshwork. The optic disc and fields are normal. Iris
whirling, stromal atrophy are evidence of an old acute attack of angle closure and represent an ischaemic process. Ocular tissues such as the iris and the ciliary body are sensitive to the ischaemic process. Damage to the optic nerve occurs at high IOP. **Signs of anterior segment ischaemia are suggestive but not pathognomonic of damage to the optic nerve.**

**Primary angle closure glaucoma** is characterised by glaucomatous optic atrophy, corresponding visual field defects with occludable angles on gonioscopy or signs of PAC.

**Epidemiology of angle closure**

**Prevalence:** One of the major factors determining susceptibility to primary angle closure is the ethnic background. Primary angle closure is more common amongst Asians. In people more than 40 years of age the prevalence of primary angle closure (number of cases present at one point in time) ranges from 0.09% in Europeans, 1.4% in East Asian and 2.6% in Alaskan Inuit. Data from India, the VES and APEDS shows a prevalence of 4.32% and 0.71% for PACG. Hospital based data suggests an equal number of people with POAG and PACG.

**Sex and Age:** PAC and PACG tend to be higher in women than men. Incidence (number of cases /100,000 persons / year for population aged 30 years and above) of PAC ranges from 4.7 % in Finland to 15.5% in Singapore. Incidence like prevalence increases with advancing age.

**Anatomical factors predisposing to PAC** include shallow anterior chamber, short axial length of the eye, increased lens thickness, forward position of the lens, and how tightly the iris hugs the lens.

**Screening for Angle closure:** ‘Anatomical characteristics (Table 2), make screening for PAC a viable proposition. The aim of screening is to detect disease at an early, pre-symptomatic phase in order to provide suitable treatment which slows or arrests progression.

Screening tests should be quick and reliable. In a routine clinical practice, screening for PAC would involve assessing all patients with age more than 30 years to determining the potential for angle closure in order to identify those who need a gonioscopic examination. Of the various tests available, two commonly used ones are 1) Flashlight test and 2) vonHerrick’s test.

**Flashlight test:** A pen torch is held at the lateral canthus to shine a narrow beam of light across the anterior chamber. A shadow is cast on the nasal aspect of the iris with a shallow anterior chamber by the anteriorly situated iris and lens. Using a half iris shadow based data from India has shown a sensitivity of 45% and specificity of 83% and using a third of the iris shadow 86% sensitivity and 71% specificity. In another clinical practice amongst Caucasian eyes sensitivity and specificity of 89% and 88% have been reported. Incorrect identification was more for eyes with plateau iris configuration.

**Von Herrick’s** test is carried out at the slit lamp. A thin bright beam falls perpendicularly on the most peripheral point of the temporal clear cornea. The optical cross section is viewed at a high magnification (16x or 25x) from the nasal side. A sensitivity and specificity of 62% and 89% for detection of angles judged to be occludable on gonioscopic examination have been reported.

In a clinic based setup where the definitive test (gonioscopy) can be done using both the flashlight test to detect eyes with 1/3 iris in shadow and the limbal based test to detect a limbal chamber depth less than or equal to one quarter of the peripheral corneal thickness, few occludable angles would be overlooked.

**Provocative test**

Depending on the criteria used, occludable angles account for 1.4 –10.3% of the studied population. A small proportion of these individuals are at risk of developing PAC at some point of time. Since a laser iridotomy is a fairly safe and simple procedure that can eliminate this risk, early identification of such patients and treating them prophylactically can help eliminate this risk. Eyes at risk can be subjected to provocative testing – dark room test, prone test, dark room prone test or the mydriatic test.

**Clinical relevance of provocative tests:** Without treatment 50% of fellow eyes of patients with acute...
angle closure glaucoma developed acute angle closure glaucoma within 5 years. In a prospective multicentric study 129 eyes considered at risk for developing ACG were evaluated by a number of provocative tests. They were then followed up for up to 6 years without any intervention. 25 eyes actually had positive provocative tests, but only six developed angle closure. However of the 35 eyes which developed angle closure, only 6 had a positive provocative test.

The overall sensitivity and specificity of provocative tests for identifying eyes at risk for angle closure is low. Of the 4870 patients, subjected to dilatation none developed acute angle closure glaucoma, even though 38 patients were found to have slit to closed angles.

Provocative testing can provide supportive evidence

1. Intermittent headache / eye ache with history of colored haloes, normal intraocular pressure, but occludable angles on gonioscopy.
2. Positive family history of glaucoma, normal IOP but suspect occludablity on gonioscopy.
3. Suspect occludablity on gonioscopy on a routine eye examination for a patient on treatment with medication which can precipitate a pupillary block.

**Gonioscopy**

Gonioscopy is the examination of the anterior chamber angle of the eye with the aid of special contact lenses and biomicroscopy. It is an essential step in the evaluation of all glaucoma patients and glaucoma suspects. The primary aim is to determine if the patient has an open angle or angle closure. Additionally, one would like to assess if the open angles have a tendency to close, or if the angles are narrow with no potential to occlude.

The angle of the anterior chamber is created by two lines. One tangential to the trabecular meshwork and the other along the iris plane. The aqueous outflow system comprises of:

**Schwalbe's line** representing the peripheral edge of Descemets membrane.

**Trabecular meshwork** the site of conventional aqueous outflow. It has two parts a lightly pigmented anterior part and a darker zone, posteriorly over the Schlemm's canal. The posterior trabecular meshwork is where more aqueous flows and hence greater iris pigment is present.

**Scleral spur** is a white band just posterior to the pigmented trabecular meshwork. It is formed by a projection from the inner scleral canal and represents the posterior boundary of inner scleral canal on which Schlemm's canal rests.

**Ciliary body band** represents the anterior aspect of the ciliary muscle, into which the root of the iris inserts and appears as a dark brown band posterior to the scleral spur.

Because of the air-cornea interface, internal reflection prevents a direct inspection of the angle. However gonioscopic lenses negate the total internal reflection and exceed the critical angle by altering the cornea-air-fluid interface. An excellent review to methodology and interpretation is available. Direct gonioscopy is not widely performed in routine clinical practice because the equipment is not readily available for the general clinician and the procedure is less convenient than indirect gonioscopy.

**Direct Gonioscopy**: Koeppes' lens, Swan-Jacob, Hoskin Barkan

**Indirect Gonioscopy**: Goldmann lenses, Thorpe and Ritch lens

**Indentation**: Zeiss, Posner, Susmann

While performing gonioscopy, the room should be dark and width of the slit beam should not cross the pupil so that light induced miosis does not result in misinterpretation of a narrow angle as not occludable. Physiological factors which can change angle configuration include parasympathomimetic (causing forward movement of lens iris diaphragm) and sympathetic stimulation (dilation which can produce additional bunching of the iris into the angle). Because of the potential variability in the appearance of the angle, more than one gonioscopic examination is often necessary to determine the risk of developing angle closure.

Q. Is this angle occludable?

When performing gonioscopy in a dark room with width of the light aperture not crossing the pupil, the aim is to assess if the drainage angle being examined has a potential to close or if there is any evidence that closure may have occurred in the past.

In order to allow comparison of studies (epidemiological research) occludable angles have been defined as one
in which the posterior, pigmented trabecular meshwork is not visible for 270 degrees or more, without indentation or manipulation of the gonioscope. Using the same definition APEDS reported 1.41% of occludable angles.

The big question is: Is this definition applicable to clinical practice. Wider angles may become occludable, and narrow angles may never close. Since gonioscopy is a dynamic process, evidence supporting suspect closure is possible.

- PAS in the superior angle are the most important and are pathognomonic of angle closure in the absence of inflammation.
- Patchy pigmentation on the trabecular meshwork the superior angle is also suggestive of angle closure.
- Alternating opening and closure of the beam, a narrow angle may be seen to close and open, demonstrating the potential for closure of the angle ("on-off" sign).

The VES defined occludable angles when 180 degrees of the posterior trabecular meshwork was not seen. (10.3%).

**Ultrasound biomicroscopy**: Ultrasound biomicroscopy of the anterior segment allows accurate visualization of the iris, iris root, corneoscleral junction, the ciliary body and lens. It is of help to elucidate the mechanism of angle closure. However it is expensive with limited availability.

**Mechanism**: The final common pathway in the development of PAC is the formation of irreversible synechial adhesions between the peripheral iris and uveal surface of the trabecular meshwork. This is preceded by the development of appositional contact between the peripheral iris and trabecular meshwork. It is important to identify the involved mechanism as this works as guide to plan the management. It is important to remember that more than one mechanism may be at work.

**a) Pupillary Block**: Obstruction to the flow of aqueous usually arises between the posterior surface of the iris, in the region of the pupillary sphincter and the anterior surface of the lens. With ongoing aqueous production, the posterior chamber bulges forward with increasing pressure and the peripheral iris comes in contact with the trabecular meshwork. **Gonioscopy reveals** a steeply convex iris which is suggestive of a pressure differential between the posterior and anterior chamber.

**b) Plateaus iris mechanism**: An anatomical abnormality, the peripheral iris crowds the recess of the angle. When the pupil dilates, the iris is thrown into circumferential folds which come in contact with the trabecular meshwork. **On Gonioscopy** the iris inverts anteriorly in the scleral spur or leaves only a narrow ciliary body band. The iris is almost flat from the periphery to the extreme periphery where it creates a narrow angle recess.

The pure form of the plateaus iris syndrome, is extremely rare and is proven by the occurrence of acute angle closure following dilatation despite a patent iridotomy with a deep central anterior chamber. Since more than one mechanism of angle closure may be present, an iridotomy should be done first. Plateaus iris, may then be treated with argon laser iridoplasty and/or miotic therapy.

**c) Lens induced angle closure**: A large and/or anteriorly placed crystalline lens can also predispose to angle closure and can worsen the pupillary block.

**d) Creeping angle closure** starts within the depth of a narrow angle and then spread anteriorly to cover the posterior trabecular meshwork and then involve the anterior trabecular meshwork. This zipper effect leading to closure of the angle made Lowe describe it as **creeping angle closure**.

Chronic angle closure can result from synechial closure of the chamber angle from previous episodes of acute or subacute angle closure. In creeping angle closure the iris base creeps on to the trabecular meshwork leading to peripheral anterior synechiae. When more than \( \frac{1}{2} \) of the angle is closed the intraocular pressure rises. Creeping angle closure may arise from an undiagnosed intermittent angle closure. Even chronic miotic therapy may cause worsening of the pupillary block. Creeping angle closure is more common amongst Asians.

**e) Cilio lenticular block**: In some cases misdirection of the posterior aqueous can cause primary angle closure. Typically the ciliary processes comes in contact with the lens equator, and/or a firm zonule/posterior capsule may cause flow of aqueous into the vitreous. The lens iris diaphragm is pushed anteriorly, occluding
the angle. Typically such eyes have narrow anterior chambers and after an iridotomy the use of cyclopilics reduces the IOP and miotics paradoxically raise the IOP. Ultrasound biomicroscopy in such situations is very helpful.

**f) Combined mechanism glaucoma**: Here both pupillary block angle closure glaucoma and open angle glaucoma coexist. Typically a laser iridotomy alone fails to control the glaucoma. This is a form of chronic angle closure glaucoma where the trabecular meshwork may be damaged by intermittent or chronic trauma from the obstruction of the peripheral iris.

In such cases the iridotomy helps to prevent further closure of the angle. The damage to the trabecular meshwork further impedes the outflow of aqueous. Here in addition to the laser iridotomy the open angle glaucoma component needs further medical therapy.

Systemic drugs can induce angle closure in predisposed patients and include phenothiazines and their derivatives, antidepressants, antihistaminics, anti Parkinson drugs, tranquilizers and parasympathomimetic and sympathomimetic agents.

Clinical presentation of angle closure:

**1) Acute Angle Closure**: The likelihood of a pupillary block producing angle closure depends on a shallow anterior chamber, short axial length of the eye, increased lens thickness and forward position of the lens and tightness of the contact between the iris and the lens. Critical anterior chamber depth most likely to lead to PACG is between 1.5 - 2.00mm. With the peripheral iris blocking the access of aqueous to flow out of the trabecular meshwork, the IOP increase.

Physiologic mydriasis (dark room, movie theater), pharmacologic mydriasis (mydriatics and cycloplegics) and anxiety (pain, fear, trauma) and emotional disturbances can precipitate acute angle closure in predisposed eyes.

**Table 3. Diagnosis of Acute Angle-Closure Glaucoma**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
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<tbody>
<tr>
<td>Pain</td>
<td>Shallow anterior chamber, convex iris</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Iritis, flare, ocular congestion</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>Mid dilated pupil, poor reaction</td>
</tr>
<tr>
<td>Halos</td>
<td>Epithelial edema</td>
</tr>
<tr>
<td></td>
<td>Glaukomflecken</td>
</tr>
<tr>
<td></td>
<td>Closed anterior chamber angle with PAS</td>
</tr>
<tr>
<td></td>
<td>Optic nerve head edema</td>
</tr>
</tbody>
</table>

**Gonioscopic proof** of a closed angle in the involved eye is the most important sign of angle closure. If visualization of the angle is prevented by the corneal edema, then the uninvolved (fellow) eye should always be examined for a narrow angle. Other possibilities to keep in mind are a non pupillary block glaucoma, secondary pupillary block and an acute glaucoma in eyes with open angles.

**2) Intermittent (sub-acute) Angle Closure**: Here attacks occur under conditions similar to acute angle closure, but resolve spontaneously. The intraocular pressure increases causing mild symptoms. However the aqueous then breaks through the pupillary block flowing though the pupil into the anterior chamber again. The peripheral iris falls back and aqueous again flows through the trabecular meshwork. The likelihood of reoccurrence is high till a laser iridotomy is performed. Without this alternate passage, intermittent closure continues. Signs and symptoms are mild, and usually resolve spontaneously. The intraocular pressure is often normal between attacks. A shallow anterior chamber with / without PAS on gonioscopy is a hallmark sign. A history of intermittent rise in intraocular pressure is often present.

**3) Chronic Angle Closure**: Typically patients with chronic angle closure glaucoma have no symptoms and are often mistaken for open angle glaucoma. Gonioscopy is the only way to identify the closure and differentiate them. Initially the closure is appositional, but with time peripheral anterior synechiae develop leading to closure of the angle. This is accompanied by a raised IOP. Medical therapy initially shows a favourable response. However the IOP often fluctuates on treatment. Synechial closure progresses even as more medications are added. The success of treatment here depends on gonioscopy for early diagnosis and laser iridotomy.

**Management**

PAC presents with a raised IOP which is often symptomatic with or without disc damage. Management resolves around immediate control of symptoms and raised intraocular pressure, modifying configuration of the angle and preventing further closure, detection and prevention of further damage to the optic disc and visual field, as well as treating the fellow eye.
Medical treatment

Table 4. Medical management of acute angle closure

1. Acetazolamide (250-500mg) oral stat, then 125 to 250 mg t.i.d./ q.i.d, until symptoms subside
2. Topical Pilocarpine 2% stat, then q.i.d.
3. Analgesics and antiemetics as required.
4. Topical beta blockers b.d.
5. Topical steroids Loteprednol acetate q.i.d

Contra-indications and hypersensitivity to drugs should be excluded prior to starting treatment

- High doses of Pilocarpine should be used with caution as there is a risk of systemic pilocarpine toxicity.
- Paradoxical shallowing of anterior chamber can further aggravate the pupillary block
- Topical steroids help reduce the inflammatory reaction
- Often patients with PAC have other medical problems. Electrolyte disturbances, particularly hypokalemia can occur. Vomiting along with use of oral acetazolamide may cause or exacerbate this disturbance. Systemic hypotensive effect of beta blockers can be aggravated by the electrolyte disturbance further increasing the risk of circulatory disturbances. Intravenous hyperosmotics can also aggravate circulatory disturbances. Analgesics and anti emetics should be used as required.

* If topical and intravenous therapy is unable to reduce the intraocular pressure within 3-4 hours, additional measures such as corneal indentation, manual compression or a laser iridotomy may be indicated.

Modification of angle configuration: A laser iridotomy is the definitive treatment for a pupillary block ACG. Since it is often difficult to rule out a pupillary block component in any case of PAC, a laser iridotomy is indicated in every case unless there is a contra indication. It is best performed when the eye is quiet, cornea is clear and there is no intraocular inflammation or uveal congestion. This rarely occurs when a patient presents with an acute ACG.

* If the cornea is clear and inflammation is less a laser iridotomy can be performed.

* In case residual inflammation is present, after successfully breaking an acute attack, the iris tissue is boggy, in such cases the laser iridotomy can be deferred for a few days, maintaining the patient on glaucoma treatment and topical steroids.

In case the cornea does not clear to allow an iridotomy despite adequate measures, a partial pupilloplasty (to peak the pupil) with low power applications of Argon laser to temporarily break the pupillary block can be considered. Alternatively the argon laser can be used to contract the peripheral iris and pull it away from the trabecular meshwork (peripheral laser iridoplasty).

As with medical treatment, neither of these alternative modalities provide permanent relief from a pupillary block and must be followed by a definitive laser iridotomy.

A laser iridotomy for angle closure glaucoma is not always successful. Treatment of acute angle closure glaucoma with an iridotomy alone or in combination with miotics controlled the intraocular pressure in 77% cases if there was no initial visual field loss. This dropped to 29% in the presence of initial visual field loss. Following laser treatment, if the glaucoma is due to a pupillary block or appositional closure the angle should open wider following treatment. However the central anterior chamber depth may not change. Failure of the angle to open following the laser iridotomy results from extreme PAS, or if the angle closure was not from pupillary block. Additional iridotomies will not remedy this.

As laser iridotomy is sufficiently safe, a trial with laser iridotomy followed by medical therapy is generally quite appropriate before proceeding to more invasive trabeculectomy.

In some eyes the angle will open sufficiently following the laser iridotomy, but the intraocular pressure remains elevated. This is usually from trauma to the trabecular meshwork or where there is an inherently reduced aqueous outflow. Such cases would require additional medical therapy, before proceeding to a filtering procedure.

Prophylactic laser iridotomy

A laser iridotomy is always indicated in the fellow eye of a patient who has suffered an acute angle closure in the first eye. Other indications include, an angle so narrow that a provocative test is dangerous and unnecessary (an angle which is narrowed to a slit or closed, or requires indentation gonioscopy to view the scleral spur. Other indications for a laser iridotomy are
presence of PAS in an eye with a narrow angle, family history of angle closure glaucoma and need for frequent pupillary dilatation in patients with narrow angles (diabetes)

Like open angle glaucoma ACG is a bilateral disease. The fellow eye almost always has an occludable angle and should be treated with a laser iridotomy, once the first eye is stable. However an iridotomy in the fellow eye may not prevent the need for treatment. 50% of patients with PACG treated with bilateral peripheral iridectomies required additional treatment of some type in the involved eye. 25% needed treatment in the uninvolved eye post laser.

Surgical Iridectomy

Given the current evidence, the sole indication for a surgical iridectomy is probably the lack of access to a laser. The risk of complications from intraocular surgery such as endophthalmitis and iris prolapse do not seem justified when a closed surgical technique is available. The technique may be of use in eyes in which a symptomatic rise in IOP which cannot be controlled by medical or laser therapy, especially those in whom corneal edema is a persistent problem.

Glaucomatous optic neuropathy in primary angle closure: Management and visual prognosis

When symptoms have settled and short term IOP control has been achieved, a full glaucoma work-up should be carried out. A detailed gonioscopic examination of both eyes, visual field assessment and recording of the optic disc status are essential to plan appropriate long-term management. If glaucomatous optic neuropathy is detected, the therapeutic options are as follows:

Laser Peripheral Iridotomy

Laser peripheral iridotomy is the treatment of choice for people with glaucomatous optic neuropathy in PAC. In one study 140 eyes of 104 people with PAC in Japan, treated by argon laser iridotomy revealed that prior to treatment 73/109 (67%) eyes had a cup: disc ratio of 0.7, the cup: disc ratio enlarged in 31 (28%) and was unchanged in 64 (59%), mean follow-up 1.7 and 2.7 years (in two groups), visual fields defects were minimal or absent in 96/118 (81%), moderate in 19/118 (16%) and advanced in 3/118 (3%). The defects progressed in only 3 patients (all with initially mild changes). IOP < 21 mmHg (with or without medication) after PI was achieved in 94% (44). IOP control was more likely to be successful if there were 0 degree PAS. There was no significant change in the amount of PAS during the follow-up period. Loss of visual acuity by more than 3 lines occurred in 19%, due to progression of lens opacities.

Another retrospective analysis of 57 Singaporeans with symptomatic PAC found that more than 24 hours delay in presentation, or the need for a laser iridoplasty to achieve short-term pressure control, was associated with worse pressure control after laser iridotomy (mean follow-up period 20 months). Another retrospective study in South Africa of 52 asymptomatic patients (78 eyes) followed for a mean period of 22 months reported that IOP was controlled (< 21 mmHg) without medication in 9%, and with medication in 51% of eyes, trabeculectomy was required in 29% of eyes, risk factors for needing trabeculectomy were: IOP on presentation > 35 mm Hg, 3 quadrants of synechial angle closure, and cup: disc ratio of >0.6. 36% of eyes with these risk factors needing trabeculectomy were controlled by PI with or without medication.

The likelihood that a non-invasive procedure will control IOP and arrest progression of optic neuropathy justifies the use of laser PI as first line treatment in all but the most severe cases.

Medical Therapy

If satisfactory pressure control cannot be achieved with a laser iridotomy alone, topical medical therapy can be used in a manner similar to that for POAG. A target pressure should be set according to the degree of nerve damage and field loss. If the iris contour has been satisfactorily changed by iridotomy (implying that pupil block was the predominant mechanism), then a first line drug as felt appropriate may be used. If the iris profile has not changed after the laser iridotomy (suggesting peripheral iris crowding is the predominant mechanism), Pilocarpine 1-2% is a more appropriate choice. An α₂-agonist is an appropriate second-line therapy.

Trabeculectomy

Trabeculectomy is indicated in cases of PAC with glaucoma that cannot be controlled by laser iridotomy
and medication. There is often concern that aqueous (ciliolenticular block) misdirection may complicate trabeculectomy in cases with PAC, although published data and anecdotal experience do not support this. Despite the finding that eyes with PAC do not seem to suffer especially high rates of malignant glaucoma, cases of this problematic complication do occur. The condition may be recognized by progressive asymmetrical axial shallowing of the anterior chamber. The disorder stems from misdirection of aqueous flow by closure of the ciliolenticular space. Dilating the ciliary ring is probably the best preventive measure and the agents of choice being either cyclopentolate or homatropine.

Primary trabeculectomy is an option for cases of PAC in which immediate pressure control cannot be achieved. Patients with very advanced PAS, optic nerve damage, and visual field loss, are often considered for primary trabeculectomy. A trial of laser iridotomy in all cases, although if synechial angle closure for more than 180 is identified after laser treatment, the patient should be considered at high risk of needing a trabeculectomy to achieve control.

**Lens extraction** Since the position of the lens determines the iris profile, and therefore the angle configuration, lens extraction is a logical choice for surgical management of raised IOP in cases of PAC with visual impairment due to cataract. Extracapsular cataract extraction was used in the management of PAC in 21 eyes of 20 patients (2 with raised IOP alone, 5 symptomatic, and 14 asymptomatic). In 14 cases lens extraction was performed in place of filtering surgery, where peripheral iridectomy or previous filtering surgery had failed. Mean IOP reduced from 31 to 16 mm Hg after surgery, 16/21 eyes did not require further medication (follow up:6-42 months), IOP was reduced even if there were extensive previous PAS, in 6 patients with previous failed filtering surgery, lens extraction gave a median IOP reduction of 17.5 mmHg (range 5-30).

**Management of the asymptomatic narrow angle**

In a multi-centre study of 129 asymptomatic patients with anterior chamber depth < 2 mm, or drainage angles that were potentially occludable, only 6% developed signs or symptoms consistent with PAC over a mean period of 2.7 years (maximum follow up 6 years) it would therefore appear that an individual risk of developing visually threatening sequelae is low on a year-to-year basis. However, **it is now an accepted practice to perform a laser iridotomy on patients with early gonioscopic evidence of angle closure, reflecting the perceived (although unproven) high benefit/risk ratio for this procedure.** This view is probably justified when one considers the potential for late-presentation or misdiagnosis under non-ophthalmic care, and low incidence of sight-threatening complications of laser iridotomy.

The management of an eye contralateral to one that had an episode of symptomatic PAC is open to less conjecture. Follow up of 200 such “fellow” eyes found 113 were managed by observation or with topical Pilocarpine. Of this number 58 developed symptomatic PAC (half within a five year period), 26 of the 58 were using topical Pilocarpine. In a further 250 patients with PAC, 72 did not have prophylactic peripheral iridectomy. Forty three developed PAC (33 symptomatic, 10 asymptomatic or unknown), 33 of these were affected within 6 years. This is overwhelming evidence in favour of prophylactic peripheral iridotomy by laser, or surgical iridectomy if no laser is available.

**The Indian Perspective:**

In the glaucoma clinic of an eye hospital, 45.9% of all primary adult glaucomas were of angle closure glaucoma. Of these 24.8% had acute angle closure glaucoma, 31.2% had subacute and 44% had chronic glaucoma. More than 80% of the chronic eyes had no significant symptoms. Nd Yag laser iridotomy alone or with topical anti glaucoma medication controlled the IOP in 48.3% of acute angle closure glaucomas, 78.8% of subacute and 30% of chronic eyes. Similar data from another tertiary setting reported 15.88% acute, 19.26% subacute and 64.86 % chronic angle closure amongst the 888 patients with Primary angle closure glaucoma. Over a period of five years, 22% of occludable angles progressed to primary angle closure glaucoma and 28.5% of the primary angle closure developed optic disc and visual field changes.

Light and electron microscopic studies have revealed accumulation of pigment in the widened trabecular
spaces and Schlemm’s canal (acute PACG). The endothelial cells were attenuated and devoid of subcellular components. Chronic angle closure was associated with loss of the trabecular architecture with narrower trabecular spaces and fusion of the trabecular beams. Loss of endothelial cells and reactive repair was visible in areas away from peripheral anterior synechiae.

Following an acute attack of PACG, long term followup is needed despite a laser iridotomy as the IOP may rise later due to progressive compromise of the outflow facility.

**Conclusion**

**Primary Open Angle Glaucoma** is characterized by a typically progressive glaucomatous optic neuropathy with correlating visual field loss. IOP is one of the risk factors responsible for this damage to the optic nerve. However even though factors other than IOP are involved in the pathogenesis of glaucoma, IOP is the only factor that can be modulated to date. The decision to treat is individualized depending on the whether the level of IOP will lead to progressive nerve damage. Available treatment algorithms rely on medical management to achieve the target IOP, failing which filtering surgery can be resorted to. In the Indian context, early filtering surgery to achieve the desired target pressure is a viable alternative. Laser trabeculoplasty is an intermediate step. The role of neuroprotection is not yet established clinically.

**Primary Angle Closure Glaucoma** : There is a significant change in the perception of PACG. The definition of PACG has undergone a change. Angle closure is now described as an anatomical disorder where symptomatology does not specify the involved mechanism. Screening for angle closure glaucoma appears tempting, but is still not a viable option. Improved detection with simple tests (flashlight test and von Herrick’s test) and confirmation on gonioscopy plays a key role in diagnosis. Provocative testing is likely to provide a supportive role in asymptomatic occludable angles. Asymptomatic, chronic angle closure glaucoma mimicking POAG is common. Gonioscopy is the confirmatory test. After the definitive treatment, laser iridotomy, angle closure is treated medically or surgically in the same manner as open angle glaucoma. Treatment of the fellow eye with a laser iridotomy is mandatory.

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Anatomical and Visual Outcomes of Surgery for Idiopathic Macular Holes

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Abstract

Purpose: To determine the rate of anatomical closure and visual outcome following vitreous surgery for idiopathic macular hole (IMH) using Optical Coherence Tomography (OCT).

Methods: Interventional case series. 23 eyes with idiopathic macular hole having a preoperative OCT macular hole diameter ranging from 280 to 1051 microns underwent vitrectomy with internal limiting membrane peeling and perfluoropropane gas injection.


Results: Type I closure was seen in 14 eyes and type II closure was seen in 7 eyes. Anatomical closure was not achieved in 2 eyes with macular hole diameter of greater than 400 microns.

Conclusion: OCT measurements are useful to predict the anatomical and visual outcomes following surgery for idiopathic macular hole.

Introduction

The first clinical description of a macular hole was published by Henry Noyes in 1871. Since then our understanding of development and pathogenesis of macular holes has improved. However, it took more than 100 years, until Kelly and Wendell reported the first successful closure of a series of macular holes by pars plana vitrectomy and induction of posterior vitreous detachment in 1991. Several authors have reported significantly higher rates of anatomical closure and visual rehabilitation in many of these cases. The postoperative success rate varies between 86% and 95% with improvement in visual acuity in a large percentage of cases.

Recent attempts to use imaging techniques such as confocal scanning laser tomograph and scanning laser ophthalmoscope to predict success suggest a correlation between the macular hole size and visual recovery. This study used optical coherence tomography (OCT) to measure the preoperative macular hole size and correlated this with the postoperative rate of anatomical closure.

OCT is a recently introduced diagnostic tool for high resolution, cross sectional imaging of the posterior and anterior segment of the eye with an axial resolution of 10µm and a transverse resolution of 30µm. OCT has been of immense use in understanding the pathogenesis of and staging of macular holes prognostication of surgical outcome and grading the surgical outcomes as well.

Materials and methods

A retrospective review between January 2005 to April 2006 of all eyes with an idiopathic macular hole that were examined preoperatively and postoperatively by OCT at our hospital was performed. Only eyes diagnosed as having idiopathic macular holes were
included in this study. Patients with previous and or coexisting diseases such as intraocular inflammation, ocular trauma and retinal detachment were excluded. Patients received a complete ophthalmic examination including complete medical and ophthalmic history, best corrected Snellen visual acuity, Amsler grid testing, intraocular pressure measurement, slit lamp biomicroscopy, indirect ophthalmoscopy and OCT. Each patient was examined with OCT by an experienced examiner through a dilated pupil and macular holes were measured in the least horizontal diameters. Informed consent was obtained prior to surgical intervention in all patients. All surgical procedures were done by a single surgeon (AG) between January 2005 and April 2006. Surgery consisted of standard three-port pars plana vitrectomy, peeling of the internal limiting membrane with subsequent intraocular gas tamponade using 14% perfluoropropane gas. Per-operatively Indo cyanine green or other dyes were not used to stain the internal limiting membrane. Internal limiting membrane was identified using Intra Vitreal Triamcinolone during surgery. After surgery patients were asked to maintain a prone position for 14 days. Patients were examined on day 1, day 10, 1 month, 2 months and 6 months. Postoperative OCT was performed at 2 months following surgery.

Anatomical success was clinically defined as apposition of macular hole edges and absence of sub-retinal fluid cuff. Anatomical success determined by OCT was restoration of full or partial thickness retinal reflection over the retinal pigment epithelium and choriocapillaries reflections. The primary outcome of the study was anatomical closure of macular hole. Parameters of interest were preoperative macular hole diameter, length of symptoms, preoperative visual acuity, Hole formation factor (HFF), and postoperative characteristic of macular hole closure as demonstrated by OCT. For the purpose of analysis of the primary outcome, macular holes were divided based on preoperative macular hole diameter into holes smaller than 400 µm (Group I) and holes equal to or larger than 400 µm (Group II). A secondary outcome of this study was visual acuity. Univariate and multivariate logistic regression analysis was performed. A p value of less than 0.05 was considered significant. Hole formation factor (HFF) was calculated according to Puliafito and colleagues (Fig. 1). The HFF and diameters measured were correlated with the best-corrected postoperative visual acuity and visual improvement.

### Result

The clinical characteristics and demographics of the patients are included in Table I.

There were 20 women and 3 men, with a median age of 63 years (Range 45 – 74 years). Preoperative macular hole diameter ranged from 239 µm to 1051 µm with a mean of 505.5 µm and a median of 487 µm. 65% of the eyes had a macular hole diameter greater than 400 µm. Preoperative visual acuity ranged from 3/60 to 6/18 with a mean of 6/36. The median length of visual symptoms ranged from 6 months to 36 months. Mean preoperative visual acuity of the eye with a macular hole diameter less than 400 µm was 6/36 and mean preoperative visual acuity with macular hole diameter greater than 400 µm was 6/60. Anatomical closure of macular hole was achieved in 21 of the 23 eyes (91%) with single surgery. For group I there was anatomical closure in all eyes. For group II, anatomical closure was achieved in 14 of 16 eyes (Figs. 2-5).
Type I macular hole closure was achieved in 14 eyes and Type II closure macular hole was observed in 7 eyes. In a subgroup analysis, Type II closure was noticed in 4 eyes in group II and in 3 eyes of group I. Type I closure was noticed in 12 of 16 eyes in group II and 4 of 7 eyes of group I. Postoperative visual acuity ranged from 6/60 to 6/9 with mean visual acuity of 6/24 (Table II).

All patients with an HFF greater than 0.7 achieved closure of macular hole whereas the 2 eyes that failed had mean HFF of less than 0.7.

**Complications**

Progression of nuclear sclerosis or posterior capsular opacification occurred in all patients after the initial macular hole surgery. Transient increase in intraocular pressure during the early postoperative period was noticed in 4 eyes. One patient had a partial rhegmatogenous retinal detachment with a horseshoe tear in the upper temporal quadrant, which was successfully managed with pneumatic retinopexy.
Surgical treatment of idiopathic macular holes had given vitreo-retinal surgeons and patients an option for visual recovery for this once untreatable condition. Although the surgical results have improved over the years, controversy still exists as regards to the exact surgical timing and also case selection.

Timing of surgical intervention, depending on idiopathic macular hole staging, size and duration has shown correlation in success rate and visual recovery. Preoperative staging has been traditionally based on the classification system proposed by Gass, judging macular hole diameter on clinical and photographic evaluation using the peripapillary vein with 125 µm in diameter as reference. Moreover, conditions such as epiretinal membrane, lamellar macular hole, cystoid macular oedema and macular degeneration can be misdiagnosed as macular hole on biomicroscopy. OCT helps to differentiate these conditions and also assess macular hole diameter correctly. The use of OCT may allow better quantification of macular hole diameter, as OCT measurements are reproducible with a transverse resolution of 30 µm. In our study all eyes with macular hole less than 400 µm achieved closure. We suggest that it is possible to use these results to conclude that smaller macular hole size attains higher rate of closure with surgical intervention. Ulrich et al have shown that preoperative measurement of macular hole size can be used as a prognostic factor for assessing anatomical success rate.

In our study 65% of eyes had an improvement of visual acuity of two or more lines. Although a trend towards greater visual acuity improvement was noticed in eyes having macular hole less than 400µm, this was not statistically significant (p=0.14, Wilcoxon sign rank test). However, postoperative visual acuity assessment in eyes after successful macular hole closure is affected by progression of cataract. Final visual acuity therefore should ideally be assessed after subsequent cataract surgery. Furthermore the effect of cataract was not accounted for in this study, as visual acuity data was a secondary outcome; the primary objective of this study was to correlate preoperative macular hole size with the rate of anatomical closure following vitreous surgery.

The diameter of the macular hole measured by OCT at the level of the retinal pigment epithelium seems to
provide a prognostic factor for assessing postoperative visual outcome. In our study all eyes with a macular hole diameter less than 400 µm had a final visual acuity of 6/24 or better with a mean visual acuity of 6/18. Freeman and coworkers who found that a macular hole with a smaller diameter was associated with better functional outcome have published similar results. The reason for this might be that a small hole diameter indicates better-preserved macula.

We also calculated the hole formation factor originally created by Puliafito. He considered the ratio between the overlying dimension and the hole base diameter to be of greater influence on the anatomical success rate than the base diameter alone. Puliafito found an 80% anatomical success rate in eyes with HFF greater than 0.9 and an anatomical success rate of less than 25% in eyes with HFF under 0.5. However in our study we did not find any definite correlation between HFF and incidence of macular hole closure. 69% of the eyes which achieved anatomical closure had HFF less than 0.9. One possible reason for our better success rate could be internal limiting membrane removal in all cases and a larger piece of internal limiting membrane was removed in eyes with larger macular hole diameter and low HFF.

No correlation could be found between postoperative gain in visual acuity and HFF (p=0.82). S Ulrich et al have showed similar results. Their series included 94 eyes and they found that all patients with a HFF greater than 0.9 achieved successful anatomical closure after the first surgery and the anatomical success rate was 67% in patients with HFF under 0.5. No correlation could be found between postoperative gain in lines and HFF (p=0.76) or with the base and minimum diameter (p1=0.19; p2=0.071).

Unexpectedly, the diameter of the macular hole measured with OCT was not influenced by the duration of symptoms. Therefore, large holes did not necessarily exist longer than small ones. This fact may be explained by our current understanding of the pathogenesis of idiopathic macular holes. The most favourable explanation for the development of macular hole is traction caused by focal shrinkage of the perifoveolar vitreous. Also glial cells and newly formed collagen may play an important part in macular hole formation by exerting tangential traction. The diameter of the hole therefore may depend mainly on traction forces and not on the duration of the macular hole. Another reason for the absence of correlation between the duration of symptoms and macular hole size may be the subjective estimation of the duration of symptoms by the patient. A macular hole may exist a long time before being detected.

Based on ophthalmoscopy or biomicroscopic examinations, the anatomical status of the macula after macular hole surgery was classified by Tornambe et al into three types. They suggested that flat and closed outcomes have a better visual prognosis than flat and open outcomes. Imai et al categorized the successfully repaired macular hole into three patterns with OCT: U-type (normal foveal contour), V-type (steep foveal contour), and W-type (foveal defect of neurosensory retina). The authors reported that postoperative visual acuity was well correlated with these patterns (U>V>W). The visual results obtained from the two types in our study were also similar. Because the borderline between the U and V pattern in the aforementioned study was sometimes unclear, and because the ophthalmoscopic appearance of postoperative macular hole status would be easily matched with one of the two types of closure in our study, our classification system seems more clinically relevant. Our study also found that the extent of postoperative visual improvement was greater in the case of type 1 closure than type 2 closure, but did not reach a statistical significance.

Complications of vitreous surgery for idiopathic macular hole includes retinal breaks, visual field defects, cataract formation and late reopening of the macular hole. Late reopening of macular holes has been reported in 5% to 9.5% of eyes in the previous studies. The only significant complication that we noticed in our series was a single case of rhegmatogenous retinal detachment which was managed successfully with pneumoretinopexy. There was no case of reopening of macular hole in our series.

Recent prospective studies have questioned the efficacy of adjuvants in the surgical management and visual recovery of idiopathic macular holes. In our study, we achieved anatomical success in 21/23 eyes without use of any adjuvants.

Since the mechanism of closure by vitrectomy and gas
injection is not clearly known, it is possible that relief of antero-posterior traction of hyaloid and tangential traction of Internal Limiting Membrane by surgical means with simultaneous prevention of vitreous fluid from entering the macular hole by a gas bubble may be sufficient for successful closure.

Limitations of this study are based in its retrospective nature and small sample size. Visual acuity assessment on a Snellen acuity chart is also one of the drawbacks of the study.

**Conclusion**

Preoperative measurement of idiopathic macular hole diameter using OCT may help predict postoperative anatomical and visual results. This gives the vitreoretinal surgeon and the patient a better understanding of the disease. Patients with type I closure have a better postoperative visual acuity as compared to patients with type II closure. HFF of less than 0.5 is a predictor for poor anatomical success.

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Varied Presentations of Brown’s Superior Oblique Sheath Syndrome

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Abstract

A retrospective study was performed in 18 patients who attended Comtrust Eye Hospital, Calicut during the period from January 2003 to January 2006 in whom a diagnosis of congenital Brown’s superior oblique sheath syndrome was made clinically and confirmed by a positive forced duction test. The presenting symptoms at the time of consultation, age at presentation, the characteristic features at presentation and the factors which decided surgical management were evaluated.

Introduction

Brown’s syndrome or Jaensch-Brown’s syndrome, which was described in 1928 by Jaensch in a traumatic case, and later in 1950 by Harold Brown, is characterised by consistent features of absence or limitation of elevation in adduction, a normal or near normal elevation in abduction and a positive passive duction test on elevation of the adducted eye. Variable features are downshoot in adduction, divergence in upgaze (V pattern), hypotropia in primary position, compensatory head posture of chin elevation or head tilt toward the shoulder of the affected side and widening of palpebral fissure on adduction. In the primary position, the eyes may show orthophoria, hypotropia of the affected eye or hypertropia of the normal eye if the affected eye is fixing.

Brown attributed the limited elevation to a short or tight anterior superior oblique tendon sheath and termed this, “Superior Oblique Sheath Syndrome”. Many controversies came up later as acquired forms of traumatic and inflammatory origin were described, which were either constant, intermittent, or exhibited spontaneous resolution. The tightness of superior oblique sheath tendon was not a consistent finding during surgery as shown by Parks who found a rather limp tendon even in the presence of a positive FDT. In 1971 Brown redefined it as (1) “true tendon sheath syndrome” which are congenital and have short tendon sheath and (2) “simulated tendon sheath syndrome” which are caused by other factors. He documented that a positive forced duction test is pathognomonic of true congenital Brown’s syndrome. So the term Superior Oblique sheath syndrome is replaced by just Brown’s Syndrome. There are few theories, of which Helveston theory of abnormal telescoping mechanism of the central tendon fibres is the more accepted one than tight or short Superior Oblique tendon. Wright has shown that the pathology lies posteriorly as inferior orbital fibrous adhesions.

Surgery is indicated only in cases of disfiguring head posture or severe hypotropia in primary position. Earlier surgeries of stripping the tendon sheath which gave poor results, and tenotomies and tenectomies of the eighties which resulted in late superior oblique paralysis, have been replaced by Silicon band expander to lengthen the tendon introduced by Wright in 1991.
Aim of the study

To evaluate the symptoms that motivated ophthalmic consultation, age at presentation, the features at presentation and the degree of severity and the factors which decided surgical correction.

Material and Methods

Eighteen cases of congenital Brown’s syndrome of age ranging from 1 year to 20 years, who attended Comtrust Eye Hospital during the period from January 2003 to January 2006 and who had the diagnosis confirmed by a positive Forced Duction Test were studied retrospectively, regarding the age at presentation, history of presenting symptoms which prompted consultation, any family history, features at presentation and the degree of severity which decided surgery. They were followed up for a period varying from 6 months to 3 years. All children had assessment of visual acuity, with Snellen’s chart when possible or by central steady maintained visual behavior. Before assessing ocular alignment, head posture was noted in each case. Ocular alignment in primary position for any hypotropia or horizontal deviation were measured with prisms whenever possible. Ocular movements in all cardinal positions of gaze were noted and limitation of elevation (in adduction, straight upgaze and in abduction); and any downshoot in adduction recorded (Fig. 1). Cases were classified as mild, moderate and severe as follows

**Mild**: where there is restriction in elevation in adduction, no downshoot in adduction or hypotropia in primary position

**Moderate**: where there is restriction of elevation as well as downshoot in adduction, but no hypotropia in primary position

**Severe**: where there is marked downshoot in adduction with hypotropia in primary position.

The presence of Binocular single vision was noted with the amblyoscope wherever possible. A detailed fundus examination with indirect ophthalmoscopy was done. All patients had forced duction test done under short general anaesthesia or during surgery under general anaesthesia except two patients who had forced duction test under local anaesthesia. Cases which had surgery were followed up and ocular movements assessed on the first postoperative day, after one month and at subsequent visits of three to four month intervals. Table of details of patients included in the study is given.

(Table : 1)

Results

None of the patients in this study gave a positive family history.
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<th>Eye</th>
<th>VAcuity R</th>
<th>VAcuity L</th>
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<th>Head posture</th>
<th>CT in primary position</th>
<th>Horizontal Pattern</th>
<th>Restricted Elevation in abduction</th>
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<td>9/F</td>
<td>Diplopia on viewing blackboard</td>
<td>RE 6/6 6/6 BSV+ Em CU+ HT-r RXT Rhypo</td>
<td>Y</td>
<td>No</td>
<td>+</td>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3/M</td>
<td>Oc sq</td>
<td>LE 6/6 6/6 Em CU LXT</td>
<td>V</td>
<td>No</td>
<td>+</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>15M</td>
<td>Sq: childhood</td>
<td>LE 6/6 6/6 Em CU AXT</td>
<td>V</td>
<td>-1</td>
<td>+</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1/M</td>
<td>Oc Sq recent onset</td>
<td>LE 6/6 6/6 Em CU AXT</td>
<td>V</td>
<td>No</td>
<td>+</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>Sq, headposture</td>
<td>LE 6/6 6/6 Em CU AXT</td>
<td>V</td>
<td>No</td>
<td>+BE</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5/F</td>
<td>Oc sq, recent onset</td>
<td>RE 6/6 6/6 Em CU RXT</td>
<td>V</td>
<td>-1</td>
<td>+</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3/F</td>
<td>Oc sq -premature</td>
<td>LE 6/6 6/6 Em CU RXT, coloboma lid</td>
<td>V</td>
<td>No</td>
<td>No</td>
<td>Mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>10/F</td>
<td>Lid defect+squint</td>
<td>RE 6/6 6/6 Em CU+ HT-r RXT Rhypo</td>
<td>V</td>
<td>No</td>
<td>+</td>
<td>severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>20M</td>
<td>Sq since childhood h/o epilepsy</td>
<td>RE 6/60 6/6 Em Nil RXT Rhypo</td>
<td>V</td>
<td>No</td>
<td>+</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>8/M</td>
<td>Sq 6m/frequent blinking, divergence</td>
<td>RE 6/6 6/9p astig BSV+ CU LXT Rhypo</td>
<td>V</td>
<td>No</td>
<td>+</td>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>11/F</td>
<td>Sq+frequent blinking</td>
<td>LE 6/6 6/6 Em CU+ HT-r LXT Rhypo</td>
<td>V</td>
<td>No</td>
<td>+</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>3/F</td>
<td>Oc sq&lt;1 year</td>
<td>LE 6/6 6/6 Em CU+ HT-r LXT</td>
<td>V</td>
<td>-1</td>
<td>+</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>5/M</td>
<td>Ref. by Paediatrician Downs’ Syndrome</td>
<td>RE 6/6 6/6 Em CU+ HT-r RXT</td>
<td>V</td>
<td>No</td>
<td>+</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>8/F</td>
<td>Blink, Blurring</td>
<td>RE 6/6 6/6 Em CU+ HT-r RXT Rhypo</td>
<td>V</td>
<td>No</td>
<td>+</td>
<td>severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>5/F</td>
<td>Sq occ 1yr</td>
<td>RE 6/6 6/6 Em Nil Nil RXT Rhypo</td>
<td>V</td>
<td>No</td>
<td>No</td>
<td>Mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oc Sq: Occasional Squinting, M-Male; F: Female; RE: Right eye; LE: Left eye; CSM B: Central Steady Maintained Binocular Vision, BSV: Binocular Single Vision, Em: Emmetropia, Astig: Astigmatism; CU: Chin Up; HT-r: Hypotropia in primary position; AXT Rhypo: Alternate exotropia Rt hypotropia; RXT Rhypo: Right exotropia with Right hypotropia; LXT: Left exotropia; L hyper: left hypertropia No Dev: No Deviation
I. Age at presentation (TABLE :2; FIG :1)

<table>
<thead>
<tr>
<th>TABLE 2. AGE AT PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 1 year</td>
</tr>
<tr>
<td>1(5.5%)</td>
</tr>
</tbody>
</table>

Though congenital, only one child presented by 1 yr and majority presented during schoolgoing age.

II. Sex Distribution : (TABLE :3; Fig :2)

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>6(33.3%)</td>
<td>12(66.6%)</td>
</tr>
</tbody>
</table>

There is a definite female preponderance with 67% affection in females.

III. Symptoms for which the patient attended the outpatient department

The main complaint for which the patient attended the outpatient department included squinting (50%); visual problems (22.2%) and abnormal head posture (16.6%). One child (5.51%) was referred to us by the Paediatrician, and another child (5.5%) had undergone psychiatric consultation (Table 4).

IV. Affected eye (Table :5, Fig :3)

<table>
<thead>
<tr>
<th>TABLE 5. AFFECTED EYE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE</td>
</tr>
<tr>
<td>9(50%)</td>
</tr>
</tbody>
</table>

FIG. 3. There is preponderance of RE involvement in our study group.

V. Head posture seen on examination (Table 6; Fig 4)

<table>
<thead>
<tr>
<th>TABLE 6. Head posture seen on examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chin up only</td>
</tr>
<tr>
<td>8(44.4%)</td>
</tr>
</tbody>
</table>

FIG. 4. Head posture seen on examination.

TABLE 4. Symptoms for which the patient attended the outpatient department

| Occasional squinting noted from 6m to 18m age |
| Visual problems of occ. double Vision, blurring, freq blinking, poor performance at school |
| Head posture only, consultation With other specialties |
| Squinting Noticed after 5 yrs only |
| Referred by Paediatrician |
| Defective vision and squint |
| 7(39%) | 4(22.2%) | 3(16.6%) | 2(11.1%) | 1(5.5%) | 1(5.5%) |
83% of our patients had an abnormal head posture. 44% had a chin up posture which 39% had a chin down posture position.

**VI Classification according to severity**

<table>
<thead>
<tr>
<th>Mild hypotropia (+downshoot) (+ hypo in Iry)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4(22.2%)</td>
</tr>
<tr>
<td>8(44.4%)</td>
</tr>
<tr>
<td>6(33.3%)</td>
</tr>
</tbody>
</table>

67% did not have hypotropia in primary position. Hypotropia when present was <12 prisms.

Surgical correction was done in five cases who showed marked chin elevation. Two bilateral and two unilateral cases had silicon band expansion of Superior oblique tendon with 240 retinal band and one had tenotomy of Superior oblique tendon. In all these patients, passive elevation in adduction was looked for at the end of surgery and was found to have become negative even though a remarkable tightness of the tendon was not observed during surgery. This has been reported before (Parks). Patients who were followed up showed improvement of head posture during follow up. Patients with the bilateral involvement showed improvement only after surgery of the second eye. Downshoot in adduction also disappeared though full elevation was not attained.

**Discussion**

Congenital Brown’s syndrome is met with not uncommonly in practice and it is found that the parents do not notice the problem or seek consultation for the infant. Quite often the squint is noticed much later and hence only a short history of complaints is obtained. This is because the divergence in upgaze is not noticed easily. One girl of nine was brought with complaints of seeing double while looking at the blackboard at school. This may be because children do not complain of diplopia or visual problems until they are older. One was referred by the paediatrician, and the parents themselves had not noticed the squint. Head posture is a predominant feature and often not recognized as an ophthalmic problem. In our series three children were brought for the abnormal holding of the head only. One of them, a ten year old girl was taken to a psychiatrist for keeping her head high even in front of teachers who considered that the child was arrogant. She had bilateral Brown’s.

As noted in literature, chin up position is a predominant feature in our study, 83% showing some chin elevation on examination. XT was less than 20 prisms in 1° position.

**Some Observations**

Four patients showed mild limitation of movement in abduction also. Binocular single vision was looked for in eight patients and six showed the presence of BSV. Most of the patients had equal vision in both eyes. All except two had emmetropic refraction. (two had mild myopic astigmatism) One twenty year old had amblyopia with only 6/60 vision in the involved eye. Four children showed a widening of palpebral fissure in adduction. Intorsion of fundus was appreciable in upgaze only in four patients.

Few associations were seen and these included 1) Goldenhar syndrome who had the coloboma lid corrected, 2) one case of Down syndrome, 3) a case of premature birth with delayed milestones and 4) a patient with h/o epilepsy since childhood.
both eyes and showed a high potential for binocularity. Binocular single vision was found to be present in six out of the eight who could be tested.

To confirm its etiology as a congenital one, forced duction test is mandatory and had been 100% positive in our series. Thus elaborate investigations to rule out any cause for the recent onset of squint was unnecessary. Most of the children had FDT done under short GA, which is ideal. Surgery had to be undertaken in 5(28%) which is more or less same as that noted in literature. All had a negative FDT on the table after surgery and the head posture improved on follow up visits. We could not find a very tight tendon during surgery as noted by many (Parks)

Conclusion

Congenital Brown’s syndrome is not uncommonly met with in our strabismological practice. It is important that we recognize the problem when a child presents with history of recent onset of squinting or occasional diplopia in a school going child since that is when they start complaining or the parents or teachers are more observant. Forced duction test which is a simple procedure, is pathognomonic if positive even if the SO sheath is not the culprit! Indications for surgery are mainly disfiguring head posture or hypotropia only, since potential for binocularity is very good.

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3. M.M. Parks, M. Brown-AJO 1975, Jan ’79(1)
4. Harold Whaley Brown—True and Simulated Oblique Sheathe Syndrome—Documenta ophthalmologica vol. 34, 21; Feb ‘73
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Ocular HIV Manifestations and Management in the Era of Antiretroviral Therapy (HAART)

Dr. Sudha V, Dr. Charles K. Skariah

The Human Immunodeficiency Virus infection, since its first detected case in India in 1986, has rapidly spread to involve about 0.9% of adult population. Ocular manifestations were seen in about 70% patients in the pre antiretroviral therapy (HAART) era, and were often an indication of irreversible end stage AIDS disease. But with the advent of effective antiretroviral therapy, more patients are surviving and therefore the eye changes are now important indicators for the initiation and effectiveness of treatment, as these manifest when CD 4 count drops below 100 cells/µl.

We conducted a study at Trichur Medical College to study the clinical profile of patients with HIV who presented at our outpatient department with ocular symptoms in order to understand the varying presentations of the disease and its progression during the course of free government HAART programme, which consists of a combination of two nucleoside reverse transcriptase inhibitors, and a non nucleoside reverse transcriptase inhibitor.

Material and methods

A total of 864 patients were initially screened at the HIV clinic at Trichur Medical College between June 2004 and June 2006. Patients with ocular symptoms like redness, photophobia, pain and visual loss were referred to our department for further evaluation.

Inclusion Criteria: All HIV positive patients with ocular symptoms.

Exclusion Criteria: Patients with neurological, psychiatric and other multisystem disorders.

Finally, 25 patients were included in the present study. All the patients underwent a complete ocular examination including visual assessment, slit lamp examination, indirect ophthalmoscopy and automated perimetry.

The HIV status was confirmed by the ELISA or the Western Blot tests. CD 4 cell count estimation was done in ten patients.

Results

Fifty eyes of twenty-five patients were examined. The patients ages ranged from eight years to forty eight years. Twenty two males and three females were assessed. The disease was found to be bilateral in nineteen (76%) eyes. The spectrum of disease manifestations are shown in Table 1. Some of the eyes showed more than one manifestation.

Table 1. Spectra of ophthalmic manifestations in HIV patients

<table>
<thead>
<tr>
<th>Presenting manifestation</th>
<th>No. of eyes</th>
<th>% of total eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV retinitis</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>IRU</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>HIV retinopathy</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>PORN</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Vernal catarrh</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Complicated cataract</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Scleritis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Deep keratitis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vitreous haemorrhage</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Night blindness</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Photophobia</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Hemianopia</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
CD4 counts were done in ten patients. Nine of them had cytomegalovirus (CMV) retinitis and one patient had herpetic retinitis. All of them had counts less than 50 cells/µl.

Thirtytwo percentage of eyes showed CMV retinitis. Two patients had unilateral zone one disease (Fig1), and both of these were given Intravitreal Ganciclovir injection (2 mg total dose) along with initiation of antiretroviral therapy. Both showed very good response with disappearance of exudates and haemorrhages from the disc within a month, and recovery of useful vision which is being maintained (Fig 2). In both these patients, recovery started after a single dose of Ganciclovir, probably because it was given under the cover of HAART.

However all of them were initiated on HAART, and all except one had rapid stabilization of their lesions with retention of useful vision. One patient expired due to development of encephalitis.

Twenty percentage of eyes showed Immune Recovery Uveitis (Fig 3) at the initial presentation. All these patients presented with photophobia and blurred vision and all had been already initiated on HAART for other indications. On examination they showed prominent vitreous cells and some anterior chamber reaction in both eyes. They were started on systemic and local corticosteroids and all of them recovered rapidly with no complications.

HIV retinopathy (Fig 4) was diagnosed in patients having cotton wool spots and hemorrhages along the vascular arcade in the posterior pole. This manifested in 8% of eyes in our study.
Progressive Outer Retinal Necrosis was seen bilaterally in a single patient (Fig 5). This patient had a vision of HM in one eye which deteriorated into total necrosis and detachment within 24 hours. The other eye had 6/6 vision on presentation with characteristic multifocal outer retinal lesions and perivenular lucency. He was started on intravenous Acyclovir along with ART and switched to oral Acyclovir after 10 days. This was continued for another 2 months, after which Acyclovir was withdrawn. He has maintained 6/12 vision in the better eye.

Anterior segment disease only was seen in 16% of eyes including a case of herpes zoster ophthalmicus. All patients resolved on standard treatment and HAART was not instituted as there was no further worsening.

Vitreous Haemorrhage was noticed in 4% of eyes. The patients were started on HAART as one of these eyes had recurrence after a parsplana vitrectomy.

One patient who presented with bitemporal hemianopia had normal fundus at the time of presentation, but subsequently developed optic atrophy. We suspected Ethambutol toxicity as he had taken anti TB treatment before. The patient is showing progressive visual loss though, and has not shown improvement on HAART.

Discussion
Our study showed Cytomegalovirus retinitis as the most common manifestation which is in accordance with other Indian and international studies. Since the CD4 count in nine of these eyes showed < 50 cell/µl, this manifestation can be considered an indication for HAART initiation. The lesions showed marked improvement with HAART even without the standard anti Cytomegalovirus regimen. This favourable outcome of HAART has been reported in other studies.

Intravitreal Ganciclovir along with HAART is a viable and cheaper alternative to systemic therapy for unilateral sight threatening Cytomegalovirus lesions. The disadvantage of not giving anti Cytomegalovirus (CMV) specific therapy during the period of immune recovery after initiation of HAART is the development of immune recovery uveitis which was seen in a high proportion of our patients. Though this can produce serious complications like Optic neuritis, cystoid macular oedema and retinal neovascularisation our study indicates that if recognized early with a high index of suspicion, it is easily manageable.

Conclusions
Anti Retroviral Therapy is an important and effective management regimen of vision threatening Ocular HIV lesions, especially in a resource-poor situation.

References
3. Cunningham ET, Margolis TP: Ocular manifestations of HIV infection; NEJM, 1998
OCT Classification of Clinically Significant Macular Edema

Dr. Anu Anna Paul, Dr. Manoj S, Dr. KGR Nair

Introduction

Diabetic macular edema is the commonest cause of visual loss in patients with non proliferative diabetic retinopathy and a common cause of visual loss in PDR. According to Early Treatment Diabetic Retinopathy study, early detection and laser treatment of clinically significant macular oedema decreases the risk of moderate visual loss by 50%. Though laser has been the standard of care till recently, many new treatment modalities are now available in the management of CSME. Even in the ETDRS, many patients treated with laser did not improve and actually had a visual drop, especially those patients with diffuse CSME. Why laser should be effective in certain subgroup and not in others could not be explained at that time.

Traditional methods of evaluating macular thickening including slit lamp biomicroscopy and fundus photography are relatively insensitive to small changes in retinal thickness and also unable to detect specific anatomic details especially at vitreomacular interface. Thus new techniques for quantitatively and qualitatively measuring retinal thickness have been explored. Recent imaging techniques can provide tomographic or cross sectional images of macula and can yield powerful diagnostic information, which is complimentary to FFA and fundus photo.

Optical Coherence Tomography (OCT) is a new medical diagnostic imaging technology which can perform micrometer resolution cross-sectional or tomographic imaging of macula. The operation of OCT is analogous to ultrasound B-mode imaging except that light is used rather than acoustic waves. OCT is established in the diagnosis of various macular disorders including CSME, macular hole, choroidal neovascular membrane etc.

Aim

The aim of the study was to identify and classify the OCT characteristics of clinically significant macular edema, its correlation to vision and to compare biomicroscopy with OCT.

Materials & Methods

This was a prospective study done between April 2006 and June 2006 in patients who attended the retina clinic of Chaithanya Eye Hospital, Trivandrum. 100 eyes (70 patients) of CSME were evaluated. The study group included both insulin dependent and non insulin dependent proliferative diabetic retinopathy and nonproliferative diabetic retinopathy patients between the age of 40 & 80 yrs. The study population had varied glycemic levels and HbA1c evaluation was not done. None of the patients in our study had undergone previous focal laser or pan-retinal photocoagulation. Such patients were excluded as these could interfere with anatomic changes at the macula and may afer the findings singularly due to disease manifestation. Few of the patients had associated other systemic diseases like hypertension, nephropathy & hypercholesterolemia and were on medications. The duration of diabetes was 7 yrs to 33 yrs. All patients underwent visual acuity estimation by Snellens Visual Acuity Chart, dilated Slit lamp -
90D examination, Fundus Fluorescein Angiography and Optical Coherence Tomography-4 by the same examiner. We considered macular edema to be clinically significant as per the definition by the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol – that is, if there was retinal thickening or hard exudates associated with adjacent retinal thickening observed within 500 +/-50 microns of the centre of foveal avascular zone or a zone or zones of retinal thickening 1 disc area or larger, any part of which was within 1 disc diameter of the center of the macula.

We classified patients into 4 groups based on slit lamp biomicroscopy findings as Gr.1a- non diffuse CSME, Gr.1b- diffuse CSME, Gr.2-CSME with ERM, Gr. 3- CSME with VMT/thickened posterior hyaloid, Gr.4- CSME with CME. A diagnosis of diffuse CSME was made if CSME involved the perifoveal region all around or atleast three quadrants. Fluorescein fundus angiography was done to classify the disease, to diagnose early PDR, CME and to rule out macular ischemia. Macular ischemia was defined on FFA as enlargement of foveal avascular zone compared to other eye with area of segmental or focal perifoveal capillary loss. Patients with macular ischemia were excluded from the study as these patients could alter the interpretation of results, which also aimed at correlating visual deficit with biomicroscopic and OCT features. OCT stratus-4 was done in all eyes, preferably a line scan programme was chosen and the image processed and analyzed. Based on OCT findings, we classified CSME into five groups, Gr.1- macular thickening with only spongy edema, Gr.2- macular thickening with ERM, Gr.3- macular thickening with VMT, Gr.4- macular thickening with CME and Gr.5- macular thickening with SRF.

**Results**

Of the total 70 patients, there were 17 patients in 40-49 yrs age group (24%), 29 in 50-59 yrs age group (42%), 21 in 60-69 age group (30%), 3 in 70-79 age group (4%) and none above 80 yrs. (Fig. 2) Males predominated in the study with 66%. The male: female ratio was 2:1. Of the 70 patients, 45 had NPDR (64%) and 25 had PDR (36%).

Biomicroscopically, 52% had diffuse CSME (Gr.Ia), 48% had focal CSME (Gr.Ib), 16% had CSME with CME (Gr.IV) and 2% had CSME associated with VMT (Gr.III) in the order of frequency. No patient had ERM and SRF clinically (Fig. 3).

OCT examination revealed (Fig. 4) macular thickening with spongy edema in all patients (100%), macular thickening (ME) associated with CME in 38%, ME associated with VMT in 10%, ME associated with SRF in 8% and ME associated with ERM in 2%. On OCT, eyes with spongy edema showed diffuse thickening of macula with small cystic spaces (Fig. 5). Eyes with CME showed (Fig. 6) large cystic spaces in the foveolar and parafoveal region. VMT (Fig. 7) was seen as
hyper-reflective band in the vitreous, which was adherent to the fovea, either centrally or paracentrally, causing traction and pulling up the macula. None of the patients had a defect suggestive of hole formation. SRF (Fig. 8) was seen as a subfoveal detachment on line scans. ERM (Fig. 9) was identified as a hyper-reflective thickening at the level of internal limiting membrane, causing distortion and flattening of the foveal surface.

Correlation of biomicroscopic and OCT finding with visual acuity revealed that 30% of eyes had a visual acuity of 6/9 or better, while 70% had vision worse than 6/9. Of those in biomicroscopy group with less vision, only 18% could be attributed to CME & VMT. No obvious clinical cause for defective vision was detected in the rest 52% eyes with visual loss. In OCT group, 58% could be attributed to CME, VMT, SRF & ERM. No obvious clinical cause for defective vision was detected in the rest 12% eyes with visual loss.

**Table 1. Comparison of CME characteristics identified by biomicroscopy and OCT**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>OCT</th>
<th>Biomicroscopy/FFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CME</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>SRF</td>
<td>8%</td>
<td>nil</td>
</tr>
<tr>
<td>VMT</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>ERM</td>
<td>2%</td>
<td>nil</td>
</tr>
</tbody>
</table>

CME: Cystoid Macular Oedema  
SRF: Sub retinal fluid  
VMT: Vitreomacular Traction  
ERM: Epiretinal Membrane

**Discussion**

- Although slit lamp biomicroscopy is highly sensitive for qualitative detection of CSME and FFA for detection of fluid leakage, various studies have ascertained that qualitative assessment and quantitative measurement...
of retinal thickening may correlate better with retinal dysfunction in patients with CSME. OCT enables the clinician to study their effects and show accurate subclinical retinal changes that may not be even detectable in FFA. Yang et al have suggested that the criteria of CSME seems to be insufficient in identifying macular edema and that OCT may be more sensitive than a clinical examination in assessing diabetic macular edema and is a better tool for documenting changes in macular thickening. OCT-identified spongy retinal thickness and or CME was seen in 58% of eyes without CSME in that series. In our series, we found spongy thickening in all the eyes and CME in 38 % with macular edema. Schaudig et al also found similar observations and in addition also showed a significant increase in macular thickening in diabetic patients without retinopathy compared to non-diabetic subjects. Browning et al had demonstrated that the agreement between clinical examination and OCT was good for moderate and severe macular thickening (>300 microns) and poor for mild macular thickening (200-300 microns). Most of these studies have also found a positive correlation between increasing macular thickening and visual loss.

With the advent of newer medical therapies, intravitreal triamcinolone, posterior subtenons injection of triamcinolone, intravitreal anti-vascular endothelial growth factor therapy and vitrectomy for CSME, the role of laser in the management of CSME is better reserved for selected groups of patients. OCT provides for a better anatomical description of CSME for identification of the medically and surgically treatable groups. Hence our characterization of CSME patients based on OCT into macular thickening with only spongy edema (Gr.-1), macular thickening with ERM (Gr.-2), macular thickening with VMT (Gr.-3), macular thickening with CME (Gr.-4) and macular thickening with SRF (Gr.-5) is more relevant. Structural changes in OCT in our series correlate with other data from literature. Otani et al found spongy retinal swelling in 88%, CME in 47% and SRF in 15% of eyes with CSME. Kim et al found spongy retinal swelling in 97%, CME in 55%, SRF in 7%, VMT in 13% of eyes with CSME. Ozdek et al had reported spongy retinal swelling in 66%, CME in 16% and SRF in 10% of eyes with diabetic macular edema. In our study, we found spongy retinal swelling in 100%, CME in 38%, SRF in 8% and VMT in 10%.
On comparing OCT with biomicroscopy, 38% of the eyes had CME on OCT, compared to 16% detected on biomicroscopy. 8% of eyes had SRF with subfoveal detachment on OCT which was not identified on biomicroscopy. 10% of eyes had VMT on OCT compared to 2% on biomicroscopy. 2% of eyes had ERM identified by OCT compared to none on biomicroscopy. Browning DJ et al had also compared stereoscopic slit lamp examination and OCT in the study of CSME and concluded that stereoscopic slit lamp examination of the macula was less sensitive than OCT for detection of diabetic macular edema. Strom et al had found an agreement of 89% on the exact location and 84% agreement on the exact area of CSME when he compared biomicroscopy with OCT and found the latter to be more superior.

In our study, 38% of the eyes had CME on OCT, compared to 16% detected on biomicroscopy. Ozdek et al also found that 40% of CME detected on OCT were not detected by biomicroscopy and 63% were not detected even on fluorescein angiography. OCT is thus a better diagnostic tool to diagnose CME in patients with diabetic retinopathy than biomicroscopy or FFA. Kim et al also had reported that the presence of CME in patients with CSME was significantly associated with worse vision. In our study, 8% of the eyes had SRF with subfoveal detachment, which could not be detected on biomicroscopy or FFA. Most series have found SRF in 8-12% of eyes with CSME. Ozdemir et al had reported that 31% of diabetic CMEs had subretinal fluid. Previously it was believed that SRF was seen in eyes with taut thickened posterior hyaloid, but many series had found evidence to the contrary. Thomas et al found SRF to be associated with taut hyaloid in only 33% of eyes and the rest without posterior hyaloid separation.

10% of eyes in our series had VMT on OCT compared to 2% on biomicroscopy. VMT has been reported by various authors between 10-60% of eyes with CSME. One study which specifically looked at vitreoretinal interface changes in CSME found no PVD in 40% eyes, 53% perifoveal PVD, 2% with incomplete PVD attached to disc and 6% with complete PVD. These results show that though PVD is not the main factor involved in the pathogenesis of diabetic macular edema, perifoveal PVD may have a role in the development of this complication. This may have a bearing on planning management strategies especially with regards to indications for vitrectomy for CSME.

ERM was also detected in 2% of eyes on OCT compared to none on biomicroscopy in our study. Subtle ERM may therefore be missed on routine clinical examination and may need OCT to diagnose it. Wilkins et al found two types of ERM in patients with CSME, globally adherent ERM in 67% and focolarly adherent ERM in 33%. This may be another indication for vitrectomy in CSME.

As macular ischemia can be a cause of visual defects in patients with CSME, the present study excluded this subgroup of patients during the analysis. Correlation of biomicroscopic finding with visual acuity revealed that 30% of eyes had a visual acuity of 6/9 or better, while 70% had vision worse than 6/9. Of those with less vision, only 18% could be attributed to CME & VMT. No obvious clinical cause for defective vision was detected in the rest 52% eyes with visual loss.

OCT evaluation of those eyes with visual acuity of less than 6/9 revealed CME in 38% of these eyes, VMT in 10% eyes, SRF in 8% eyes and ERM in 2% of eyes, thereby offering a better understanding of the cause of visual loss in these patients. Akuraya et al had reported that there was a positive correlation between the type of OCT finding and visual acuity. Patients with CME and VMT had worse vision. Most of the other series had reported that the visual acuity correlated better with macular thickness, i.e more the central foveal thickness, worse the vision. It is also known that the central foveal thickness increases with the different types of OCT presentations, being least for spongy thickening, moderate for CME/SRF and highest for VMT and thus visual loss mirrors these changes.

Thus these structural changes correlate better with the visual defects the patients with CSME have in the absence of macular ischemia in our series. Detection of these findings has a bearing in planning treatment strategies. Eyes with CME and SRF will probably respond poorly to conventional laser and require additional medical management in the form of IVTA or PST. Eyes with VMT and ERM probably are poor candidates for laser and are better managed by primary vitrectomy. Identification of these findings on OCT will optimize treatment in CSME, which will have a bearing on the final visual acuity maintained or achieved.
Conclusion

We found that OCT is a useful technique for quantitative measurement and helps in better anatomical characterization of CSME and thereby more relevant while planning management strategies, followup, explaining prognosis and predicting visual outcome. OCT characterization of CSMEs identified groups that correlate better with visual acuity than slit lamp biomicroscopy. Patients with CSME and only spongy macular thickening on OCT probably respond better to conventional therapy. Patients with CME and SRF respond best to IVTA and PST injections with or without focal laser and patients with ERM and VMT respond best with vitrectomy.

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Presumed Toxoplasmic Optic Neuropathy

Dr. Meena Chakrabarti, Dr. Valsa Stephen, Dr. Sonia Rani John, Dr. Arup Chakrabarti

Toxoplasmic Optic Nerve Involvement is a rare and potentially treatable form of optic nerve infection. This condition should be considered in the differential diagnosis of acute disc oedema with acute visual loss in a young adult. Optic nerve involvement accounts for 9% of ocular Toxoplasma infection. The manifestation may be as Papillitis or Neuroretinitis. The diagnosis is generally missed as vitritis may or maynot be present and because active or healed retinochoroiditis may be absent. Delay in diagnosis is common. Early diagnosis and institution of therapy ensures good recovery of visual function with persistence of visual field defects. Recurrence in 40% of patients warrants long term monitoring.

Acute Disc Oedema with acute visual loss in five young adults seropositive for Toxoplasma was followed up serially with Fluorescein angiograms and visual fields and presented in this report.

Materials and Methods: A retrospective case record analysis of all patients presenting with unilateral or bilateral disc oedema and who had a positive antibody titre of toxoplasma gondii were analysed. Patients with a followup record of atleast 6 months were included in the study. The data analysed included 1) age 2) sex 3) laterality 4) visual acuity at presentation 5) presenting clinical features 6) angiographic characteristics 7) visual field changes 8) any additional finding 9) duration of follow up 10) presence of recurrence.

A thorough neurological assessment and necessary investigations had been performed in all the patients prior to referral for ocular evaluation. A baseline uveitic workup including total count, differential counts, ESR, VDRL Mantoux, as well as Elisa for Toxoplasma gondii IgG and IgM antibodies were available for evaluation. All patients who were toxo positive had received a combination of Clindamycin and oral prednisolone acetate. (1mg/kg body weight) and the therapy was continued for 3 weeks.

Results

The clinical, angiographic and visual field changes at presentation are tabulated in Table 1.

The patients were young, and immunocompetent of the age group ranging from 5yrs to 28yrs. The presentation was unilateral in two patients and bilateral in three.

Case 1 – presented with unilateral papillitis and juxtapapillary choroiditis (Fig 1: a –d), in his right eye. Fundus examination of the right eye revealed a hazy media, due to Grade II vitritis, disc oedema, and a patch of active juxtapapillary choroiditis (Fig 1a). Fundus examination of the left eye showed an area of healed retinochoroidal scar (Fig 1b). Fluorescein angiography of the right eye revealed hyperfluorescence of disc with diffuse leak from the peripapillary retina (Fig 1c). Fundus examination of the left eye showed an area of healed retinochoroidal scar with scleral staining (Fig 1d). This patient was followed up for 48 months. He developed sectorial disc pallor, healed retinochoroidal scar (Fig 1 e & f ) and persistence of sectorial field defect.

Case 2 – A 5 year old child with congenital bullous ichthyosis presented with subacute onset of defective vision in both her eyes. She presented with a visual acuity of counting fingers in her right eye and 5/60 in her left eye. Fundus examination revealed grossly oedematous discs with flecks of hard exudates in the macular area in the form of an incomplete macular star.
TABLE 1. CLINICAL FEATURES AT PRESENTATION

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Age/Sex</th>
<th>Laterality</th>
<th>Vision</th>
<th>Clinical Features</th>
<th>FFA</th>
<th>Visual Field</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17/M</td>
<td>U/L</td>
<td>5/60</td>
<td>Papillitis &amp; Juxta Papillary Choroiditis</td>
<td>Hyper fluorescence Of Disc</td>
<td>Sector</td>
<td>Vitritis – Recurrence After 2 Years</td>
</tr>
<tr>
<td>2</td>
<td>5/F</td>
<td>B/L</td>
<td>CF 3m &amp; 5/60</td>
<td>Neuroretinitis With Macular Star</td>
<td>Hyper fluorescence Of Disc</td>
<td>Altitudinal</td>
<td>Congenital Bullous Ichthyosis</td>
</tr>
<tr>
<td>3</td>
<td>28/F</td>
<td>B/L</td>
<td>CF 1mt &amp; CF 3m</td>
<td>Neuroretinitis With Peripapillary Glistening Hard Exudates</td>
<td>Hyper fluorescence Of Disc</td>
<td>Nerve Fibre Bundle Defect</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18/M</td>
<td>U/L</td>
<td>5/60</td>
<td>Neuroretinitis With macular Star</td>
<td>Hyper fluorescence Of Disc</td>
<td>Sector</td>
<td>Recurrence</td>
</tr>
<tr>
<td>5</td>
<td>20/F</td>
<td>B/L</td>
<td>CF 3m &amp; CF 2m</td>
<td>Neuroretinitis With macular Star</td>
<td>Hyper fluorescence Of Disc</td>
<td>Altitudinal</td>
<td></td>
</tr>
</tbody>
</table>

M-Male; F: Female, U/L: Unilateral; CF: Counting Fingers; OU: both eyes; RPE degn: Retinal Pigment Epithelial Degeneration; F/U: Follow up

TABLE 2. FOLLOWUP DATA

<table>
<thead>
<tr>
<th>CASE</th>
<th>Followup Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE 1</td>
<td>Sectorial Disc Pallor Healed Peripapillary Choroiditis, VF 6/6 Sectorial F/U 4 Years, Recurrence After 1 Year</td>
</tr>
<tr>
<td>CASE 2</td>
<td>Gliosis On Disc Resolved Macular Star, RPE Degen 6/60 OU Patchy Nerve Fibre Bundle Defects 6 Months F/U</td>
</tr>
<tr>
<td>CASE 3</td>
<td>Gliosis On Disc Resolved Macular Star, RPE Degen 6/36 &amp; 6/24 Sectorial F/U 2 Years Recurrence After 1 Year</td>
</tr>
<tr>
<td>CASE 4</td>
<td>Sectorial Disc Pallor 6/60 Altitudinal 12 Months F/U</td>
</tr>
<tr>
<td>CASE 5</td>
<td>Gliosis On Disc Resolved Macular Star, RPE Degen 6/60 OU Altitudinal 12 Months F/U</td>
</tr>
</tbody>
</table>

VF: Vitreous Floaters
Fig 1(a) Fundus examination of the right eye revealed a hazy media, due to Grade II vitritis, disc oedema, and a patch of active juxtapapillary choroiditis.

Fig 1(b) Fundus examination of the left eye showed an area of healed retinochoroiditis scar.

Fig 1(c) Fluorescein angiography of the right eye revealed hyperfluorescence of disc with diffuse leak from the peripapillary retina.

Fig 1(d) Angiography of left eye was consistent with healed retinochoroidal scar and showed scleral staining.

Fig 1(e) & (f) This patient was followed up for 48 months. He developed sectorial disc pallor, healed retinochoroiditis scar and persistence of sectorial field defect.
Fig. 2  (a) Fundus examination revealed grossly oedematous discs with flecks of hard exudates in the macular area in the form of an incomplete macular star.

Fig. 2  (b) Fluorescein Angiography revealed hyperfluorescence of the disc in both eyes.

Fig. 2  (c) Fundus photography after 1 month showing resolution of the disc oedema and a gradual improvement in visual acuity to 6/60 in both eyes. However patchy field defects persisted and there was gliosis on the disc.
Fig 3  (a) Fundus photo showing bilateral disc oedema with peripapillary retinal oedema, flecks of hard exudates and retinal haemorrhages

Fig 3  (b) Fluorescein angiography showing hyperfluorescence of the optic disc

Fig 3  (c) Persistence of field defects after resolution in case 3 and 4
suggestive of neuroretinitis (Fig 2a). Fluorescence angiography revealed hyperfluorescence of the disc (Fig 2b). She had already undergone a detailed neurological workup. Investigations revealed a highly positive antibody titre to toxoplasma gondii. Treatment with a combination of clindamycin and systemic steroids lead to gradual resolution of the disc oedema and a gradual improvement in visual acuity (Fig 2c) to 6/60 in both her eyes. However patchy field defects persisted and there was gliosis on the disc.

Case 3: Presented as bilateral neuroretinitis (Fig 3a) in a 28 year old woman, with hyperfluorescence on angiography (Fig 3b) and nerve fibre bundle defects (Fig 3c). There was good resolution on followup with recovery of 6/60 vision, at 2 years followup (Fig 3d).

Case 4: Presenting as neuroretinitis in a 18 year old male unilaterally (Fig 4a &b) was investigated for papilloedema. Antitoxo regimen with systemic steroids lead to resolution and some amount of visual recovery.

Case 5: Presented as bilateral neuroretinitis with macular star and was subjected to detailed neurological work up. Resolution occurred with antitoxoplasma regimen and systemic steroids.

The followup data of all patients is given in Table 2.

**Discussion**

Toxoplasmic optic neuropathy accounts for 9% of ocular manifestations of toxoplasmosis. It can manifest as papillitis (3%) or as neuroretinitis (6%). Toxoplasmic papillitis presents with a foci of inflammation on or adjacent to the optic nerve head in association with an...
adjacent patch of retinochoroiditis or presence of focus of retinochoroidal scarring in the periphery. Vitritis of moderate severity is present in 69% of patients. The response to treatment is favourable, with good visual recovery. Neuroretinitis presents as primary involvement of the optic nerve without adjacent foci of retinochoroiditis. Vitritis is usually absent. Presence of florid disc oedema, and macular star are pathognomonic of this condition. Response to therapy is less dramatic and nerve fibre bundle defects persist after recovery. Usually a diagnosis of papilloedema is made and the patient would have been subjected to unnecessary neurological evaluation. The diagnosis is generally missed as vitritis may or may not be present and because active or healed retinochoroiditis may be absent. Delay in diagnosis is common. Early diagnosis and institution of therapy ensures good recovery of visual function with persistence of visual field defects. Recurrence in 40% of patients warrants long term monitoring.

Investigations performed usually are given in Table 3 full baseline uveitic workup is necessary. Ocular toxoplasmosis may be an initial manifestation of AIDS and hence screening for HIV is essential.

The main conditions that can be considered in the differential diagnosis are enumerated in Table 4. Toxoplasmic papillitis must be differentiated from optic neuritis, AION, disc vasculitis, multiple sclerosis, CMV, HSV, HZV infections. Lebers idiopathic stellate neuroretinitis, syphilis, Lymes disease, cat scratch fever as well as Grade IV Hypertensive retinopathy. An element of suspicion, the typical presentation, and a positive toxo antibody titre confirms the diagnosis in the majority of patients.

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Intravitreal Injections

Dr Biju John MS

Introduction

Man’s invasion into the sacred inner space of the eye-the vitreous cavity began around the same time he was attempting to invade the outer space i.e. in the 1950s. Von Sallman in 1944 demonstrated the efficacy of Intravitreal antibiotics in a study in which he successfully cured endophthalmitis in rabbits by Intravitreal Penicillin injection. And thus began the era of Intravitreal antibiotics. First (1955-1975) it was just antibiotics and steroids mainly for the treatment of Endophthalmitis. Further experience with Intravitreal injections was gained through the use of pneumatic retinopexy. Intravitreal ganciclovir and foscarnet injections were utilized in the early 1990s for the treatment of cytomegalovirus (CMV) retinitis. The approval of Pegaptanib sodium, and Ranibizumab (for treating age-related macular degeneration, ongoing studies using these agents in diabetic macular edema, as well as the widespread off-label use of triamcinolone acetonide and bevacizumab (Avastin) for a variety of conditions, are all refocusing interest in Intravitreal injection as a method of drug delivery.

This article is not intended to be a comprehensive review of all the available Intravitreal medications and their use, but a brief overview of the commonly used ones and the ones of current interest-viz Antibiotics, Steroids and Anti VEGF agents.

Why Intravitreal injections

Intravitreal injections have provided the logical method to the VR surgeons to bypass the blood retinal barrier so as to provide clinically effective doses of therapeutic agents to the target tissue. Therapeutic intraocular concentrations of the drug can be achieved immediately and effectively without the danger of systemic absorption and toxicity.

Intravitreal medications currently in use

1. Gas Bubble (pneumatic retinopexy)
2. Antibiotics (Endophthalmitis)
3. Antivirals
   a. Ganciclovir
   b. Foscarnet
   c. Cidofovir
4. Methotrexate (For intraocular lymphoma)
5. Triamcinolone
6. Anti VEGF agents
   a. Pegaptanib Sodium (AMD)
   b. Ranibizumab (AMD)
   c. Bevacizumab
   d. VEGF Trap
7. Ovine Hyaluronidase (For Vitreous Hemorrhage)

Intravitreal Antibiotics

These are the mainstay in the management of Endophthalmitis and can be sight saving when used early in the course of the disease. This is the only route of administration by which antimicrobial agents can be made to neatly bypass the blood retinal barrier and achieve therapeutic concentrations in the vitreous. The medications have to be administered observing all sterile precautions (see later) and the dose have to be exact as any change in the concentrations can be catastrophic.
At present the most preferred Intravitreal antibiotics in case of Gram +ve bacterial endophthalmitis are Vancomycin and Cefazolin in that order. For Gram –ve infections we have Ceftazidine; Amikacin and Gentamycin in the order of increasing toxicity. Even though all the 3 are comparable in efficacy Ceftazidine is preferred due to considerably less retinal toxicity. Gentamycin is best avoided due to the risk of producing macular infarction. At the time of initial presentation as the organisms are not known, the dictum is to administer 2 agents, one for Gram +ve and the other for Gram –ve organisms. A combination of Vancomycin and Ceftazidine is definitely the first choice. In Fungal endophthalmitis we have only one agent of proven efficiency viz Amphotericin B. Recent study results with intravitreal Voriconazole have been very encouraging. Most surgeons favour use of Intravitreal steroids like Dexamethasone in Bacterial endophthalmitis along with the Intravitreal antibiotics, so as to minimize the tissue damage and this should be considered in Fungal Endophthalmitis, caused by filamentous fungi.

**Preparation of Intravitreal agents in the treatment of Endophthalmitis**

The following principles should be observed while preparing the Intravitreal antibiotics for injection

**Principles**

1. Surgeon must prepare the solution himself
2. Even though the Surgeon believes he remembers the procedure of preparation of the solution, he must consult as a ritual a Printed Reference Paper every single time. (any mistake in quantity injected may be catastrophic). Such a paper or a display sheet have to be pasted in the OT or in the Wards for ready reference
3. A Tuberculin /Insulin syringe with detachable needle has to be used to administer the agent.
4. After aspirating the initial amount (say 0.1ml) of the original concentration of the antibiotics, discard the hypodermic needle (usually 23 gauge with the barrel full of antibiotics, not accounted towards the total quantity of antibiotics to be injected) use a new needle with an empty barrel to draw the diluent (saline or water)
5. Discard the excess of 0.1 ml to a container, which can be destroyed
6. Use surgical gloves

Several regimen and mixing procedures are there so as to achieve the necessary concentration in 0.1 ml, which is the usual quantity, injected. One such regimen (based on Dr Lalit Verma et al’s article in the AIOS CME series with some modifications) is given below.

1. **Vancomycin hydrochloride**  
   (Dose: 1000ug in 0.1ml)

   The drug is available as a powder in strength of 500mg (Fig 1). Reconstitute this with 10ml of sterile solution for injection or saline (Fig 2). This gives strength of 50mg in 1.0ml. Then 0.2ml of the drug (10mg) is drawn into a tuberculin syringe and this is further diluted with 0.8ml of sterile saline to give a strength of 10mg in 1.0 ml and hence 1000ug (1 mg) in 0.1 ml. (Figs 3 & 4)

2. **Ceftazidime hydrochloride**  
   (Dose: 2.25mg in 0.1ml )

   The drug is available as a 500mg powder. This is reconstituted by adding 2 ml of the diluent (Sterile water for inj or Sterile Saline) to give a concentration of 250mg (225mg of active ingredient) in 1ml and so 22.5mg in
0.1 ml). 0.1 ml of this is withdrawn into the tuberculin syringe as for vancomycin and is made up to 1 ml by adding another 0.9 ml of the diluent into the tuberculin syringe. This gives a concentration of 22.5 mg in 1 ml and so 0.1 ml of this will contain 2.25 mg of the drug.

3. **Cefazolin (Dose: 2.25 mg in 0.1 ml)**

   Available as 500 mg powder. The required concentration is achieved by following the same steps of dilution indicated above for ceftazidime.

4. **Amikacin sulfate (Dose: 400 µg in 0.1 ml)**

   Available in strength of 100 mg in 2 ml vial. 0.08 ml (4 mg) is taken into a tuberculin syringe and then made up to 1 ml by adding sterile saline or water for injection into the syringe. So now we have 4 mg in 1 ml and so 0.1 ml will be having 0.4 mg, which is the required dose.

5. **Gentamicin sulfate (Dose: 200 µg in 0.1 ml)**

   This is not generally used now.

   Available as a solution of 80 mg in 2 ml vial (40 mg in 1 ml)

   0.10 ml (4 mg) of the drug is drawn into a tuberculin syringe and diluted further with 1.9 ml of sterile solution to give a strength of 4 mg in 2 ml (2 mg in 1 ml) and hence 200 µg in 0.1 ml

6. **Amphotericin B (Dose: 5 µg in 0.1 ml)**

   Reconstitute a 50 mg vial with 10 ml of 5% Dextrose

   Withdraw 0.1 ml of this and dilute further with 9.9 ml of 5% Dextrose

   Now concentration is 500 µg in 10 ml (50 µg / ml)

   0.1 ml of this = 5 µg

7. **Dexamethasone (Dose: 400 µg in 0.1 ml)**

   Commercial prep: 2 ml vial (4 mg/ml)

   So 0.1 ml will contain 0.4 mg (400 µg)

   So 0.1 ml withdrawn directly into tuberculin syringe without dilution and same to be given

   Intravitreal injections for endophthalmitis can be repeated after 48-72 hours depending upon the response.

### Intravitreal Antivirals

Intravitreal Antivirals have been in use since early 1990s. The major use is in the treatment of Cytomegalovirus Retinitis particularly in the setting of HIV infections. The other situations where they have been found to be useful is Varicella Zoster Retinitis, Acute Retinal Necrosis etc. The major indication today is in the treatment of Viral Retinitis in HIV patients particularly CMV Retinitis.

1. **Ganciclovir**

   Original dose used was 200 or 400 mcg in 0.1 ml but almost all injections given today are 2000 mcg in 0.05 to 0.1 ml. The injections are given on a weekly basis.

2. **Foscarnet**

   Used in the dose of 2.4 mg per 0.1 ml. The half-life is shorter than ganciclovir’s, and studies have used twice-weekly injections for induction and once a week for maintenance. Foscarnet injections may be particularly helpful in cases of resistant CMV disease. Combinations of high-dose intravitreal ganciclovir (3.0 mg twice a week) and foscarnet (2.4 mg twice a week) may be effective in patients who fail to respond or are intolerant to conventional therapy.

3. **Cidofovir**

   The long half-life and potent anti-CMV activity of Cidofovir make it an attractive candidate for intravitreal injection. Studies in rabbits suggested that 100 mcg was a safe dose. However, other animal and human trials have demonstrated excessive toxicity (especially uveitis and hypotony). But many studies report encouraging results without much serious adverse effects with 10 to 15 microgram injections.

### Intravitreal Steroids

It was Machemer who first popularized the use of Intravitreal steroids in 1979 in an effort to halt cellular proliferation after retinal detachment surgery. What he used was Dexamethasone. Short acting steroids like Dexamethasone is currently given along with antibiotics in the treatment of Bacterial Endophthalmitis as already mentioned. But it is the long acting depot steroid preparations like Triamcinalone that have created so
much interest in Intravitreal injections. Now Retinal surgeons are trying IVTA (Intravitreal triamcinalone) in practically every retinal disease with macular edema.

**Intravitreal Triamcinalone**

History is replete with stories of accidents leading on to amazing discoveries. The same is true of Intravitreal Triamcinalone also. It happened in 1979 when Dr M Michael of Michigan while giving a periocular injection of Triamcinalone for a case of pseudophakic CME of Vn 20/200, discovered that it had accidentally gone into the vitreous cavity. He followed up the cases and to his surprise found that Vision had improved to 20/70 at 6 wks and to 20/25 at 3 months.

He repeated the same for 9 more cases and got comparable results in 8 of them. The only patient who did not respond was found to have ARMD with hemorrhage at macula

**How does it work?**

Corticosteroids are known to have an inhibitory effect on angiogenesis and inflammatory reactions by reducing the migration and activation of inflammatory cells. Up-regulation of the extra cellular-matrix protein plasminogen activator inhibitor-1 by steroids has a direct angiostatic effect. Steroids also inhibit the production of vascular endothelial growth factor (VEGF). Corticosteroids are known to stabilize endothelial and basement membranes and reduce vascular permeability and vascular leakage through their inhibitory effect on plasmin. In addition, steroids down-regulate intercellular adhesion molecule expression, which is an important stimulus in the development of neovascular membranes and an inflammatory mediator released by photodynamic therapy (PDT).

So, theoretically there is every reason to expect that IVTA could potentially work for a number of retinal conditions characterized by inflammation, vascular leakage, and new blood vessel growth. However, the exact mechanism of action in each of these situations remains to be determined.

A broad overview of some of the situations where intravitreal Triamcinolone Acetonide injection (IVTA) has been found to be useful is given below. All of these have Macular edema as the main underlying pathology, which is targeted by IVTA

### 1. Diabetic Macular Edema

IVTA is a promising therapy for patients with Diabetic Macular Oedema especially the diffuse type, refractory to laser treatment. Data from various studies show that in such patients IVTA has helped in decreasing the macular thickness as measured by OCT; absorption of hard exudates and a resultant improvement in visual acuity. To summarise a few studies (Table 1).

While there is no doubt about the short-term effectiveness of IVTA in these cases, the long-term effects are not so encouraging. Generally the positive effect reaches its peak by 1-3 months. This is followed by a decline in vision and increase in macular thickness over the following months and so the injection may have to be repeated again. Notwithstanding this drawback, IVTA has proved to be a new and effective weapon in tackling the vexing problem of diffuse diabetic macular edema against which the laser is very often found to be ineffective.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Dose of IVTA</th>
<th>Improvement in visual acuity</th>
<th>Decrease in Macular thickness by OCT</th>
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<tbody>
<tr>
<td>Martidis et al</td>
<td>4 mg</td>
<td>2.4, 2.4, and 1.3 Snellen lines at 1,3 &amp; 6 month follow up</td>
<td>55%, 57.5%, and 38%, at 1,3 &amp; 6 mth follow up</td>
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<tr>
<td>Jonas et al</td>
<td>25 mg</td>
<td>In 81%</td>
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<tr>
<td>ISIS-DME</td>
<td>2mg Vs 4 mg</td>
<td>≥3 ETDRS line increase in 33% &amp; 21% at 3 Months and 6 months respectively. Better results for 4 mg</td>
<td>40% mean reduction from baseline at 1 month and 3 months. But no significant reduction at 6 months</td>
</tr>
<tr>
<td>Pollack JS et al</td>
<td></td>
<td>Was not significant when compared to controls</td>
<td></td>
</tr>
<tr>
<td>Massin et al</td>
<td>4 mg</td>
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2. Retinal Vein Occlusions

IVTA has been shown to be effective in treating macular edema secondary to Central Retinal and Branch retinal vein occlusions; in several studies. However results were not favorable in the Ischemic type of CRVO. A multicenter, randomized clinical trial funded by The National Eye Institute, USA has been going on since October 2004, to ascertain the safety and efficacy of IVTA injections for the treatment of macular edema associated with central and branch retinal vein occlusion. This study referred to as “The SCORE Study” (The Standard Care vs. Corticosteroid for Retinal Vein Occlusion) is hoped to help us decide whether IVTA can be safely used in Retinal Vein Occlusions and confirm its effectiveness.

3. Macular Edema due to other causes

IVTA has also been widely used in treating Psuedophakic Cystoid macular edema, Uveitic Cystoid macular edema and Macular edema in Retinitis pigmentosa with variable results. Even though many authors have reported favourable results, use of IVTA for these conditions is not currently recommended.

4. IVTA in Wet Age Related Macular Degeneration

Photodynamic therapy after injection of Verteporfin dye is now a proven modality of treatment for Choroidal Neovascular membrane of wet AMD. But the tissue effects associated with photodynamic therapy (PDT) may reduce its benefit. Often the benefits are only marginal with high recurrence rate necessitating repeated PDT sessions, which puts a huge economic burden on the patient and health care institutions. Often there is only a temporary improvement with no long-term benefits. This is mainly because the mechanism of action of PDT-preferential endothelial injury, thrombosis, and obliteration of the neovascular network-does not address the underlying pathogenic drive of angiogenic stimulation. Thus, reperfusion of obliterated vessels and further neovascularization occurs, with consequent loss of vision. Reducing vascular reperfusion and neovascularization should significantly alter the vision loss documented in the TAP and VIP studies.

Now in most centers PDT is combined with IVTA injections which have considerably improved the results both visual and angiographic. The number of retreatments required to achieve persistent resolution of the CNVM could also be brought down considerably by employing combination therapy. To quote a few representative studies:

1. After a mean follow-up of 18 months, combination therapy resulted in vision gain in 7%, stabilization in 50%, and vision loss in 43% of patients. (Rechtman E et al BJO 2004: 88(3)

2. In a series of 41 patients with occult CNV, combination therapy achieved visual improvement in 54% of eyes at 24 months, while vision loss was documented in 7% only. (Augustin A et al Meeting of the Macula Society; 2004)

3. Number of re-treatments necessary to achieve absence of leakage using combination therapy ranged from 1.2 to 2.7, significantly lower than with PDT monotherapy.

4. Triamcinolone-Assisted Vitrectomy Surgery

Triamcinalone injected into the vitreous cavity during vitrectomy is of great help in identifying the vitreoretinal tissue planes and thereby facilitate complete removal of the vitreous and easy induction of PVD etc. This is particularly useful during vitrectomy in complicated PDRs. Membrane peeling, complete removal of Vitreoretinal tractions etc are greatly facilitated by administering Triamcinalone intravitreally during the surgery.

What is the ideal dose of Intravitreal Triamcinolone?

The dose of Intravitreal triamcinolone used internationally varies from 1mg to 25 mg. While the ideal dose is yet to be ascertained by randomized control studies, the most widely used dose is 4mg in 0.1 ml. The preliminary data from the Intravitreal Steroid Injection Study (ISIS) reported at the Vail Vitrectomy Society showed that the 4-mg dose was more effective than the 2-mg dose. Currently two important studies are underway to ascertain the optimum dose of IVTA:

1. The Diabetic Retinopathy Clinical Research Network Study- a prospective, randomized trial comparing laser treatment with Intravitreal injection of 1-mg and 4-mg doses of a new formulation of triamcinolone acetonide for diabetic macular edema.
2. The Standard Care vs. Corticosteroid for Retinal Vein Occlusion Study (SCORE) evaluating 2-mg and 4-mg purified triamcinolone acetonide vs standard of care for the treatment of macular edema due to vascular occlusions.

These large randomized studies are expected to shed some light on the appropriate dose necessary to treat retinal diseases. Both these studies are using a new, unpreserved preparation of triamcinolone acetonide, in the hope that this formulation will be safer to use in the eye than the commercially available one.

**Intravitreal injections of Anti-VEGF agents**

Anti VEGF (Vascular Endothelial growth factor) agents are all set to revolutionize the management of many retinal conditions having neovascularisation as the underlying pathologic process. The main focus now is on Wet AMD. However even in conditions like Proliferative diabetic retinopathy, Neovascular glaucoma these agents are being increasingly used and are even touted by many physicians as likely replacement for Laser. And of course the preferred route of administration is Intravitreal for obvious reasons. Currently 2 drugs Pegaptanib Sodium (Macugen) and Ranibizumab (Lucentis) have been approved for Intravitreal use in the treatment of Wet AMD. One more drug, which is also widely, used Off Label now viz Bevacizumab (Avastin) is awaiting FDA approval.

### 1. Intravitreal Pegaptanib Sodium (Macugen)

The effectiveness of this was proved by the VISION Study (VEGF Inhibition Study in Ocular Neovascularization). The conclusions were:

1. Pegaptanib sodium was effective in all forms of exudative AMD compared with standard of care. (at 54 wks 70% protected from moderate visual loss i.e. <15 letters)

2. Effect seen as early as six weeks after the first injection, and treatment benefit was seen throughout the first year of treatment.

3. The second year data illustrates that treatment benefit is greater for two years of sustained treatment rather than one year or standard care.

Three doses were used in VISION Study (0.3mg; 1mg; 3mg), given every 6 wks for a total of 9 –18 injections (12-18 months). FDA approval was obtained for 0.3 mg Pegaptanib sodium for treatment of Exudative AMD.

### 2. Intravitreal Ranibizumab (Lucentis)

The fight against AMD received a real shot in the arm on June 30, 2006, when the FDA approved ranibizumab, an anti-vascular endothelial growth factor (VEGF-A) agent, for the treatment of this disease. For the first time the retina specialists are talking confidently of actually improving the AMD patient’s vision rather than

<table>
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<tr>
<th>Study</th>
<th>Dose &amp; Schedule</th>
<th>Results</th>
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<tr>
<td>MARINA</td>
<td>0.3 mg or 0.5 mg monthly injections for 24 months</td>
<td>By 2 years, 90% of patients receiving 0.3 mg ranibizumab avoided a 15-letter loss. Mean visual acuity was also improved at 2 years by more than 1 line in the treatment group as opposed to a mean loss of nearly 3 lines in the control group</td>
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<tr>
<td>ANCHOR</td>
<td>Same as above</td>
<td>1 yr results in 0.5mg group Stable or improved vision: 96.4 % patients (Vs 64.3% with PDT) Gain of 15 letters of Visual acuity: 40.3% patients (Vs 5.6% with PDT)</td>
</tr>
<tr>
<td>PRONTO</td>
<td>Monthly injections for 3 months and retreatment decisions were based on OCT results</td>
<td>At 1 year, 82% of patients had stable or improved vision. Visual acuity improvement of 15 or more letters occurred in 35% of patients. OCT data demonstrated fluid resorption as early as 1 day after injection, with an acuity response by 2 weeks</td>
</tr>
<tr>
<td>PIER</td>
<td>0.3 or 0.5 mg monthly for 3 doses and then every 3 months afterwards</td>
<td>Results proved the efficacy of the agent to prevent visual loss (1.6 &amp; 0.2 letters loss Vs 16.3 letter loss in Placebo), but did not appear as impressive as those from the MARINA and ANCHOR trials, which involved monthly dosing. A direct head-to-head comparison of monthly vs quarterly dosing was not performed.</td>
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stabilizing it. The quality of different studies and their results are superior to those conducted with any other drug currently available. (Table 2).

Even though monthly dosage scheduling of the injections were used for most of the studies, it is unlikely that this will be the regimen that is going to be followed in the coming years. The ideal schedule will evolve after further studies and in the meanwhile most specialists will be tailoring it as per the individual patient responses. Any way Intravitreal Ranibizumab seems to be destined to become the standard treatment for CNVM secondary to wet AMD.

3. Intravitreal Bevacizumab

Ever since the Systemic Avastin for Neovascular AMD (SANA)\textsuperscript{23} trial demonstrated the effectiveness of Intravenous Bevacizumab in Wet AMD patients, a lot of studies have been done on Intravitreal administration of the same drug.\textsuperscript{24,25,26,27} The action of this drug is similar to that of Ranibizumab. But two things that aroused wide interest for this drug among Retinal specialists is that (1) the cost is only a fraction of that of Ranibizumab and (2) the Intravitreal half life may be twice as long as Ranibizumab. This means the frequency of administration of the drug can be brought down. The dose used is 1 to 1.25 mg in 0.04 to 0.05 ml. The drug has not been approved for Intravitreal use by FDA but this has not prevented its widespread off label use by retinal specialists worldwide. A set protocol is still not in place but most surgeons give either a single injection or 3 sequential injections at 1-month interval and then reassess. Further injections are given if necessary depending on the response or lack of it. Once the safety and effectiveness of Bevacizumab is proved by a large multicentre clinical trial, this has the potential to emerge as the most widely used management option for a lot of retinal conditions like wet AMD, Diabetic Retinopathy etc due to its relatively low cost and easy availability.

What are the risks involved in Intravitreal injections

Although Intravitreal injections are generally considered safe when given observing standard guidelines there are definitely some risks involved. Even though the benefits outweigh the risks, we have to give due consideration to these especially when it entails multiple injections.

The complications of Intravitreal injections can be those related to the procedure itself and those specific to the agent used

Complications related to the procedure

The risks associated with Intravitreal injections can be divided into defined risks, for which there are known incidence, and rare complications.

Defined risks, which should be included in every informed consent for an Intravitreal injection, include:

1. Endophthalmitis (2 year incidence of 0.16% in over 10,000 injections);\textsuperscript{28}
2. Retinal detachment (2 year incidence of 0.15% in over 10,000 injections); and\textsuperscript{28}
3. Lens trauma/acute cataract (2 year incidence of 0.07% in over 10,000 injections)\textsuperscript{28}

Rare complications include

1. Hemorrhage;
2. Precipitated angle closure;
3. Elevated intraocular pressure (IOP) with perfusion compromise;
4. Wound leak and hypotony;
5. Anaphylactic reaction to either the agent or periprocedural materials.

Complications related to the agent used

A. Triamcinalone

1. Non-infectious Endophthalmitis (Incidence 0.87 to 5%\textsuperscript{29})

Mainly supposed to be due a reaction to the diluent in which the Triamcinalone crystals are suspended and presents as in Fig 4 with a sterile hypopyon in a relatively quite eye.

Another presentation is white crystalline deposits in the anterior chamber as in Fig 5. This could be due to migration of the Triamcinalone crystals into the anterior chamber. Clues to differentiating this from true endophthalmitis include earlier onset, better visual acuity at presentation, lack of growth on culture or organisms on gram stain, and better final visual acuity.
The new preservative-free steroid formulated specifically for Intravitreal injection are currently available, and may help alleviate these problems.

2. **Ocular hypertension (usually in 1st 3 months)**
Various studies have reported mild to moderate IOP elevation seen in 28%-42% of patients, which may occur as early as one to two weeks but more commonly at around six to eight weeks after the injection. But generally this can be easily controlled by medications. However Singh et al have reported three cases of intractable glaucoma following IVTA injection, which required surgical glaucoma intervention. A fourth patient required filtration surgery and vitrectomy to remove residual steroid. Although these cases are rare, these problems need to be kept in mind. This is all the more important in known glaucoma patients as steroid responders are more in this group.

3. **Steroid induced cataract (10-30 %)**
The cataractogenic effect of steroids is well known. Gilles et al reports Cataract surgery being performed in 29% eyes treated with Triamcinolone acetonide versus 5% in placebo group (P = .003) after 12 to 34 months of follow up. Another study reported a significantly increased degree of cataract in all layers of the lens after a mean follow-up of 7 months. The increase in the degree of cataract correlated significantly with the duration of follow-up and the number of injections with IVTA.

B. **Antibiotics**
Retinal toxicity of some of these drugs has to be considered while giving Intravitreal antibiotics. The dose has to be exact as the margin of safety between the “therapeutically effective” and “toxic to retina” concentration is narrow. For instance, gentamycin, one of the most effective antibiotics against Gram-negative organisms like Pseudomonas, has been notorious for the causing macular infarction, when more than the prescribed dosage of the drug had been injected intravitreally.

**Intravitreal injections –Guidelines for maximising the safety of the procedure**
The number of Intravitreal injections is set to grow exponentially as the number of agents available for such injections and the number of diseases where these have been found effective are increasing. In order to ensure optimal outcomes and to minimize complications, strict adherence to proper procedure and guidelines is required.

An expert committee was set up in May 2004 for formulating this. The recommendations of this committee form the basis of the current best practice guidelines for safe Intravitreal injections.

**Pre-injection Protocol**
1. Obtain informed consent
   - Take time to talk to the patient and make sure that his expectations are realistic. The pros and cons are to be discussed and also about what to expect postoperatively and what to do and what not to do. In case of drugs used off label (eg Triamcinalone; Bevazizumab etc) the same should be mentioned specifically and the patient apprised of this fact.
2. Obtain pre injection visual acuity, IOP and dilate the patient.
3. Check the eye lid margins and, if blepharitis is present, first treat the same with eye lid scrubs twice daily and topical antibiotic ointment for 3-5 days prior to injection and recheck lids before injection. This however may not be possible in emergency situations like Endophthalmitis. In such cases a full shielded speculum should be used during the procedure, which will act as a physical barrier to the meibomian gland secretions.
4. Glaucoma is a relative contraindication for Intravitreal Triamcinalone. But if central vision is threatened then the same may be given after explaining the risks to the patient and after the intraocular pressure is medically controlled.
5. Pretreat with topical antibiotics.
   - Use 3rd or 4th generation fluoroquinolones (less resistance and broader coverage).
   - Use antibiotic drop four times daily for three full days prior to injection, (every 5 minutes over 15-20 minutes immediately before injection is another suggested regimen).

6. Try to elicit history of allergy. If povidone allergy is suspected, confirm with skin patch test.

**Peri Injection Protocol**

1. Take time to confirm the eye with patient and double check with case records and objective data (angiogram and/or OCT).
2. Standard aseptic precautions like draping the patient and sterile gloving should be employed. Use fresh pair of disposable gloves for each patient. (Draping was however not considered essential by the expert's committee)(Fig. 6)
3. Apply drop of topical anesthetic (proparacaine or tetracaine).
4. Insert sterile cotton tip applicator soaked in 4% lignocaine into the inferior fornix for three applications several minutes apart.
5. Apply povidone iodine to eyelid margins, eyelashes, and conjunctival surface. But do not scrub the lid margins.
6. Insert sterile speculum soaked in povidone iodine (placed in a small sterile glass or metal cup).
7. Supplemental subconjunctival anesthetic in addition to topical anesthetics are used by many surgeons, but is not necessary. (Fig. 7)
8. Apply additional drop of povidone iodine to the site of injection.
9. Insert needle 3 mm (aphakic & pseudophakic) to 4 mm (phakic) posterior to limbus in the inferotemporal quadrant ie 5 or 7 o'clock location. (Fig. 8,9)
10. Always use a fresh needle and not the one that was used to draw up the medication. Needle of 27 G. or smaller with a length of 1/2 to 5/8 inches is generally recommended. Gently inject the therapeutic agent, and wait for 10 seconds and then remove needle. Apply a tamponade/light pressure with a sterile cotton-tipped applicator to the needle track as you withdraw the needle. Then maintain the tamponade for a few seconds. Check for an expanding localized area of subconjunctival fluid/vitreous. If present, reapply tamponade with a sterile cotton-tipped applicator for 30 additional seconds.
11. An anterior chamber tap is best avoided, but has to be considered if there is a risk of compromising the central retinal artery perfusion on account of the volume added to the vitreous. Up to 0.1 cc of a liquid (noncompressible) and as much as 0.35 cc of a gas (compressible) can be injected without the need to tap the anterior chamber.
12. Gently remove speculum.
13. Check with indirect ophthalmoscope for vitreous hemorrhage and optic nerve perfusion.
14. Check vision. If patient is not counting fingers, inspect the retina for perfusion of the central retinal artery. Wait up to five minutes for perfusion to return. If it doesn't then reprepare with povidone iodine and perform an anterior chamber tap.
15. Apply topical antibiotic ointment to inferior fornix.
Post Injection Protocol

1. Instruct patient not to touch or rub eye, particularly for next 72 hours. If patient or guardian feels patient will rub eye, consider patching eye for first 24 hours.

2. Prescribe post-injection Topical antibiotics (3rd or 4th generation fluoroquinolones preferred) for four days.

3. Monitor IOP after injection and provide therapy when elevated IOP warrants intervention. However there is no clear consensus regarding the intraocular pressure level at which the patients can be comfortably discharged.

Follow Up

First follow up is generally at 1st week. The patient is also instructed to contact the clinician or the hospital immediately in case of any increased redness, pain or blurring of vision or any other discomfort. Further follow up after the 1st visit will be dictated by the specific needs of the patient and at the discretion of the surgeon.

Conclusion

A variety of conditions are now treated with Intravitreal injections, including neovascular age-related macular degeneration, proliferative and non-proliferative diabetic retinopathy, cystoid macular edema and retinal vein occlusions and the results have been quite encouraging. As new and new agents are getting approved for Intravitreal injection, this mode of treatment is all set to revolutionize the way we approach some of these potentially blinding retinal diseases. Many more randomized controlled studies are required and are being done to establish the safety and effectiveness of these medications and to standardize the dosing. The safety and efficacy of the procedure itself is a very important factor deciding the outcome of the treatment and strict observance of the guidelines is important to ensure the desired outcome with no complications.

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Optical Coherence Tomography in Macular Disorders

Dr Valsa Stephen, Dr Meena Chakrabarti, Dr Sonia Rani John, Dr Arup Chakrabarti

A retinal specialist uses a wide variety of techniques to evaluate retinal pathology such as fundus photography, fluorescein and indocyanine green angiography and ultrasonography. However these techniques of imaging do not give detailed information on the cross sectional retinal anatomy nor do they provide quantitative retinal thickness measurements.

A need has existed in medicine for a technology capable of ‘optical biopsy’ imaging at or near the resolution of histopathology without performing an excisional biopsy. Advances in optics, fibre optics and laser technology has led to the development of a non contact, high resolution, optical biomedical imaging technology called “Optical Coherence Tomography.”

Thus Optical Coherence Tomography (OCT) provides a technique of imaging that is non-invasive, non-contact, provides high degree of resolution and provides cross-sectional images of the retina of 10 micron resolution comparable to a histopathological section. OCT yields information about retinal tomography that is complementary to the conventional topographic techniques.

Principle

The working of OCT is similar to ultrasound, but with two major differences.

In ultrasound, a high frequency sound wave is launched into the eye with the help of a probe and the sound wave is reflected from different boundaries between microstructures. However, the OCT uses light rather than ultrasound. The speed of the light is almost a million times faster than sound and this difference allows the measurement of structures with resolution of =10 µ compared to 100µ scale for ultrasound. Secondly OCT does not require contact like the ultrasound.

A broad band–width near infrared light beam (820nm) is projected on to the retina. It gets reflected from the boundaries between the microstructures and also gets scattered differently from tissues with different optical properties. It then compares the echo time delay of the light that is reflected from the various layers of the retina with the echo time delay of the same wavelength that is reflected from a reference mirror at a known distance. The interferometer then combines the reflected pulses from the retina as well as reflecting mirrors resulting in a phenomenon known as interference. This interference is then measured by a photo detector, which determines the distance traveled by various echoes by varying the distance to the reference mirror. This finally produces a range of time delays for comparison.

The interferometer integrates several data points over 2mm of depth to construct a tomogram of retinal structures. It is a real time tomogram using false color scale. Different colours represent the degree of light back scattering from different depths of retina.

The image thus produced has axial resolution of =10µ and transverse resolution of 20µ.
**OCT Vs Standard Techniques of Imaging**

1) **A + B Scan USG**

Requires physical contact with the eye and are routinely used in ophthalmic diagnosis with a typical resolution of 150 µ compared to 10 µ available with OCT.

2) **Digital Fluorescein Angiography**

Macular hyperfluorescence seen on DFA correlates well with increased retinal thickness measured with OCT. Though FFA provides information about the origin of macular fluid leakage and retinal vascular abnormalities, it does not give information about cross sectional retinal morphology or high magnification surface topographic images like the OCT.

3) **Retinal Thickness Analyser & Heidelberg’s Retinal Tomography**

HRT and RTA are the other commercially available instruments in addition to OCT to measure retinal thickness and evaluate retinal morphology. RTA may produce falsely elevated retinal thickness measurements and produces images less effectively than OCT in eyes with media opacities.

The HRT may be more effective than RTA and OCT to image the ocular retina in the presence of retinal haemorrhages and hard exudates. However, the images are acquired relatively slowly.

**Ultra Resolution Optical Coherence Tomography**

This enables in vivo cross sectional imaging of macular pathologies with an axial resolution of 3 µ and visualisation of sub cellular as well as intra retinal pathologies. All the major intraretinal layers can be visualized non invasively in vivo by this.

**Normal macular OCT Scan**

On a 10mm horizontal line scan passing through the foveal centre (A), one can clearly demarcate two major landmarks namely optic disc towards the right and fovea towards the left. The optic disc is easily identifiable by its contour- the central depression representing the optic head cup and the stalk continuing behind the anterior part of the optic nerve. The vitreous anterior to the retina is non reflective and is seen as a dark space. The interface between the non-reflective vitreous and back scattering retinal fibre layer (NFL) is highly reflective and increases in thickness towards the optic nerve. The posterior boundary of the retina is marked by a hyper reflective layer that represents the Retinal Pigment Epithelium (RPE) and choriocapillaries. The choroid and sclera are not seen well on tomograms as the signal attenuates by the time it reaches these structures. Just anterior to RPE-choriocapillaries complex is a minimally reflective layer that represents photoreceptors. Above this layer of photoreceptors are alternating layers of moderate and low reflectivity that represent different layers of neurosensory retina. The retinal blood vessels within the neurosensory retina show back scatter and also cast a shadow behind.

![Fig 1. Normal macular scan](image)

**Image Interpretation**

There are two ways of interpreting the OCT scan - Objective and Subjective.

**Objective**

Pathologies can be hyperreflective or hyporeflective. Hyperreflective lesions include hard exudates, blood and scars. Hyporeflective lesions include retinal oedema and hypopigmented lesions of RPE.

**Subjective**

Subjective can be qualitative and quantitative. Qualitative includes retinal thickness/ volume analysis as well as change analysis.
This technique has been increasingly used to evaluate and manage a number of retinal diseases such as
1) Diabetic Macular Oedema
2) Macular holes and cysts.
3) Age related macular degeneration
4) Identify Vitreomacular traction and epiretinal membranes.
5) CSR
6) Identify and quantify macular oedema and atrophy.
7) Measure retinal thickness change in response to therapy.

**Diabetic Macular Oedema**

The conventional 2-dimensional imaging techniques including fundus photographs and fluorescein angiography give a topographic view of the retina that helps delineate treatable lesions but are unable to depict the changes occurring within the retinal layers. In addition to allowing appraisal of intraretinal changes, OCT helps to diagnose macular traction, taut posterior hyaloid membrane, foveal serous detachment and lamellar macular holes which are often missed by clinical examination alone.

**Role of OCT in Diabetic Macular Oedema**

1) Defining the disease pattern: Flattening of the foveal pit may be earliest sign. Five distinct patterns seen are
   i) Sponge like retinal thickness- Seen as macular thickening with reduced optical back scatter. Hard exudates are seen as hyporeflective lesions with shadowing effect (Fig. 2).
   ii) Cystoid macular oedema : Seen as hyporeflective spaces of varying size mainly in outer retina Fig 3.

2) Monitoring response to an intervention. OCT gives an ultra structural detail of changes in the retinal layer and quantifies retinal thickness thus making it easier to monitor response to therapy.

3) Defining indications for Parsplana Vitrectomy. Foveal tractional detachment and taut posterior hyaloid membrane are definite indications for surgery while cystoid macular oedema or serous detachment due to mechanical traction are relative indications.

**Macular Holes**

OCT is a very useful tool in the diagnosis and management of macular holes.

1) It helps in differentiating various retinal lesions that cannot be clinically distinguished. eg: lamellar or full thickness macular holes, macular cysts, foveal detachment of retinal pigment epithelium or neurosensory retina and epiretinal membrane with pseudo-hole. Full thickness macular holes show a breach in all layers of retina while lamellar macular
hole shows only partial loss of tissue Fig. 5(A & B) with steep foveal contour. RPE detachment (Fig. 7) and macular cysts (Fig. 6) are characterized by the presence of a well defined, round, localized area of hyporeflectivity in the outer retinal layers subretinally. Macular pseudoholes are characterized by contour of foveal pit, thickened edges, steep foveal contour, presence of retinal tissue at the base.

2) OCT helps in staging of macular holes that helps in evaluating surgical intervention.

OCT has led to a new classification of macular holes.

Stage 1 A: Partial thickness pseudocyst with perifoveal vitreous detachment (Fig. 8).
Stage 1 B: Full thickness pseudocyst with roof (Fig. 9).
Stage 2 A: Full thickness tear or pseudo macular hole: Partial opening of roof, focal vitreous attachment to flap.
Stage 2 B: Full thickness operculated macular hole; Traction to retina released. <400µ
Stage 3: Full thickness operculated macular hole >400µ Traction to retina released.
Stage 4: Full thickness macular hole; PVD complete.

3) OCT gives quantitative information regarding the diameter of macular hole that helps in prognosticating response to surgical intervention.

4) OCT helps in surgical decision making in macular holes surgery
   a) Stage 2 A holes require only limited surgical intervention in the form of limited pars plana vitrectomy and fluid air exchange
b) Stage 2 B or larger holes alone will require pars plana vitrectomy with ILM peeling.

5) Perioperative OCT evaluation shows the following 4 foveal patterns on OCT as described by Desai VN, Hee HR, Wong C, Puliafito C (1999).

1) Open: Full thickness macular hole indicating failed surgery.
2) Closed: Re-approximation of hole edges with relatively normal foveal contour and normal foveal thickness.
3) Thin: Closed macular hole with foveal thickness \(=100\mu\).
4) Foveolar Detachment: Reapproximated edges but separated from RPE.

6) OCT Pattern of closure determines the visual prognosis. Two Patterns are described by Vishali Gupta, Amod Gupta, Mangat R Dogra.

Type 1 Closure: Closure without neurosensory deficit.

Type 2 Closure: Closure with neurosensory deficit.

Smaller sized holes have better prognosis as they tend to show type 1 closure.


U Type: Normal foveolar contour
V Type: Steep Foveal Contour
W Type: Foveal Defect of neurosensory retina

Visual return = U > V > W

The larger holes are associated with poor visual outcome and closure without restoration of neurosensory retina. Hole Form Factor of less than 0.5 is reported to be associated with poor surgical closure rates.

Fig 10. Stage 2A macular hole

Fig 11. Stage 3 macular hole

Fig 12. Stage 4 macular hole

Fig 13. Demonstrating the calculation of HFF

\[
\text{Hole Form Factor} = \frac{c+d}{d}
\]

a = diameter of base of hole.
b = minimum diameter of hole
c = length of left arm
d = length of right arm

Age Related Macular Degeneration

OCT is complimentary to clinical examination, fluorescein angiography and indocyanine green angiography in disease categorization.

Drusens: Drusens are seen as areas of focal elevation of RPE with no optical shadowing underneath. (Fig. 14)

Geographic Atrophy: Seen as increased optical reflectivity from the choroid due to increased penetration of the light through the overlying atrophic retina.
Neovascular ARMD

1. Classic CNVM: there is disruption/thickening of the RPE-Chorio-capillaries band with the thickened edges demarcating the boundaries of CNVM.

2. Occult CNVM: Here boundaries are poorly defined. They also have accompanying subretinal fluid/retinal oedema that helps differentiate them from pigmentary atrophy.

3. Serous PED: Elevation of RPE with an optically clear space underneath and optical shadowing.

4. Fibrovascular of PED: Elevation of RPE with a clear demarcation between RPE and underlying structures that appear as yellow/green. Optical shadowing is absent.

5. Hemorrhagic PED: Same as serous PED but with back scattering from RPE which attenuates towards the outer retina with absent choroidal reflections.

6. Disciform Scar: Seen as area of increased reflectivity from underlying choroids that is consistent with atrophy of overlying RPE. There is no associated subretinal fluid (Fig. 15).

Epiretinal Membranes

OCT helps in confirming the diagnosis of epiretinal membranes. It demonstrates the extent of the membrane, vitreoretinal interface, status of posterior hyaloid membrane associated changes like cystoid macular oedema, vitreofoveal traction, macular hole etc. This helps in prognosticating the outcome of surgery in these eyes. OCT also helps in followup of eyes following Pars Plana Vitrectomy, thus obviating the need for repeat fluorescein angiography (Fig. 14).
Central Serous Retinopathy

Like fluorescein angiography, OCT shows certain characteristic features including

1) Serous Retinal Detachment: Characterised by elevation of neurosensory retina due to fluid accumulation between RPE and neurosensory retina. (Fig. 18).

2) PED: PED is seen in almost all cases of CSR and has been found to correspond to the point of leak on fluorescein angiography (Fig. 19).

Small PEDS which may be missed on clinical examination can be demonstrated by OCT. The complication of central serous retinopathy can be diagnosed such as CNVM, subretinal fibrin, RPE rip or atrophy. It is helpful in diagnosis of a typical cases and differentiating them from ARMD, metastatic deposits etc.

Retinal Vascular Occlusions

OCT documents either macular oedema or atrophy. The area of ischaemic pale retina appears hyperreflective during acute phase and regains its original reflectivity over a period of time. OCT thus helps in documenting improvement by quantifying retinal thickness.

Retinal Vasculitis

OCT is helpful in diagnosing macular oedema, cystoid macular oedema, epiretinal membranes, pseudo macular holes and tractional retinal detachment. It is also helpful in monitoring response to treatment objectively.

Retinal Trauma

Closed globe injuries can damage the retina and underlying choroids and include commotio retinae, choroidal ruptures with choroidal neovascular membrane, macular cyst, macular hole, retinal detachment, subretinal hemorrhage etc. OCT helps in diagnosing and monitoring the development of new changes and monitoring response to therapy.

Chorioretinal Inflammations

OCT is able to define the extent, depth and thickness of the inflammatory lesion and the layer involved. The associated secondary changes like cystoid macular oedema, choroidal neovascular membrane, epiretinal membrane, subretinal fluid and sub retinal fibrosis can be demonstrated.

Other Uses

OCT can diagnose macular involvement in various retinal diseases such as heredodystrophic disorders, juxtafoveal telengectasia, intraocular metastasis, and for macular involvement following retinal detachment surgery.

Reproducibility

OCT measures retinal thickness with a high degree of accuracy and reproducibility for a given patient from one examination to the next and also when the examination is performed by different examiners.

Disadvantages

Although OCT is an extremely valuable technique, there are limitations and pitfalls to its use.

1. OCT images are degraded in the presence of media opacity like dense cataract.

2. The scan quality depends on the skill of the operator

3. OCT may not be possible with uncooperative patients.

4. Foveal thickness measurement may be inaccurate if scan is not centred on the fovea.

NEWER DEVELOPMENTS IN OCULAR IMAGING

OCT/SLO Combination Imaging Systems

This system generates OCT images using multiple T-scans instead of A-scans as in the conventional OCT systems. The result is superior image quality with the added advantage of simultaneous C-Scan SLO confocal imaging. There is a simultaneous confocal pixel to pixel correlation between the SLO image and OCT image. It is possible to register where the pathology is located and how it is oriented on the fundus. This overcomes one of the major drawbacks of conventional OCT. The fast C-Scan OCT stack features provides both 3D topographic volumes and surface topographic maps.
These can be compared using subtraction to detect retinal thickness changes over time and assess response to treatment.

**Spectral OCT**

Offers ultra fast acquisition rates of OCT images with improved resolution (4-6 microns) and a higher signal to noise ratio (SNR). This system also provides a simultaneous confocal scanning ophthalmoscope (SLO) image of the fundus and generates full 3D Topographic and tomographic images. Software allows users to automatically compare two topographic maps, subtract them from each other and evaluate changes over time. A new 3D advanced software allows users to automatically remove different layers of the vitreo-retinal and inner retinal structure to improve the observation and assessment of the pathology.

**3D OCT With Non-mydriatic Retinal Camera**

3D OCT images are got up to 50 times faster than existing time domain technology to reduce patient eye movement and to increase patient comfort. It provides a three dimensional virtual microscopic view of the specific targeted area, with accurate retinal registration for the most reliable and reproducible measuring results.

**References**


**ON A LIGHTER VEIN**

Of Pupils… and Teachers

Dr. Raghu Varma

Our temper and temperament; diagnosis and dealings; in fact the whole philosophy of life would have been inculcated into us by or experiences - in and out of classrooms. And much of it can be attributed to our peers and teachers. All of us have had remarkable and not so remarkable teachers and friends. Some of them simply refuse to fade into oblivion.

During my undergraduate days I had a classmate who was a body builder-turned-medical student. He was, in fact, the ‘Mr.Kerala’ of the previous year and had got in to the medical college via the sports quota. In spite of his remarkably formidable physique, he was very queasy about the sight of blood and sickness, and dead bodies in particular. And needless to say, he had to make several attempts before he could pass Anatomy. But we remained close to each other in spite of him being four batches behind me in clinics; and we used to have ‘combined study sessions’. He was a firm believer in what he called ‘spontaneous cure’. “There is no point in treating any disease”, he would say. “Because if the patient is going to get well, he will; and if he is going to die, he will”. His dictum in his own peculiar English was “what what things will happen; that that things will happenae happen”, enunciated with an elongation of the happen-ae part (italics are mine). When I see the unexpected results of some of the surgeries and other procedures we do I really feel like agreeing with him.

He reminds me of another huge senior of mine, who was in fact my first roommate too. On our first night together I discovered why he didn't have a roommate. He use to SNORE. And I, who never had a roommate before was left sleepless. Being about half his weight and size, I was reluctant to wake him up and tell him to snore a little less loudly. Suddenly he turned over in his sleep and fell totally and eerily silent. I bolted upright and after a few suspenseful seconds went over and put my hand under his nose. What a relief! He was breathing. Friends, in the OT, when the pulse-oxymeter falters, it gives one a little flutter like the one I had that night!

Many are such happenings and happenstances that crowd into ones memory at unexpected moments in one’s OP and OT.
Trabeculectomy - revisited

Dr. Thomas George T., MS

Evolution of the procedure

The seminal importance of the intraocular pressure in pathogenesis of glaucoma led to a wide variety of surgical procedures being devised to reduce the intraocular tension. These procedures evolved over a period of time to the trabeculectomy, which has stood the test of time the longest. William Mackenzie, in 1830, suggested a sclerotomy to relieve tension. By 1854 he preferred using a paracentesis. Luis de Wecker, pupil of the great Von Graefe, first suggested the idea of a filtering cicatrix and developed the anterior sclerotomy (using a Von Graefe knife puncture counterpuncture and an incomplete Von Graefe ICCE incision leaving a bridge of conjunctiva at the superior limbus – effective temporarily till healing occurred). Col. Robert Henry Eliot, superintendent of the Madras Eye Hospital - the present Regional Institute of Ophthalmology, Chennai, developed and popularized his corneoscleral trephine, further improving on the filtering scar concept. Felix Lagrange in 1907 combined a sclerectomy with an iridectomy and established a more permanent filtering scar. Cairns in 1968 described a new concept of partial thickness filtering procedure – trabeculectomy. Thus it took one and a half centuries for the basic concept to evolve. Further refinements are still being developed.

Type of surgery and mechanism of action

It is a guarded filtration procedure. This means that a partial thickness scleral flap lends resistance to flow of aqueous from the anterior chamber to the sub conjunctival space (Figure 1). There is a basal peripheral iridectomy to deal with any pupillary block component and more importantly prevent the underlying iris from plugging the trabeculectomy osteum by excising it. Quite often the surgical osteum is anterior or includes more than just the trabecular meshwork and hence the term filtering surgery is more accurate in description. But the good old name has stuck.

Indications

The only real indication is medically uncontrolled glaucoma. The target intraocular pressure for that patient is not achieved with medications that the patient can tolerate and can afford for chronic therapy. In Chronic angle closure glaucoma with more than half the angle closed by synechiae used to be an indication, but now with more options among medicines for IOP reduction one can put in a PI and try medical therapy for IOP reduction. Having said this I know that medical
therapy fails and we have to opt for surgery more often in angle closure and secondary glaucomas when compared to primary open angle glaucoma

**Procedure**

The patient is worked up as for any intraocular procedure and informed consent obtained. The anaesthesia can be monitored local anaesthesia or general anaesthesia depending on age and patient’s ability to cooperate.

Preparation and draping is as for any intraocular procedure. Superior quadrants are preferred for trabeculectomy as inferior quadrant filtering blebs are notorious for infections. Exposure is obtained by a speculum and a traction suture (a Superior rectus bridle suture or a 5-0 silk corneal limbal suture). A clear corneal paracentesis is done slowly to prevent a supra choroidal haemorrhage if IOP is high, both to decompress the globe and for ease of entry later to reform the AC. The conjunctival incision can be limbal (fornix based flap) or 7-8mm behind limbus (limbus based flap) to expose sclera of 5mm square. If antimitotic is to be used, one can use the same in a sponge at this stage. Light cautery is used for haemostasis and a one third to half thickness scleral flap is fashioned in a shape of the surgeon’s choice (Square or triangle) till clear cornea is reached in the bed of the flap where a rectangular window is cut out (anatomically this would be at the limbus anterior to Schwalbe’s line). A basal peripheral iridectomy is done via this osteum to prevent iris tissue from blocking it. Now apposing sutures are put at the apices of the scleral flap to close it lightly (not tightly). The conjunctiva is closed.

**Factors determining IOP after surgery**

As any glaucoma surgeon will swear, the post operative IOP after glaucoma surgery is determined mostly by factors beyond our control (even supernatural). But then there are a few factors we can use to our advantage to adjust resistance to flow of aqueous and thereby the IOP.

**Lateral overlap**

The overlap of the flap from the edge of the excised block is usually less to the side than to the flap’s posterior edge (Figure 2). Thus the resistance to flow of aqueous is less laterally than to the posterior edge. This distance therefore determines the resistance to filtration. Most surgeons who use triangular flaps also excise rectangular blocks in the bed. Here the least resistance would be determined by the distance from the apex of the block to the side of the triangle.

Thus if one uses a 4mm wide rectangular scleral flap and a 3mm block excision the lateral overlap would be the same as a 3mm flap and a 2mm block excision i.e., half a millimetre on either side. Theoretically both should have the same resistance to flow of fluid. (In practice the bigger scleral flap has a slightly higher resistance).

**Flap Thickness**

If the flap is thinner the filtration is more. Ideally the flap should be one third to half scleral thickness. Less than this and the flap will overfilter through it like a sieve. And a thicker flap will snugly fall back in the depression from which it was dissected and seal the wound fully.

**Sutures**

The next determinant for IOP would be the scleral flap closure. Sutures at the apex / apices of the flap, i.e., the corner sutures, are more effective in closure than subsequent sutures. If these are too tight they work as efficient sutures closing the flap tightly and the IOP will rise. Subsequent sutures, in between, have less of an effect on filtration in comparison to the apical sutures. So if a releasable suture is used or if a suturolysis is done it should be an apical suture to achieve reasonable pressure adjustment.
IOP in immediate post op

If in the immediate post op period the IOP is low then the aqueous inflow is decreased by the ciliochoroidal detachment. This means less fluid goes through the trabeculectomy osteum to maintain the bleb in the immediate post op period. This would cause the bleb to heal into a small or flat bleb. Eventually, when the aqueous inflow picks up the IOP would go up and out of control.

Healing

Healing or fibrosis is the biggest determinant in late post operative IOP. Sub scleral flap and subconjunctival fibrosis cause the resistance to flow after a trabeculectomy (Figure 3). Of these two the subconjunctival fibrosis contributes maximally. To maximally control this we need to understand the factors that contribute to increased fibrosis.

Ring of steel

This is a relatively new concept (Figure 4). This phenomenon came into being after the advent of wound modulation using antimitotic agents. Antimitotic agents kill dividing cells (in the subconjunctival area this reads as Fibroblasts). So when mitomycin is placed over a limited area of sclera all the fibroblasts there are killed and no fibrosis can occur here. The edge of this zone has less effectively killed or partly killed cells. These cells release tissue breakdown products for a long time (months to almost a year). This again incites inflammation that attracts viable fibroblasts from surrounding areas (not affected by the antimitotic) causing an exaggerated fibrosis than what would have occurred without use of antimitotics.

This fibrosis causes a “ring of steel” that delimits the bleb posteriorly. Now we have an avascular thin walled (bubbles like) bleb with congested edges. This bleb can have a high IOP if the wall is thick enough or it can extend anteriorly and overhang onto the cornea.
the cornea or dissect into it. Sometimes the wall is so thin that fluid “weep” or exudes out through its surface (now it is a time bomb for blebitis).

To prevent this from happening, it has been suggested that the antimitotic be used over a wider area surrounding the bleb rather than the area of scleral flap alone.

**Wound modulation in Filtering surgery**

The logical answer to fibrosis is to knock out the fibroblasts by inducing their apoptosis. There are a few options explored for this:

1. **Antimitotic drugs** - Mitomycin C, 5 Fluorouracil
2. **Anti transforming growth factor β2**
3. **Gene therapy** - insert antiproliferative gene using adenovirus carrier
4. **β irradiation of conjunctiva** - 1000 rads.
5. **Photodynamic therapy** - Carboxy fluorescein, Blue light radiations
6. **Suramin** - Inhibits a wide range of growth factors.

Of all these, the only one widely used now is the antimitotic drugs. The two drugs in use are worth comparing. Mitomycin is about a hundred times more potent, gram to gram, when compared to 5-fluorouracil. It penetrates deeper and acts for a longer time. The accelerated apoptosis of fibroblasts continues for a year with mitomycin explaining the late postoperative hypotonies seen in children and young adults. Both are water soluble and diffuse out of the sponge fast.

<table>
<thead>
<tr>
<th>Drug</th>
<th>5 – FU</th>
<th>MITO C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>X</td>
<td>100 X</td>
</tr>
<tr>
<td>Solubility</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Penetration</td>
<td>Shallow – does not go past sclera</td>
<td>Deep – diffuses up to ciliary body</td>
</tr>
<tr>
<td>Diffusion</td>
<td>Fast - out of sponge in 3 minutes</td>
<td>Fast - 68% out of sponge in 1 minute</td>
</tr>
<tr>
<td>Concentration</td>
<td>50mg/ml</td>
<td>0.2-0.4mg/ml</td>
</tr>
</tbody>
</table>

Both the drugs can be used for per operative application sub conjunctivally (with such fast diffusion it makes little difference if placed sub scleral flap) for 2 – 4 minutes as is decided depending on age of patient, chance of fibrosis and inflammation. Applications over one minute to be effective need change of sponge to compensate for diffusion loss from the sponge. Excess drug is washed off with balanced salt solution after application. And the surgery proceeded with.

Post operative top up by subconjunctival 5 fluorouracil can be done with 5 mg in 0.1ml sub conjunctival injections (these are effective in the first 3 weeks). These injections can be given daily in the inferior fornix for up to 7 injections. The appearance of punctuate erosions on the corneal epithelium is a contraindication for further injections (figure 5).

An encysted bleb can be needled and a 0.1 ml injection of either 50mg/ml 5 FU or 0.2mg/ml mitomycin subconjunctivally away from the trabeculectomy osteum can be given to salvage a trabeculectomy in the immediate post op (works till about 3 months).

**Complications**

**Intra Op**

Conjunctival button hole or perforation can occur and a meticulous microsurgical repair is to be done.

The scleral flap can be amputated. Here if the inner osteum is not yet fashioned, the best option would be to start again in another quadrant. If the inner osteum is already made a meticulous reapproximation of the flap will need to be done.

Haemorrhage into the subconjunctival area can compromise filtration by fibrosis but nothing much can be done about it. Hyphema can be washed out. Sudden decompression can trigger a suprachoroidal haemorrhage with sudden flattening of the anterior chamber with rise in IOP and a change of glow in the pupil to dusky red. This needs to be identified and the flap sutured down tightly (before it proceeds to become an expulsive haemorrhage).

![Fig. 5. Punctate erosions are a contraindication to further 5 FU injections](image-url)
Choroidal effusion and malignant glaucoma can rarely develop intra operatively (management described later). One can also injure other intraocular tissues inadvertently. The PI can become a CI. One can injure the lens capsule or the zonules while doing a PI and caused vitreous loss. The pull on the iris root or an entry behind the scleral spur during the trabecular block excision can result in a cyclodialysis cleft.

**Immediate Post op**

Ocular hypotony develops due to excessive filtration or ciliary shutdown (or inadvertent continuation of antiglaucoma medications!). Excess filtration would have a large diffuse bleb if there is no conjunctival edge leak. If on the Siedel test there is a leak then the conjunctival edge needs to be tacked down with horizontal mattress sutures at the limbus and additional sutures elsewhere. One can use large diameter bandage contact lenses for small leaks (Often the hypotonous globe infolds and the contact lens falls off!).

Hypotony soon develops into shallow anterior chamber as choroidal detachment develops. Here the shallow AC is uniformly shallow and not an iris bombe as in pupillary block. **Hypotony → ciliochoroidal detachment → apposition of lens equator to the ciliary processes → misdirection of aqueous behind the vitreous face → now IOP goes up → this pressure on the vitreous now dehydrates it and makes it less permeable to water, thus trapping fluid behind it → IOP rises drastically with a flat AC → MALIGNANT GLAUCOMA.**

Another reason for a flat AC with high IOP is a late suprachoroidal haemorrhage. Medical treatment of shallow AC is atropine drops. It works for pupillary block, helps in ciliochoroidal detachment and often controls malignant glaucoma. If it fails we proceed to perform the Chandler’s **three step diagnostic and therapeutic procedure.**

This procedure deals with diagnosis and management of post operative shallow anterior chamber. **Step 1:** Peripheral iridectomy, to rule out and treat pupillary block. In a trabeculectomy we make sure the PI is patent and not bound down by synechiae.

**Step 2:** Sclerotomy. In the inferotemporal quadrant after limited peritomy and cautery a 3mm radial sclerotomy is fashioned centred 3.5 mm from the limbus (so as to be anterior to the vitreous face and behind the lens equator). This would drain a ciliochoroidal effusion as clear fluid and supra choroidal haemorrhage as blood and the AC can easily be formed via the paracentesis. If the sclerotomy is dry a presumptive diagnosis of malignant glaucoma is made and we proceed to step 3.

**Step 3:** Deep vitreous surgery. Chandler used a Wheeler knife (sharp on both sides like an MVR knife) to go into the vitreous at 3.5 mm from limbus aiming for the “centre of the globe” for 12mm and sweep the knife to incise the vitreous face. This was followed by aspiration of fluid using a 26 G needle. In this day we can go in with a vitrectomy cutter 3.5 mm form the limbus and do an anterior vitrectomy to achieve the same end. With these 3 steps we have definitive diagnosis and would have treated the concerned condition.

Blebs can cause dellen formation. Uveitis, hyphema and cataract can develop post op. And of course infection. In advanced cases with macular split fixation on fields, there is a ten percent risk of wipe out or snuff out of vision after surgery, due to either a spike in IOP or a macular haemorrhage due to hypotony. This should be informed to the patient prior to surgery and consent obtained. **Late**

Bleb infection or blebitis is definitely the most disastrous complication in this group. These are very difficult to cope with. It is essentially a corneal ulcer starting with a perforation already in place. Treatment is as for any post op endophthalmitis though results are poorer than with post cataract scenario. And if the eye is saved the trabeculectomy invariably fails thanks to the inflammation.

Cataract tends to mature faster after glaucoma surgery. Cataract surgery should be undertaken as late as possible and an interval of one year reduces chances of failure of the trabeculectomy. Bleb leaks can occur late now with use of antimitotics (cellular apoptosis goes on for a year with use of mitomycin). These late leaks are best managed with a
conjunctival autograft over a wide area (if conservative treatment with acetazolamide fails to close the fistula by reducing flow through it).

Scleral staphyloma and sympathetic ophthalmia are also described as complication after trabeculectomy.

Hypotony with diffuse bleb can be treated by autologous blood injections peribleb. If this fails in 2 weeks, the blood is injected intrableb. Blood and its breakdown products encourage fibrosis. If these measures fail, one can incise conjunctiva radially to limit the bleb and suture it down with absorbable continuous suture onto sclera to incite fibrosis to limit the bleb.

Thus though trabeculectomy is the most widely used glaucoma surgery, it is still not the final solution. It has its advantages and definitely its limitations. Quite often the bigger skill is not in the surgery but in deciding “when” and “when not” to operate.

References


Peter Roget and his Thesaurus

Prof. Padmaja Krishnan, Kozhikode

All of us are familiar with dictionaries where words are arranged in alphabetical order with their correct pronunciation, meanings, derivation and usage.

Not so well known perhaps is a thesaurus, a book of synonyms and antonyms. Here a word is listed according to its meanings and distinctions are drawn between similar words and their opposites. In both Greek and Latin the word literally means a “treasure or storehouse”. The thesaurus helps writers choose the right word and use it in the right context. For those who use it regularly, it is as important a reference book as the Bible or Webster’s Dictionary.

The first of its kind, Roget’s Thesaurus, was published on 26th April 1852. The first edition had 15,000 words and is still preserved in the Karpeles Manuscript Library in the USA along with Roget’s autobiography. The thesaurus has never gone out of print and each new edition has been larger.

Peter Mark Roget, born on January 18th 1779 in London, was an English doctor, writer, inventor and theologian. His father was a Swiss clergyman who died young. After his father’s death, Roget went to Edinburgh University to study Mathematics and Medicine. He was a naturally gifted child who became a doctor in 1798 when he was just 19 years old.

He inundated the scientific establishment with numerous inventions and papers, including those on Tuberculosis and on the effects of Nitrous Oxide. In 1814 he invented a slide rule to calculate the roots and powers of numbers. This formed the basis of slide rules that were common currency in schools and universities until the age of the calculator. Later in life, he attempted to construct a calculating machine. He wrote a paper on how the kaleidoscope could be improved as also on a wide range of other topics, contributing to encyclopaedias of the day.

Roget worked in Bristol and Manchester and for a time was a private tutor, travelling with his charges to Europe. In 1808, he moved to London, where he continued to lecture on medical topics.

He was made a Fellow of the Royal Society of Medicine and served as its Secretary from 1827 to 1848. In 1840 Roget effectively retired from medicine and spent the rest of his life on the project that has made his name, ‘Roget’s Thesaurus of English Words and Phrases’. As early as 1805 he realised the need for a book to find meanings and opposites of words easily. He started compiling, for his own use, a small indexed catalogue of words which he used to enhance his prolific writing. This was two years before Webster started on his dictionary. For a period of 47 years Dr. Roget used it as his personal, secret, treasure trove.

After he left his job in the Royal Society, he found the leisure and the time for his life’s work and improved upon his catalogue of words. However, only at the age of 73 did he decide to reveal and publish this great manuscript. Roget’s contribution to Ophthalmology was his demonstration of persistence of vision. On December 9, 1824, Roget presented a paper entitled “Explanation of an Optical Deception in the Appearance of the Spokes of a Wheel when seen through Vertical Apertures”. In it he proved that the image of an object is held on the retina for approximately 1/16th of second after the object actually disappears - TV and movies rely on this illusion to produce apparent ‘reality’ on screen.

He died on September 12th 1869 while on holiday and is buried in St. James’ Church in West Malvern, Worcestershire.

Interestingly, ‘Amarakosam’ in Sanskrit probably quite unknown to Peter Roget, was perhaps the first ever Thesaurus in the world.
Excimer Laser Trabeculotomy – A Novel, Minimally Invasive Procedure for Patients with Glaucoma

Dr. M. Chockalingam DO DNB FRCS (Glasgow) PGDHM, Dr. Anup Chirayath MS FRCS (Glasgow)

**Introduction**

Primary open angle glaucoma is one of the world’s leading causes of blindness\(^1\),\(^2\). Lasers play an important role in the management of open angle glaucoma. Various methods of laser treatment along with the newer surgical procedures like viscocanalostomy and deep sclerectomy have been attempted which are aimed at minimizing the complications of trabeculectomy (with antimetabolites) like hypotony, shallow anterior chamber, wash out phenomenon and a range of bleb related complications like bleb leak, endophthalmitis\(^3\) and most commonly eventual failure of the filtering bleb itself\(^4\). The newer surgical procedures have not become popular because of the longer learning curve and difficulty in doing the procedure even in experienced hands and the uncertain and often less desired outcome in terms of intraocular pressure reduction.

**The Excimer Laser Trabeculotomy**

The trabecular meshwork and the inner wall of the Schlemm’s canal constitute 75% of the outflow resistance of the aqueous\(^5\). Attempts to improve the outflow facility with laser procedures like Argon laser trabeculoplasty, Selective laser trabeculoplasty and Nd: YAG puncture have yielded less satisfactory outcomes because they produce thermal effects with coagulation of trabecular meshwork\(^6\). Consequently, the irregular edges of the opening created never produce a successful hole due to the healing response and subsequent scar tissue formation that they inherently stimulate.

To be successful, a procedure has to bypass the outflow obstruction at the juxtacanalicular trabecular meshwork accurately and stealthily producing little or no healing response. Excimer laser trabeculotomy (ELT) ab interno – a new, minimally invasive surgical procedure to reduce the intraocular pressure in patient with open-angle glaucoma or ocular hypertension – precisely fulfills both these requirements. The 308 nm wavelength used in this procedure allows the removal of trabecular meshwork by photoablation without inducing thermal damage. Therefore it minimizes healing response and scar formation. ELT reestablishes physiological aqueous outflow through the endogenous drainage pathway without creating an external filtration bleb\(^6\).

**Theoretical and Physical Aspects**

Ablation of tissue structures containing and surrounded by water differs from tissue ablation at a surface, not only theoretically but also in its outcome. In contrast to the situation often observed with surface ablation, trabecular meshwork in the anterior chamber of the eye can be ablated cleanly and accurately with excimer laser without causing collateral thermal damage\(^7\). The reason for this is that in the trabecular meshwork, the ratio of radiation-absorbing tissue to water –
which absorbs very little energy – is very small. A marked cooling effect thus results, which permits the development of only a very small amount of collateral damage at the boundaries of the ablation zone. Therefore with the excimer laser, tissue can be removed with minimal thermal effects, necrosis and negligible scar tissue formation.

**Histopathological Studies**

The aim of ELT is to create an open communication between the anterior chamber and the Schelmm’s canal. With the excimer laser a selected ablation of the trabecular meshwork and the inner wall of the Schelmm’s canal are done to create pores and enhance outflow facility. Histopathological changes studied in animal models have shown mild stimulation signs with very little obvious inflammation. Local fractures in the trabecular meshwork and openings into the Schelmm’s canal were detected in all tissues samples. Mitochondria were found to be turgescant and endoplasmic reticulum was found to be dilated under electronic microscope in the early postoperative period. With time, all trabecular cells returned to normal, however no fibroblasts were detected.

**The Excimer Laser Settings**

The excimer laser used is XeCl, with wavelength of 308 nm, instead of the standard argon fluoride (193 nm) excimer laser which has been used for ab-externo photoablation. The surgeon applies laser energy (AIDA Excimer laser system, TuILaser, AG, Germering, Munich, Germany) directly to the trabecular meshwork by means of fiber – optic delivery system (LAGO 200 or LAGO 200 ENDO; TuILaser AG). The pulse energy available is 1.2 mJ at the fiber tip, the laser pulse duration is between 10 ns to 60 ns and the repetition rate is 20 Hz.

**The Procedure**

Excimer laser trabeculotomy (ELT) is indicated in patients with open-angle glaucoma or ocular hypertension and having -

1. increased IOP under maximum tolerated medical therapy
2. progressive glaucomatous damage
3. allergies or intolerance to medications
4. non – compliance with medical therapy

It is contraindicated in patients with -

1. narrow anterior chamber angle (Shaffer I – II) and higher levels of angle closure either appositional or synechial
2. an abnormal iris configuration
3. dysplasia of trabecular meshwork
4. neovascularisation of iris
5. poor visualization of the angle structures due to hazy media

Prior surgery does not constitute a contraindication to performing ELT but procedures that compromise distant outflow channels such as argon laser trabeculoplasty (ALT) may compromise the efficacy of ELT.

The technique involves using a microscope and visualizing the angle using a modified Trokel goniolens. The pupil is constricted to open the angle and enhance visibility of the trabecular meshwork. Under full aseptic precautions and after a regional anesthesia, the anterior chamber is entered with a paracentesis incision. The anterior chamber is filled well with viscoelastic and the probe is passed across the anterior chamber via the paracentesis incision towards the opposite chamber angle to contact the trabecular meshwork (figure 1).

Fig. 1. This schematic diagram of ELT shows how the fiber-optic approaches the trabecular meshwork across the anterior chamber.
The modified Trokel goniolens is placed on the cornea and the probe is placed so that its edge rests on the Schwalbe’s line. The probe is gently aligned to the angle and up to 10 shots (trabeculostomies) are fired with each shot being 1 to 2 probe diameters away distributed over one quadrant (approximately 90°). The surgeon monitors the fiber position with either the goniolens or an endoscope (figure 2).

2–4 hours after the procedure and the next day. The intraocular pressure is reassessed after 4–8 weeks. The patient is advised to continue all pre-procedure ocular hypotensive medications. Steroid eye drop is prescribed for a few days after the procedure. Once the intraocular pressure stabilizes, glaucoma medications are sequentially discontinued.

Complications include hyphema, increased intraocular pressure especially if all the viscoelastic is not removed. All complications related to a procedure involving entry into the anterior chamber are possible. However, since the chamber is water tight throughout and after the procedure chances of sudden ocular decompression, choroidal detachment, hypotony and shallow anterior chamber are negligible.

Pressure Reduction with Excimer Laser Trabeculotomy

The reduction of intraocular pressure occurs from 4 to 6 weeks after the procedure. Studies have shown that a stable intraocular pressure is achieved between 4 months to one year post-operatively and the pressure lowering effect reduces overtime necessitating an increase in the glaucoma medications or performing surgery to lower the pressure. Erbium laser trabeculotomy can be combined with cataract surgery and can be performed through the same corneal incision. ELT has been found to reduce the intraocular pressure for at least 1 to 2 years and in combination with phacoemulsification is more effective in intraocular pressure reduction than when performed alone. It is
also more effective in patients with high preoperative intraocular pressure levels.

**Drawbacks of Excimer Laser Trabeculotomy**

Excimer laser trabeculotomy is an invasive procedure. It requires good aseptic conditions and operation theatre setup. The instrumentation is expensive. The effect of procedure like other laser procedures wanes with time as shown by the few long term studies available.

**Role of Excimer Laser Trabeculotomy**

Excimer laser trabeculotomy is at best an additional procedure to lower the intraocular pressure and subsequent use of multiple glaucoma medications in patients who are already on maximum medical treatment or who are unfit, unwilling or waiting for filtration surgery. The effect of this procedure appears to be transient and thus cannot completely replace the role of surgery or medical treatment. The lack of long–term studies and the high cost of this equipment along with the need for theatre settings have precluded the widespread acceptance of this procedure.

No serious complication of ELT has been reported so far. ELT creates no filtering bleb or hypotony and leaves the conjunctiva intact. Moreover, the microsurgical method of pinpoint ablation of the trabecular meshwork results in very minimal trauma to the eye which leaves all other options of subsequent successful surgical intervention open. ELT thus holds promise as a new, minimally invasive procedure for patients with glaucoma.

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Twenty five years back on 5th June 1981, a report appeared in the morbidity and mortality weekly report (MMWR) which described five young and previously healthy gay men with *Pneumocystis carinii* pneumonia (PCP) in Los Angeles, USA. One month later, a second report appeared in MMWR which described 26 men in New York and California with Kaposi’s sarcoma and 10 more PCP cases in California. Nobody imagined that this was the first glimpse of a global pandemic. Twenty five years later, the human immunodeficiency virus, the cause of acquired immunodeficiency syndrome (AIDS) has reached virtually every corner of the globe infecting more than 65 million till date. Of these, 25 millions have died. There are about 14,000 new HIV infections occurring every day globally, of which more than 95% are in developing countries.

HIV was first identified in India in 1986 in prostitutes in Chennai and later in IV drug abusers in Manipur. Currently, there are about 5.21 million HIV infected people in India. We reported the first case of ocular lesions in AIDS in 1995. Subsequently, we reported ocular lesions in a series of 100 consecutive patients of HIV infection. Since then, we have seen a total of 851 cases till 31st August 2006 and published 18 reports of various ocular lesions in AIDS patients.

**Why ophthalmologists need to be concerned about AIDS?**

AIDS can affect all organs including the eye. The lifetime cumulative risk of developing at least one abnormal ocular lesion for a HIV positive, ranges from 52 to 100% in various studies. Such lesions are varied and affect almost any structure of the eye. Ocular lesions usually occur in the late phase of HIV infection but can be an early manifestation also. Ophthalmologist can be the first clinician to detect an AIDS patient. Some of the ocular lesions can lead to serious visual impairment including blindness. Therefore the role of the ophthalmologists is quite important in the management of AIDS patients.

**Causative agent**

Human Immunodeficiency Virus is the causative agent of AIDS. It is a human retrovirus with RNA genome with unique ‘Reverse transcriptase enzyme’

HIV is of 2 types, HIV 1 and HIV 2. Most human diseases are caused by HIV 1. The HIV 1 subtypes prevalent in India are A, B & C.
The virus (Virion) is 120 nm in diameter consisting of an outer envelope, a core shell of protein and a cone shaped inner core containing RNA genome, ‘Reverse transcriptase’ enzyme and core polypeptides (Fig. 1). HIV - 2 is supposed to have a milder and slower effect on the immune system. People who have AIDS-like symptoms but test negative for HIV-1 should be tested for HIV-2

Transmission of HIV
- Predominantly by sexual contact - 70%
- Intra venous drug use - 27%
- Blood transfusions - 2 – 3%
- Perinatal transmission - 1%
- Rare instances of transmission through organ transplantation
- No case has been reported from corneal transplantation

Landmark events in AIDS
There have been many historical events in the evolution of AIDS and its treatment.
- 1981: Epidemic first identified
- 1982: The term “AIDS” first coined
- 1983: Identification of the HIV virus
- 1985: First commercial test to detect HIV
- 1987: First antiretroviral drug released (AZT)
- 1991: 2nd and 3rd ARVs released (DDI, DDC)
- 1995: First protease inhibitor released (Saquinavir)
- 1998: 3-drug therapy (HAART) shown to delay sickness and death
- 1998: First non-nucleoside inhibitor released

The treatment of any patient with AIDS involves
1. Inhibiting the replication of the virus using anti retrovirals
2. Treatment of opportunistic infections
3. Psychosocial support

Highly Active Anti Retroviral Therapy (HAART)
Introduction of highly active anti retroviral therapy (HAART) is a landmark event in the history of AIDS therapy. The advent of HAART, including protease inhibitors in the treatment of AIDS, has resulted in improvement of immune status in many patients with HIV disease, as evidenced by laboratory and clinical reports. It has remarkably reduced systemic and ocular morbidity among patients with AIDS. Many AIDS patients are now living longer and enjoying a higher quality of life. However, a small percentage of patients develop ocular lesions in spite of HAART therapy due to various reasons. The HAART mediated improvement of immune function in patients with AIDS may also alter the way the eye responds to both opportunistic infections especially CMV and to treatment, resulting in changes in the clinical manifestations of ocular lesions in AIDS. There have been newer ocular diseases in these patients on HAART.

HIV uses a unique viral enzyme, reverse transcriptase to transfer the genetic code from viral RNA to viral DNA. This is then integrated into the host cell DNA which on activation produces new viruses. Various drugs that are used in the treatment target specific sites in this process. Anti retroviral therapy
- Inhibits viral replication
- Preserve immune function
- Prevents disease progression
- Reduces the incidence of opportunistic infections
- Prolongs survival

The combined use of three or more of these agents is referred to as highly active anti retroviral therapy (HAART)

Highly active anti retroviral therapy (HAART) was first introduced in 1995 by Dr. David Ho and coworkers. It has revolutionized the treatment of AIDS and has had a profound impact on the morbidity and mortality of patients with AIDS. There are 3 main groups of anti retroviral drugs.

1. Nucleoside analogues

Side effects
- Zidovudine : Nausea, headache, fatigue, anemia, neutropenia
- Didanosine : Nausea, diarrhoea, pancreatitis, peripheral neuropathy
• Zalicitabine : Peripheral neuropathy, pancreatitis
• Stavudine : Peripheral neuropathy
• Lamivudine : Usually none
• Abacavir : Nausea, headache, diarrhoea, vomiting, fatty liver, skin rash, hypersensitivity reaction

**Mechanism of action:** Nucleoside reverse transcriptase inhibitors (NRTI's) latch onto the new strand of DNA that reverse transcriptase is trying to build.

2. **Non nucleoside reverse transcriptase inhibitors**

• Nevirapine Rash, hepatitis
• Delavirdine Rash, headache, hepatitis
• Efavirenz Light headedness, rashes, anxiety

**Mechanism of action:** Non-nucleoside reverse transcriptase inhibitors (NNRTI's) hook onto reverse transcriptase and stop it from working.

3. **Protease inhibitors**

• Indinavir Nausea, headache, diarrhoea and
• Nelfinavir abnormal fat distribution
• Ritonavir
• Saquinavir
• Agenerase Nausea, headache, diarrhoea
• Lopinavir (in combination with ritonavir)

A short review of ocular lesions in AIDS is provided below.

**HIV Related Microvasculopathy of the Retina**

It is the most common ocular finding in patients with AIDS, occurring in about 50-70% of cases. It is characterized by retinal hemorrhages, microaneurysms and cotton wool spots. They are usually distributed along the vascular arcades. These are probably the result of both an underlying microvasculopathy and hematologic abnormalities such as increased leukocyte activation and rigidity. They generally regress on their own in 6-9 weeks. (Fig 2)

**Opportunistic Infections**

These opportunistic organisms can infect the ocular adnexa, anterior segment or posterior segment.

Opportunistic ocular infections are caused by

• Cytomegalovirus
• Herpes Zoster / Varicella zoster virus
• Toxoplasma gondii
• Mycobacterium tuberculosis
• Mycobacterium avium intracellulare
• Cryptococcus neoformans
• Pneumocystis carinii
• Histoplasma capsulatum
• Candida
• Molluscum contagiosum
• Microsporidia and others

Either the anterior or posterior or both segments of the eye may be involved in these infections.

**Anterior Segment Lesions**

**Herpes Zoster Ophthalmicus**

Herpes zoster ophthalmicus affects 5-15% of HIV positive patients. It is a vesiculobullous dermatitis caused by varicella zoster virus. Concurrent or delayed keratitis, scleritis, uveitis, retinitis or encephalitis may also occur. Apparently healthy young individual who present with herpes zoster lesions of the face or eyelids should be investigated for HIV. (Fig 3)
Treatment is with intravenous acyclovir 10mg/kg of body weight 3 times per day for 7 days followed by an oral maintenance regimen 800mg 5 times a day.

**Molluscum contagiosum**

Molluscum contagiosum is a common skin infection caused by a large DNA poxvirus. Molluscum lesions can occur in children with normal immunity and are fewer and unilateral. In adults, this virus can be transmitted through sexual intercourse. In HIV positive individuals, such lesions can occur in the eyelid and conjunctiva and are characteristically larger in number and size, often confluent, bilateral and resistant to therapy. (Fig 4)

**Treatment:** Electrocautery, chemical cautery, cryotherapy and surgical excision are the various treatment modalities. High recurrence rate has been observed in AIDS patients.

**Conjunctiva microvasculopathy**

Seventy to eighty percent patients have some form of asymptomatic conjunctival microvascular changes. This includes segmental vascular dilatation and narrowing, microaneurysm formation, comma shaped vascular fragment and slogging of the blood columns.

**Abscess in the Eyelid**

Infections of the eyelid and conjunctiva are rare in patients with AIDS. Dermal abscesses due to staphylococci, acid fast bacilli, and cytomegalovirus have been reported in molluscum lesions in patients with AIDS indicating the tendency of such lesions to secondary infection.

Diagnosis is by smear and culture. Treatment is with topical and systemic antibiotics.

**Neoplasms**

**Kaposi’s sarcoma of the eyelid and the conjunctiva**

Kaposi’s sarcoma of the eyelid and conjunctiva is rare in Indian subcontinent possibly due to the rarity of the probable causative agent, Human herpes virus 8, in India. Kaposi’s sarcoma occurs in 30% of all AIDS patients in USA. 10 to 20% of the patients with Kaposi’s sarcoma have eyelid lesions. This can be the initial manifestation of AIDS. Kaposi’s sarcoma of the eyelid appears initially as purplish blue macules (Fig 5). It progresses to become solid nodules. Kaposi’s sarcoma in the conjunctiva can appear as subconjunctival haemorrhage or pyogenic granuloma.

Treatment includes surgical excision (if the lesion is small), cryotherapy, radiotherapy and chemotherapy.
Squamous cell carcinoma of conjunctiva

This shows spindle cells with frequent abnormal mitotic figures. Incidence was about 0.28% in our series. Squamous cell carcinoma as the initial presenting sign due to HIV-2 was reported by us.  

Opportunistic Infections of Posterior Segment

Cytomegalovirus Retinitis

Cytomegalovirus (CMV) is the most common infectious agent affecting the retina or the optic nerve or both in AIDS patients. CMV retinitis develops in 15% to 40% of patients with AIDS. It has been found to have a strong correlation with low CD4 + T-lymphocyte count and is usually seen when CD4 count <50 cells/mm³. Patients may present with diminished vision or may be asymptomatic. Floaters could be an early warning sign if vitritis is present. Well established CMV retinitis is easily recognized as a full thickness retinal opacification associated with hard exudates and hemorrhages. They are often perivascular in distribution. This appearance is also called “Cottage cheese with tomato ketch up” or “pizza pie” appearance. It can have a yellow-white margin of slowly advancing retinitis at the border of atrophic retina (brushfire pattern) and the granular pattern which is found in the periphery as focal white granular lesions without associated hemorrhage.

Vitritis is typically absent or minimal. 6% of CMV retinitis can have frosted branch appearance. Retinal detachment is seen in 30% of cases in the healed stage. Very early CMV retinitis lesions may resemble cotton wool spots.

CMV in the era of HAART

Prior to HAART, CMV retinitis was known to occur in 15% - 40% of patients with AIDS, and the median elapsed time between diagnosis of AIDS and the development of CMV retinitis was about 9 months. However more recent studies have shown that this infection can occur as long as 3-5 years after the diagnosis of AIDS and usually develops when CD4 cell counts are less than 50 cells/mm³.

Prior to the introduction of HAART, the median survival time following the diagnosis of CMV retinitis was 6 weeks in patients receiving no treatment. Anti CMV treatment increased the survival time to 10 months in patients who responded partially.

In the era of HAART, CMV retinitis is associated with substantial risk of incident vision loss. Those who have HAART induced immune recovery have approximately 50% lower risk of visual acuity loss. Presence of immune recovery uveitis at baseline attenuated the protective effect of immune recovery for moderate vision loss but not for blindness.

Management

Currently 5 medications are approved for treatment of CMV retinitis in USA. These are ganciclovir, foscarnet, cidofovir, fomivirsen and valganciclovir.

Ganciclovir

Ganciclovir, a nucleoside analogue that acts as a competitive inhibitor and faulty substrate for CMV DNA polymerase, is the most common drug used. Activation of ganciclovir requires monophosphorylation by the CMV enzyme, protein kinase. Ganciclovir is virustatic, and thus, viral replication will resume when the drug is removed. Ganciclovir has been shown to be initially effective in 90% to 100% of cases of newly diagnosed retinitis. It takes 2-3 weeks before the clinical effect is apparent and 3-6 weeks before an inactive border is achieved (Fig 6). Without maintenance treatment, disease will relapse usually within 3 weeks of cessation of induction treatment. Resistance to the drug is very common after prolonged use.

- Intravenous
- Oral
- Intravitreal in the form of injection or implant
Intravitreal ganciclovir

The dose used is about 2mg/0.1 mL. They are usually well tolerated, highly effective, and relatively inexpensive. The primary risks are endophthalmitis, retinal detachment, and vitreous hemorrhage.

Valganciclovir (Valcyte) is the valine ester of ganciclovir and is rapidly converted to ganciclovir in the intestinal wall. It is administered orally and can achieve intravenous ganciclovir levels with a dosage of 900 mg twice daily for induction and once daily for maintenance.

Foscarnet

Foscarnet is a pyrophosphate analogue that inhibits DNA polymerase and reverse transcriptase by directly affecting the pyrophosphate binding site. It does not have to be phosphorylated to become active. This agent is also virustatic, and viral replication will resume when the drug is removed. It has an intrinsic anti-HIV effect. It is used in a dose of 90mg/kg twice a day for induction for 14-21 days followed by once a day for maintenance. Ganciclovir resistant retinitis can be treated with foscarnet because the mechanism of action differs. Combined therapy with ganciclovir and foscarnet has been shown to decrease emergence of resistance.

Cidofovir

Cidofovir (HPMPC) is a nucleotide analogue and phosphorylation by viral encoded enzymes is not required for activity. CMV DNA polymerase is the target of the drug. It is eliminated primarily by glomerular filtration, partially by tubular secretion. Increased proteinuria and elevations in serum creatinine were the major dose-limiting toxicities. Saline hydration and concomitant administration of probenecid were found to reduce the risk for renal toxicity. Uveitis and ocular hypotony (50% reduction in intraocular pressure), due to its toxicity to the ciliary body, was observed in 12% of patients and these occur when administered intravenously.

Progressive Outer Retinal Necrosis (Porn)

Progressive outer retinal necrosis (PORN) is a rare infection due to herpes zoster virus or other viruses in the herpes family. Presentation is with sudden loss of vision and floaters. It has a characteristic fundus appearance involving outer retina, progresses circumferentially and spares retinal vessels.
vasculature, typically described as the ‘cracked mud appearance’. (Fig. 7) As infected areas of retina become necrotic, large retinal breaks occur leading to rhegmatogenous retinal detachment in the majority of the affected eyes.

**Acute Retinal Necrosis**

Acute retinal necrosis which is usually seen in healthy immunocompetent patients, can occur in patients with AIDS. They present as deep retinitis with minimal hemorrhages. Clinical picture is similar to that of immunocompetent patients. A prior history of cutaneous zoster may be present.

**Treatment:** Intravenous acyclovir 1500 mg/sq. meter of the body for 10 to 14 days followed by oral acyclovir 400 to 800 mg 5 times per day for a minimum of 6 weeks to 3 months.

**Pneumocystic Carinii Choroidopathy**

Pneumocystic carinii, a unicellular protozoa, is the most common opportunistic infection in patients with AIDS usually presenting as Pneumocystis pneumonia (PCP). It spreads to the choroidal layers through haematogenous route. *P. carinii* choroidopathy is often seen in patients treated with aerosolized pentamidine for PCP prophylaxis. *P. carinii* choroidopathy can be an initial sign of disseminated life threatening *P. carinii* infection.

**Treatment:** Intravenous pentamidine daily for 3 weeks followed by maintenance therapy.

**Ocular Syphilis**

Syphilitic lesions of the eye are the most common intraocular bacterial infection. About 1-2% of HIV positive patients are found to have ocular syphilis. Ocular findings include chorioretinitis, optic neuritis, papilloedema and optic perineuritis. An unusual manifestation of syphilis is acute necrotizing retinopathy. It can mimic acute retinal necrosis. In HIV positive patients, ocular syphilis is more closely associated with neurological abnormalities.

In the era of HAART with improved immunity, syphilis can present with vitritis or panuveitis. Patients often show abnormal CSF findings. Diagnosis can be very challenging as up to 38 % of HIV positive patients can be seronegative despite active syphilitic disease. Treatment of ocular syphilis is similar to that of neurosyphilis.

**Fungal Endophthalmitis**

Candida and cryptococcus are the most common intraocular fungal infections. Candidal endophthalmitis is remarkably uncommon in contrast to systemic candidal infection in HIV positive patients. Majority of the patients have indwelling venous catheters or are intravenous drug abusers. Eye could also be part of disseminated candidal infection. Fluffy-white chorioretinal lesions along with snowball like masses are usually seen. Other lesions are creamy-white multiple chorioretinal masses with overlying vitreous inflammation.

Cryptococcus neoformans is the most common fungal infective agent in AIDS. It usually causes chronic meningitis, which usually results in papilloedema, optic neuropathy and chiasmal involvement. It can involve all parts of the eye, but most commonly causes chorioretinitis. Cranial nerve palsies indicate a poor prognosis.

**Treatment:** Systemic and intravitreal antifungal agents

**Mycobacterial Infection**

Tuberculosis (TB) is one of the most common opportunistic infections in AIDS patients in India. HIV/TB co-infection is of special concern in India, where background rates of TB are among the highest in the world. Ocular TB can present with protean manifestations including choroiditis, choroidal granulomas, chorioretinitis, endophthalmitis, subretinal abscess and panophthalmitis.

Extrapulmonary and disseminated tuberculosis is seen more commonly in HIV positive patients. However, choroidal tuberculosis has not been found to be as common as systemic tuberculosis in patients with AIDS. We have presented the largest series of Ocular TB in AIDS recently. We had 15 cases (19 eyes) (1.95%) of ocular TB in 766 HIV infected/AIDS patients. We found no definite correlation of the occurrence of
ocular tuberculosis with CD4 counts. It occurs in all ranges, unlike cryptococcal meningitis, toxoplasmosis or other opportunistic infections, which occur at very low CD4 counts. Polymerase chain reaction and histopathologic examination are very helpful in diagnosis. Ocular course may not coincide with systemic TB. Patients with AIDS can have aggressive manifestations of ocular TB which sometimes may not resolve with ATT even in the context of improving systemic infection. Initiation of HAART before ATT can lead to florid inflammation and paradoxical worsening of tuberculosis due to a newly emerging trend of immune reconstitution inflammatory syndrome (IRIS). Systemic and ocular co-infections can pose challenges in diagnosis and management. Regular ophthalmic screening for ocular TB is imperative in all HIV cases in India, inspite of relatively preserved CD4 counts and current highly active anti-retroviral therapy (HAART). While atypical mycobacteria like mycobacterium avium intracellulare infection can occur around 15-20% of AIDS patients, such organism has been demonstrated in autopsy eyes in the choroid in 1-6% of patients.\textsuperscript{33}

Toxoplasma gondii, a protozoa, affects about 10% of AIDS patients. However, toxoplasmosis retinochoroiditis is relatively rare and accounts for 1% of AIDS related retinal infections. In HIV-infected patients, ocular toxoplasmosis is much less common than toxoplasmic encephalitis, probably due to the difference in parasite load in the eye and the central nervous system (CNS). There can be a single lesion or multifocal lesions in one or both eyes with broad areas of retinal necrosis. The retina appears to have a hard, ‘indurated’ appearance with sharply demonstrated borders with little retinal haemorrhage. When patients with AIDS develop necrotizing retinitis, toxoplasmosis must be considered in the differential diagnosis, along with cytomegalovirus retinitis, progressive outer retinal necrosis, and syphilitic retinitis. Unlike cytomegalovirus retinitis, progressive outer retinal necrosis, and syphilitic retinitis, toxoplasmosis can cause a progressive intraocular infection, panophthalmitis, and orbital cellulitis in patients with AIDS.\textsuperscript{34} It is usually caused by newly acquired infection. CNS lesions are seen in 29% to 50% of HIV-infected patients with ocular toxoplasmosis. Serologic diagnosis is often difficult due to a depressed antibody response, in which IgM and IgG titre may not be of much use. Nested Polymerase chain reaction testing of aqueous fluid may help in confirmation of diagnosis.\textsuperscript{35}

**Treatment:** Pyrimethamine in combination with a sulfonamide or clindamycin or both is the treatment of choice. Long term or repeated therapy is often necessary. Atovaquone has been used successfully but is expensive and has yet to be shown to be superior to standard therapy.\textsuperscript{36}

**Neuro-ophthalmic Lesions**

**Papilloedema & Optic Atrophy**

Ocular involvement secondary to intracranial infections may manifest as papilloedema, optic atrophy and ophthalmoplegias. Patients may present with headache, vomiting or diplopia. The most frequent finding is papilloedema from elevated intracranial pressure. Cryptococcal meningitis, meningeal and parenchymal lymphoma, neurosyphilis and toxoplasmosis are the most frequent causes. MRI followed by a lumbar puncture to obtain CSF for a cell count, cytologic studies, culture and antibody and antigen testing help to clinch diagnosis.

**Extraocular Muscle Palsy**

Cranial nerve involvement occurs in 4% of patients with ocular lesions in AIDS. Palsy of the third, fourth, sixth and seventh cranial nerves have been reported in AIDS, and may be bilateral or combined. The majority of these cranial nerve palsies were due to focal brainstem toxoplastic lesions. Others were due to cryptococcosis, varicella zoster, cytomegalovirus, progressive multifocal leucoencephalopathy, central nervous system and orbital lymphoma and cavernous and orbital apex eosinophilic granuloma. Patients may present with diplopia, squint and/or headache. Radiation and chemotherapy in case of lymphoma and specific anti-microbial therapy in identified infections are the measures adopted.

**HAART Responders**

Those patients who show an improvement in CD4 cell
counts of greater than 60 cells / cumm and has maintained it for more than two months is by definition a person who has shown response to HAART therapy. HAART therapy leads to decreased plasma levels of human immunodeficiency virus (HIV) RNA and increased CD4 T-lymphocyte counts, with improved immune function in patients with HIV infection. This immune recovery has resulted in substantial decline in opportunistic infections and has allowed some patients with cytomegalovirus retinitis to discontinue specific anti cytomegalovirus therapy without reactivation of eye disease. Clinical reports show a decrease in the incidence of cytomegalovirus (CMV) retinitis since the introduction of HAART. Tural et al and Mac-Donald et al demonstrated some patients who respond to combined antiretroviral treatment with an increase in CD4 T-lymphocyte levels regain the ability to suppress CMV without specific anti-CMV therapy, thereby providing clinical evidence of partial immune recovery in these patients.

Before the introduction of protease inhibitors, patients with cytomegalovirus retinitis typically had CD41 T-lymphocyte counts less than 50 cells/ml with minimal intraocular inflammation. Substantial intraocular inflammation has now been reported in some patients with cytomegalovirus retinitis who have had improved immune function with highly active antiretroviral therapy. The ocular inflammation associated with clinical immune recovery in patients taking potent antiretroviral regimens is known as immune-recovery uveitis.

Immune Recovery Uveitis

IRU or immune recovery uveitis (IRU) is a chronic intraocular inflammatory syndrome, the clinical spectrum of which includes anterior segment inflammation, cataract, vitritis, papillitis, CME, ERM, vitreous hemorrhage, retinal neovascularization, and PVR. Since immune recovery uveitis does not commonly occur in patients without CMV retinitis, the ocular inflammation is postulated to be due to the CMV infection itself, which causes breakdown in the blood ocular barrier. This may allow CMV antigens to leak out of the eye and give the antigen access to lymphoid organs and stimulate an antigen specific immune response. In the laboratory and the clinic, HIV continues to resist our efforts to find a cure (eradication of the virus from an infected individual), or a vaccine. In 25 years, there has not been a single well-documented report of a person whose immune system has completely cleared the virus, with or without the help of the ART. But HIV remains an entirely preventable disease in adults; and behaviour modification, condom use and other approaches have slowed HIV incidence in many rich countries and a growing number of poor ones. The existing HIV treatments and prevention modalities when appropriately applied can be enormously effective. The development of next generation therapies and prevention tools, including topical microbicides (efavirenz – virasert) than can empower women to directly protect themselves are important steps in that direction.

Various ocular lesions in AIDS can be classified as below

Table 1. Common ocular adnexal lesions in AIDS patients
- a) Herpes zoster ophthalmicus (HZO).
- b) Kaposi’s sarcoma of eyelid, conjunctiva.
- c) Molluscum contagiosum of the eyelid.
- d) Conjunctival microvasculopathy.
- e) Pyogenic infection of eyelid and adnexa.
- f) Allergic or Infective conjunctivitis.

Table 2. Common anterior segment lesions in AIDS patients
- a) Dry eye.
- c) Infective keratitis (Varicella zoster, herpes simplex, microsporidia)
- d) Anterior uveitis.
- f) Cidofovir induced.
- g) Rifabutin induced.
- h) Spill over from cytomegalovirus retinitis.
- i) Herpes zoster ophthalmicus (HZO).
Table 3. Common posterior segment lesions in AIDS patients.

<table>
<thead>
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<th>Table 4. Common orbital lesions in AIDS patients.</th>
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<tbody>
<tr>
<td>a) HIV retinopathy.</td>
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<td>b) Cytomegalovirus retinitis.</td>
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<td>c) Progressive outer retinal necrosis.</td>
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<td>d) Acute retinal necrosis.</td>
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<td>e) Herpes zoster retinopathy.</td>
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<tr>
<td>f) Pneumocystis carinii choroidopathy.</td>
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<td>g) Ocular syphilis.</td>
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<td>h) Fungal endophthalmitis (cryptococcus, candida)</td>
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<tr>
<td>i) Mycobacterial infection.</td>
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<td>j) Toxoplasmic retinochoroiditis.</td>
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Table 4. Common orbital lesions in AIDS patients.

<table>
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<th>Table 5. Common neuroophthalmic lesions in AIDS patients.</th>
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<td>a) Burkitt's lymphoma.</td>
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<td>b) Orbital cellulitis (aspergillus).</td>
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<td>c) Cranial nerve palsies.</td>
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<td>d) Papilloedema.</td>
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<td>e) Headache</td>
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<tr>
<td>f) Retroorbital pain.</td>
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<td>g) Optic neuropathy</td>
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Table 5. Common neuroophthalmic lesions in AIDS patients.

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<th>Table 6. Drugs used in the treatment of CMV retinitis</th>
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<tr>
<td>Drug</td>
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<tr>
<td>Ganciclovir</td>
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<td>Foscarnet</td>
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<tr>
<td>Cidofovir</td>
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Key words: Parafoveal telangiectasia, diabetic retinopathy

Retinal telangiectasia, a term proposed by Reese\(^1\), refers to a developmental retinal vascular disorder characterized by an ectasia of capillaries of the retina, in which irregular capillary dilatation and incompetence occur in the retinal periphery or the macula. If only the capillaries of the foveal avascular zone are involved, it is known as parafoveal telangiectasia. It is a condition characterized by microaneurysmal and saccular dilatation and capillary non-perfusion of the parafoveal capillaries.

Parafoveal telangiectasia can be broadly divided into two basic forms;
1) A developmental or congenital vascular anomaly
2) An acquired form found in middle-aged and elderly persons. Although the cause of parafoveal telangiectasia is unknown, the association of the acquired form with diabetic retinopathy is well known.

Case report

A 49-year-old lady presented with dimness of vision in the right eye. She was a known case of type 2 diabetes mellitus since 10 years on regular treatment. Systemic examination was unremarkable. On ocular examination, her best-corrected visual acuity was 6/9 in the right eye and 6/6 in the left eye. Anterior segment examination and intraocular pressure by applanation tonometry were unremarkable. Fundus photograph of the right eye showed changes of moderate non-proliferative diabetic retinopathy and a zone of retinal whitening in the temporal parafoveal region (Fig.1). Left eye fundus photograph (Fig.2) also revealed changes of moderate non-proliferative diabetic retinopathy. There were hard exudates located temporal to macula about two disc diameters from the fovea. There was also a zone of retinal whitening in the parafoveal region, more marked temporally.

Fundus fluorescein angiography confirmed the findings of moderate non-proliferative diabetic retinopathy in both eyes. FFA of right eye (Fig.3) in the arteriovenous phase showed capillary dilatation of the parafoveal capillary network, more marked temporally. In the late phase of FFA (Fig.4) right eye showed cystoid accumulation of the dye in the temporal macula and there was staining of the parafoveal retina.

FFA of left eye in the arteriovenous phase (Fig.5) showed vascular abnormalities in the form of capillary dilatation and microaneurysmal dilation of the parafoveal capillary network, which were more marked temporally. In the late phase of FFA (Fig.6) left eye showed increased leakage of the dye from the vascular abnormalities and typical staining of the parafoveal retina.

Discussion

We present a case of parafoveal telangiectasia along with diabetic maculopathy. Though the association of
Fig. 1. Fundus Photograph of the Right Eye showing changes of non-proliferative diabetic retinopathy and a zone of retinal whitening temporal to the parafoveal area.

Fig. 2. Fundus photograph of the left eye showing changes of non-proliferative diabetic retinopathy and a zone of retinal whitening temporal to the parafoveal area.

Fig. 3. Fluorescein angiography of right eye: Arterio-venous phase of the angiogram showing telangiectasia of the parafoveal net.

Fig. 4. Late phase angiogram of the right eye showing cystoid accumulation of the dye in parafoveal area and staining of the retina.

Fig. 5. Fluorescein angiogram of the left eye showing aneurismal dilatation of the parafoveal capillary net.

Fig. 6. Late phase angiogram of the left eye showing progressively increasing leakage of the dye from the vascular abnormality of the parafoveal area and staining of the temporal retina.
parafoveal telangiectasia and diabetic retinopathy is well known, there are very few case reports. Green et al.\textsuperscript{2} described clinical and histopathologic features of parafoveal telangiectasis in a 58 year old woman. Light and electron microscopy had demonstrated narrowed capillary lumina. Localized endothelial defects were found in the temporal parafoveal area. There was degeneration of the pericytes with accumulation of lipid within the capillary walls and the presence of multilaminated basement membrane. These retinal capillary changes were similar to those observed in the diabetic and pre-diabetic state. Diaz-Rodriguez \textsuperscript{3} also reported that the changes found in parafoveal telangiectasia are similar to those that appear in the beginning of diabetic retinopathy. Millay et al.\textsuperscript{4} postulated that parafoveal telangiectasia may be caused by abnormal glucose metabolism. This view is also supported by Chew et al.\textsuperscript{5}

The purpose of this case report is to highlight the association of parafoveal telangiectasia with diabetes mellitus and diabetic retinopathy. Parafoveal telangiectasia has got characteristic clinical and angiographic features and it should not be confused with diabetic maculopathy. Whereas CSME in diabetic maculopathy responds to focal laser photocoagulation to microaneurysms, there is no role for laser photocoagulation in parafoveal telangiectasia.

References
Calotropis Keratitis

Dr. Mohammed Haneef, MS DO, Dr Manoj Venugopal, MS, DNB, FRCS Edin, Dr O U Mallika MS, DO, DNB, Dr Padma Sree K M MBBS

Introduction

Calotropis procera (‘Erukku’ in Malayalam) is a commonly seen shrub with a world wide geographic distribution. (Fig. 1) It is commonly harvested for its medicinal properties. It exudes copious milky sap when cut or broken. (Fig. 2) Ironically, the sap is highly irritant to human tissues especially the skin and mucous membrane.

This article attempts to highlight the importance of recognizing the damaging effects of this plant sap when it comes into contact with the eye and therefore the care one must take while handling this shrub.

Case Report

A thirty year old male who works in an Ayurvedic pharmacy presented with defective vision, redness, irritation and watering in his right eye following accidental exposure to the milky sap of Calotropis (Fig 3a & 3b). (The leaf of Calotropis is used in Ayurvedic system of medicine for the treatment of joint inflammations) Another twenty four year old male presented with similar complaints in his right eye following exposure to the sap while plucking the flowers of Calotropis to make a garland out of it.(Fig 4a & 4b). (The garland made from Calotropis flowers is offered to the deity in temples)

Both these patients had identical findings on the slit lamp which revealed lid oedema in one of them due to contact dermatitis, circum corneal congestion, chemosis, corneal haze due to corneal oedema and numerous Descemets Membrane folds. The corneal epithelium was found to be intact. No significant AC reaction was seen. The visual acuity was CF 2M in the affected eye in the first case while it was CF 4M in the second case. IOT was within the normal range in both the eyes. Both the patients responded well to topical Prednisolone Acetate. Over a period of one week, cornea cleared well and the visual acuity improved to 6/6 in both the patients.

Review of literature revealed that intracorneal penetration of Calotropis latex results in permanent endothelial cell loss with its morphological alteration as confirmed with confocal and specular microscopy. Corneal oedema is believed to resolve well if sufficient viable endothelial cells are still present after resolution of keratitis.

Conclusion

We wish to improve awareness of “Calotropis keratitis” amongst our fellow ophthalmologists, an entity which to the best of our knowledge has not been reported much in the literature. This plant due to its irritant sap can result in corneal blindness when not carefully handled.
Fig 1. Calotropis shrub

References


Fig 2. Sap of the plant

Fig 3   a & b. Patient 1 Gross & Slit lamp microscopy

Fig 4   a & b. Patient 2-Gross & Slit lamp microscopy
Orbito-Cranial Penetration By A Wooden Foreign Body-A Case Report

Dr. K.V. Raju MS, DO, Dr. Arun Kumar MS, DO, Dr. Anitha Jose, Dr. Anoop B

A sixty-year-old man was presented to the casualty with a piece of wood, which had pierced below the right lower eyelid and was partially protruding out.

On examination

Patient was conscious and oriented with stable vitals. A piece of wood was seen piercing between the inferior orbital margin and globe of the right eye. Part of it was protruding out.

Eyelids were normal. Extra ocular movements were tested and elevation and depression were found to be decreased. Slit lamp biomicroscopic examination revealed an apparently intact globe, normal conjunctiva and cornea, shallow anterior chamber, a mid dilated pupil with effenter pupillary defect, a clear lens, and a grossly normal fundus with mild media haze. Visual acuity in the right eye was finger counting at 2 metres and the intraocular pressure was found to be low.

Left eye was normal. Direct and consensual pupillary reflexes were normal.

Considering the nature of the foreign body, an MRI was ordered.

MRI showed the foreign body of length seven centimeters to be passing between the right globe and inferior orbital margin, passing laterally, piercing the inferior orbital fissure and reaching the infratemporal fossa.

Assistance from the Neurosurgery and ENT departments were obtained and the emergency exploration and removal of the foreign body under general anesthesia was performed.

Surgery

An incision was placed below the entry site, separating the soft tissues around, in an attempt to delineate the foreign body. It was abutting the globe and pushing it up. While supporting the FB from below and applying firm traction from above, visualizing it all through out, the FB was taken out. A lot of fragments were left behind which were taken out individually.

A suction drain was put and the wounds were closed. On examining the globe, the anterior chamber was shallow, the pupil was mid-dilated and the eye was very soft however no breach of the sclera was found. The eye was padded with antibiotics. Patient was put on broad-spectrum antibiotics and anti-fungals.
First post operative day: Evaluation on the first postoperative day showed a stable general condition, and normal extraocular movements. Slit lamp biomicroscopy revealed a clear cornea, formed anterior chamber mid dilated pupil non reactive to light, lens subluxation and a quiet anterior chamber. The patient’s vision improved steadily from 6/60 on first postoperative day to 6/9 at the end of the first week.
Discussion

Transorbital intracranial penetration by a wooden foreign body is unusual. The resilience of the sclera and ability of the globe to be displaced usually protect the eye from perforation. The reason for the efferent pupillary defect could be an injury to the ciliary ganglion. The low intraocular tension can be attributed to a ciliary shut down due to the mechanical effect of the foreign body.

Metallic objects and glass fragments are the foreign bodies most often encountered in the orbit, although CT, is excellent in identifying these high density objects, it is much less sensitive for low density objects. MRI is more sensitive for delineating the extent of orbital injury and is safe when non-magnetic foreign body such as wood is suspected. The porous organic nature of wood and its frequent proximity to soil makes it an ideal reservoir for bacteria and fungi.

Children are particularly prone to Transorbital cranial injury because the orbital bone offers little resistance. The spectrum of intracranial complication as a result of penetrating orbito cranial injury includes immediate structural injury, which is potentially fatal or can lead to permanent neurological deficit. Vascular complications include thrombosis, occlusion, pseudo-aneurysm, rupture and carotico- cavernous fistula. Infectious complications are more common in Transorbital injuries compared with other types of cranial injury due to the proximity of the orbit to the Para nasal sinuses. Ocular complications include optic nerve damage and resultant severe loss of vision, extra ocular muscle palsy secondary to direct muscle trauma or nerve damage, proptosis and macular edema. In our case, since the foreign body did not damage any vital structures, the patient did not develop any neurological complications.

Conclusion

Orbital foreign bodies constitute an interdisciplinary challenge and help from Neurosurgery and ENT departments should be sought in every case.

References

A case of recurrent graft rejection

Dr. Anthrayose Kakkanat1, Dr. Anil Radhakrishnan2, Dr. Charles K. Skariah3, Dr. Freddy T. Simon4, Dr. Noel Moniz5, Dr. C.V. Radha Devi6, Dr. Tony Fernandez7, Dr. Thomas Kuriakose8

Case History

38 year old male patient with a history of defective vision & watering both eyes since 8 yrs of age, underwent Penetrating Keratoplasty four times in his right eye and three times in the left. The surgical procedures and the sequence in which he underwent them is enumerated below

1 RE – Penetrating Keratoplasty 22 yrs back at Little Flower Hospital, Angamaly
2 LE – Penetrating Keratoplasty 21 yrs back at Little Flower Hospital, Angamaly
3 RE - Combined cataract extraction with Intraocular lens implantation & Penetrating Keratoplasty 15 yrs back at Little Flower Hospital, Angamaly
4 LE – Combined cataract extraction with intraocular lens implantation and penetrating keratoplasty 14 yrs back at Little Flower Hospital, Angamaly
5 RE – Penetrating keratoplasty 5 yrs back at Little Flower Hospital, Angamaly
6 LE – Penetrating keratoplasty on 3/8/03 at Jubilee Mission Medical College, Thrissur
7 RE – Penetrating keratoplasty on 7/1/06 with graft of a 7 yr old donor with good endothelial count at Jubilee Mission Medical College, Thrissur

Visual acuity in January 2006 was 6/36 in the right eye (immediate postoperative period), and counting fingers at one metre in his left eye

There was no history of similar illness in his family. The patient did not give any history suggestive of herpes or diabetes.

Postoperatively the patient was treated with topical and systemic steroids and followed up regularly. At present, the patient maintains a visual acuity of counting fingers at 1 metre in both his eyes. Slitlamp biomicroscopy showed diffuse corneal haze involving the stroma and endothelium suggestive of rejection. There was no evidence of vascularisation, intraocular inflammation or glaucoma in the right eye. The left eye on examination revealed an opaque cornea, minimal peripheral vascularisation and no evidence of glaucoma or inflammation.

Urinary screening test for Mucopolysaccharidosis – Negative

We request your expert opinion regarding

1. Reasons for recurrent graft failure in this patient
2. Further management in this case
3. In case of attempting repeat penetrating keratoplasty, precautions to prevent graft failure
4. Comments on recurrent graft failure
5. Any other systemic or metabolic causes for repeated

Fig. 1. Fullface photograph showing irritable and congested eyes, narrowing of palpebral aperture and bilateral opaque corneas
Expert Comments

Dr. J K Reddy

In this very unfortunate patient two important things to look at are,
1) The etiology or the diagnosis of the primary corneal condition that necessitated the corneal transplant and
2) The intraocular pressure during the post operative period.

Each condition has its own success rate for corneal transplant. Looking at the details given, I am of the opinion the patient may be a case of Congenital hereditary endothelial dystrophy. In that case the short term corneal survival rates are good, but the long term prognosis is not good.

These patients need multiple grafts in their life time. As the number of re-grafts goes on the inflammation is more and chances of failures are more. Very often these young patients are steroid responders and the intraocular pressures goes up to very high levels and results in graft failures.

The IOP assessment rather than measurement in the both eyes is to be done as the cornea is very hazy and edematous. In case the intraocular pressures are normal, we can plan for PKP with trabeculectomy in the left eye. During the pre operative waiting period he can be put on topical Prednisolone eye drops 6 times a day in the left eye and IOP should be measured after one month. Regarding the Donor selection, I like to go for A grade cornea with Blood group match. Regarding the Surgical technique, interrupted suture with 10-0 prolene or merselene is preferable for re-grafts. In the immediate post operative period the patient should be put on systemic steroids or / and immuno-suppressants like Cyclophosphamide or Azathioprine for 4 to 6 months, and then tapered with low dose maintenance. Topical Cyclosporine or Tacrolimus are to be instilled along with a potent topical steroid like prednisolone. Accurate measurement of post operative IOP is very important. In the unlikely event of further failure of the graft with in a short period, say 4 to 6 months, the only option is Keratoprosthesis.

Dr. Noel Moniz

This young man has undergone multiple graft failures. It may not be possible to revive the present graft since I am sure intensive measures would already have been tried. It is best to wait for at least 6 months before going in for a regraft. IOP should be checked at all times ideally with an instrument like the tonopen. It would be best to get a specular count of the donor eye with an eye bank specular microscope. I usually prefer to do smaller grafts than the previous size. The multiple grafts have already made us go in for large grafts and enlarging it further would be going too close to the limbus and also a cause for glaucoma. Care should be taken to form the anterior chamber well to prevent postoperative glaucoma. I would start the patient on systemic steroids on the day of surgery and intense topical steroids from the 1st postoperative day. As the steroids are being tapered around day 10 – 15 I would start the patient on Azathioprine (Imuran 50mg) OD and wean the patient off systemic steroids. Imuran can be continued for a long time and so also topical steroids. Any signs of vascularisation should be watched for. We should always keep a look out for the complications of topical and systemic steroids and also imuran. The above regimen has worked well in my hands.
The only other newer drug I would like to try is cyclosporine drops. I would also like to give tear substitutes.

**Dr. Thomas Kuriakose**

This sort of scenario is not uncommon when one has been doing cornea for some time and one wonders if PKP is the final answer for corneal blindness and is it time we changed the practice whenever possible.

The reasons for recurrent graft failure are not hard to find because once a graft rejection has occurred then all the factors which normally gave the corneal graft its privileged position goes. Blood vessels, increased amounts of antigen presenting cells (APC) in the periphery, sensitization of the system etc increases the chances for recurrence. I doubt if any of the measures like trying to close the vessels of by laser etc really helps.

If facilities are available then the best chance for survival of a regraft in this patient would be to do a repeat keratoplasty using a HLA matched, high quality donor material. Systemically he should be managed like any other solid organ transplantation and should be put on systemic Cyclosporine or Tacrolimus in addition to steroids. If one is not used to this one can enlist the help of a nephrologist well versed in its use for renal transplantation.

I am not being funny when I say that the best way to prevent a graft rejection is by not doing one. Thus I discourage patients with corneal opacity in only one eye to undergo PKP. I think when possible one should do only a Deep Anterior Lamellar Keratoplasty using the big bubble technique so as to reduce the chances for rejection. Besides systemic immuno-suppression one should also use systemic long term antiviral to prevent graft failure if there is a viral etiology.

**Dr. S. Tony Fernandez**

The reasons for graft failure.

From the history it is obvious that this is an Immune mediated graft rejection. The reasons are the following. Such graft reactions occur mainly in the young people. The first graft was done 22 years ago and the other eye was grafted the next year. The rejection started late. When the first graft rejects the possibility of recurrent graft rejections are possible. Other risk factors, like vascularisation, loose sutures, infection glaucoma, or eccentric and large grafts are not there. Such graft rejections does occur in about 16 to 30 % of people. Though normally the cornea is an immune privileged tissue and therefore transplantations are regularly successful, some young patients have a tendency for Immune mediated graft rejections. They should be treated and managed with extreme caution and care we give to kidney or other organ transplantations. As stated here the following precautions can be undertaken.

Tissue typing and ABO typing can be done. As we take blood from the cadaver as a routine procedure such tests are worth starting in institutions where transplants are routinely done. Though this is not necessary in normal cases, in such case it might be of value.

Selection of better donor material preferably preserved in M.K. Medium should be used. An endothelial study should be done before this is selected.

Removal of epithelium from the donor material is suggested by some, but it is controversial. As the recipient cornea is not healthy enough I feel it should not be done because epithelial defect can occur.

Immuno- suppressants should be used as in other organ transplantations and they should be monitored carefully. Regular follow ups are necessary.

**Dr. Freddy T Simon**

The apparent reasons for rejection in this case are

1. In the Collaborative Corneal transplant Studies (CCTS) the number of previous grafts proved to be a strong risk factor for graft failure. With each additional graft the risk increases by 1.2%. Since the host is presensitized the subsequent graft rejections can occur sooner as in this case.

2. Higher incidence of graft rejection is seen in younger recipients.

3. The picture given shows a large graft, again a predisposing factor.

4. Previous anterior segment surgeries were also found in CCTS to predispose to graft failure.
The other causes to be kept in mind are anterior synechiae, vascularization more than 2 quadrants, and raised intraocular pressure. The IOP should ideally be measured with a tonopen and the discs checked for any damage.

The treatment options for this patient are

1. Treat the present rejection episode aggressively and save the graft if possible.
2. If a further graft is required
   a. Use a smaller graft
   b. Use ABO and HLA matched donor if possible
   c. Use an organ culture stored cornea, (if available) since cornea stored for sometime loses some of its antigenicity.
   d. It is most important in this case to use immunosupression either cyclosporine A or Mycophenolate mofetil. CSA needs close monitoring of the blood levels to keep it within 120-150 ng/ml to avoid side effects, MMF was found to be as effective as CSA while being more cost effective and safer. (Alexander Reis et al).

It is important that the patient is followed up closely and aim for vision only in one eye.

**Recurrent graft failure - Comments**

**Dr. Charles K. Skariah**

Going through the history of this patient his symptoms started early in childhood and the first keratoplasty was done by the age of 16 years in the right eye and 17 years in the left eye. The preoperative diagnosis or a photograph showing the corneal condition at that period is not available. Being a bilateral disease in young age with symptoms of watering, foreign body sensation and defective vision, the possibility of stromal dystrophies, metabolic storage disease, keratoconus or even rarely HSV infection are the possibilities to be considered. Keratoconus and HSV rarely warrant bilateral keratoplasty at the age of 16 years. So in all probability the original diagnosis could have been either corneal dystrophy or a metabolic storage disorder like mucopolysaccharidoses both of which are likely to recur following keratoplasty.

From the clinical history, the regrafting was done after 7 years which was coupled with cataract surgery. There is no mention in the history as to how long the graft remained clear. Even after repeated graft failure there are no signs of inflammation and deep vascularisation in the graft. So it is unlikely to be a case of graft rejection and hence most probably this is a case of recurrence of disease leading to graft failure.

**What may be the disease recurring in this graft?**

- Stromal dystrophy
- Schies syndrome
- HSV infection

Most of the stromal corneal dystrophies tend to recur after 3-12 years following PKP. Among the stromal dystrophies, macular dystrophy tends to produce early onset of visual impairment than others and warrants early PKP. Although most of the corneal dystrophies show a tendency to recur after PKP, the most common type to recur is Lattice and then macular dystrophy. Among the storage disorders the most common to produce early corneal clouding and which recurs after surgery is Scheie's syndrome (MPS type-1 S). This is produced by deficiency of the enzyme alpha-L iduronidase leading to deposition of Heparan sulfate and Dermatan sulfate in the cornea. Unlike Hurlers disease, Schies syndrome may not have all the classical features of MPS type-1 and may be missed by a casual examination. The only features may be claw hand deformity and bony changes in the feet. Although there is no history of HSV infection, this possibility has also to be thought of in all cases of recurrent graft failure of unexplained etiology.

**Risk factors for rejection:** Several host factors have been identified as conferring “high risk” status to the host leading to graft rejection or failure. These include:

1. Young recipient age
2. Large grafts
3. Previous failed / rejected grafts (especially when two or more grafts have previously failed)
4. More than two quadrant vascularisation with associated lymphatics
5. Herpes simplex keratitis
6. Uveitis
7. Preoperative glaucoma
8. Multiple surgical procedures at the time of grafting
9. H/O previous anterior segment surgery
10. Anterior iris synechiae
11. Silicon oil keratopathy
12. Vitreous adhesions
13. Blood group ABO incompatibility

Graft rejection is largely mediated by the major histocompatibility antigens, minor antigens, and perhaps blood group ABO antigens and some cornea-specific antigens. Just as rejection is mediated by active immune mediated events, the lack of rejection (tolerance) is also sustained by active immune regulatory mechanisms. The anterior chamber associated immune deviation (ACAID) and probably, conjunctiva associated lymphoid tissue (CALT) induced mucosal tolerance, beside others, play an important role.

**So how do we proceed from here?**

A complete immunological work up and Tissue matching for HLA and ABO compatibility will be beneficial to reduce the incidence of rejection. A detailed multi disciplinary clinical examination and biochemical work up may be worthwhile to rule out any metabolic disease contributing to the recurrent graft failure. Conjunctival biopsy can confirm classic histopathology. Specific diagnosis requires biochemical assay for enzymes in tears, leucocytes, cultured fibroblasts, or amniotic cells and for elevated urinary excretion of Heparan sulfate and Dermatan sulfate. The corneal deposits stain with alcian blue and colloidal Iodine. An enzyme linked immunosorbant assay (ELISA) can measure sulfated keratan which may be useful in diagnosis of macular dystrophy.

**Prognosis**

The chances of graft failure following another surgery are very high as this falls in the very high risk category. Prognosis is very much guarded as abnormal storage material may accumulate again in the graft. Matching the patient and donor blood type (ABO compatibility) and HLA compatibility might be effective in improving the patient outcome. Explaining and educating the patient about the high chances of failure, a repeat grafting of smaller size may be done with a fresh cornea with normal endothelial count.

Although one is not sure of the cause of failure in this case, immunosuppression with high dose of topical and systemic corticosteroids and Cyclosporine are indicated. Good patient compliance and close follow up are the keys to successful corneal transplantation in high risk individuals. If signs of rejection are identified, pulsed intravenous methyl prednisolone and/or oral prednisolone may be initiated at the earliest evidence of rejection.

In cases of storage diseases, regression of corneal clouding following successful donor stem cell bone marrow transplantation has been reported.

**Dr C V Radha Devi**

**Comments on graft failure**

Despite the improving results in penetrating keratoplasty, graft failure still remains a significant problem. It is important to differentiate between graft failure and graft rejection. Graft failure can occur due to various causes any time after keratoplasty. Immediate graft failure is due to some defect in the donor material. Technical problems can also lead to graft failure but are not frequent. Even after good evaluation and selection of donor cornea, graft failure can occur. Some damage or fault in the donor corneal endothelium will lead to thickening of the graft and haziness. This may be associated with local inflammation and topical steroids may be helpful. Sub-conjunctival or systemic steroids may not be of much help. Prolonged shallow anterior chamber or adherence of iris or vitreous can also lead to graft failure. Endothelial dysfunction can occur due to surgical trauma. Excessive irrigation and improper handling of the graft can lead to endothelial damage.

Intraocular pressure should be monitored and if raised, should be controlled appropriately. Any chance of pupillary block can be prevented by iridotomy and/or adequate medication postoperatively. Antiglaucoma drugs if used prior to surgery should be continued postoperatively.

In the late postoperative period, even with uneventful keratoplasty, graft failure can occur due to attrition of endothelial cells. Postoperative inflammation can be an added cause. Common and leading cause of graft failure in the late post operative period is graft rejection.
This is specifically due to immunologically mediated process. Here, the graft remains clear in the initial stages for several weeks, and suddenly becomes oedematous, associated with inflammatory signs. If the symptoms are identified early and adequate treatment given with topical steroids supplemented with systemic steroids and if required, with immunosuppressants, reversal of the graft reaction may be possible.

Following points are important and should be remembered in keratoplasty. Vascularisation of the recipient cornea is one of the main factors for allograft reaction. This should be controlled prior to surgery. Peritomy may be helpful in some cases. This can be done before or during keratoplasty. Sutures invite vascularisation and this should be noted on postop review and if present, timely treatment should be given. Smaller the graft size usually gives better results. Large size grafts are associated with more chance of graft failure.

Associated conditions like cataract, or glaucoma calls for additional procedures which may increase the chances of graft failures. Also longer duration of surgery and older recipient age can lead to graft failure.

It is important to remember that in repeated keratoplasty, successive grafts will not have as good a prognosis as the initial grafts.

Selection of good donor material, sutures, technique and careful tissue handling are important to obtain clear grafts. Review of the case should be done daily in the initial postoperative stage and treatment instituted as and when required. Use of topical steroids or immunosuppressants and if required, systemic steroids and or immunosuppressants, in the postoperative period may be of great help to prevent graft failure.

**Dr. Anil Radhakrishnan**

In any case of repeated graft failure it is imperative to know the reason, whether it is recurrence of primary disease, immunological rejection, endothelial decompensation or any other obvious pathology to address the cause.

The recurrence of primary disease as in corneal dystrophy presents with stromal haze [usually without oedema] with progressive increase in stromal deposits usually first seen along suture tracks. Immunological rejection is associated with stromal oedema, usually though not always associated with anterior chamber inflammation. Progressive depletion of endothelial cells or endothelial decompensation is also associated with stromal edema. An optical section by slit lamp biomicroscopy can help in differentiation. In stromal oedema, in addition to haze, the stromal thickness is increased along with appearance of Descemet’s folds. High pachymetry values also suggest stromal oedema.

In this case, with the available information it appears more like a stromal haze with anterior stromal deposits rather than stromal oedema. The presence of stromal deposits initially along suture tracks, its centrifugal spread and early recurrence in a graft, in the absence of inflammation all suggest recurrence of primary disease, most likely a corneal dystrophy. Being fortunate to come across a few cases of homozygous granular dystrophy, I am tempted to presume it is so. However, the long interval between first and second graft in both the eyes and subsequent early graft failures suggest a diagnosis of immunological rejection.

Granular dystrophy is caused by mutation in the kerato-epithelin gene [type1- Arg 555 Try, type2- Arg 124 Hist, type3- Arg 124 Leu / Arg 555Gln]. If it is a heterozygous mutation, as in most cases, typical phenotype of granular dystrophy is evident, characterized by bilateral symmetric bread crumb like stromal opacities separated from one another and limbus by clear stroma. If the mutation is homozygous, a severe phenotype with juvenile onset, placoid lesions and severe opacification of cornea and early recurrence following keratoplasty is seen. Genomic DNA analysis of blood leucocytes can pick up the presence of mutation. Phototherapeutic keratectomy or even scraping of epithelium and anterior stroma that may have to be repeated multiple times is effective for visual improvement, as the recurrence is initially confined to the epithelium with slow antero-posterior spread.

Gelatinous Droplet Like Dystrophy [GDLD] is another possibility. Primarily, it presents in the first or second decade of life with multiple, bilateral, mulberry-like elevations due to subepithelial accumulations of amyloid. It has been mapped to chromosome 1p due to mutation in M1S1 gene. Recurrence is the rule after corneal grafting.

Mucopolysacchridoses [MPS] or mucolipoidoses [MLS] can also present with early recurrence, but unlikely in
this age group. MPS typically occurs in the first few years of life, has a family history and is associated with systemic involvement, presence of urinary glycosaminoglycans, and specific enzyme deficiency evident in blood or lacrimal fluid and positive conjunctival biopsy. Co-existent ocular pathology like retinitis pigmentosa or open angle glaucoma is present in most cases. Mucolipoidoses also present with typical systemic features, quite often associated with mental retardation early in life.

Penetrating limbo-keratoplasty [limbal stem cell transplantation + keratoplasty] is a major step towards augmenting recurrence-free interval in corneal dystrophies, as the site of origin of mutated keratoepithelin gene is taken care of, but is not time-tested. The experience from available literature does not vehemently support the use of limbo-keratoplasty over routine keratoplasty probably due to progressive depletion in stem cell population over time. But, probably for GDLD and certainly for MPS it is justified. However, limbo-keratoplasty necessitates intensive prolonged follow-up and lifelong immuno-suppressive medications, for which cost is a major consideration in our set-up.

On the other hand, if stromal oedema is the cause for opacification of the graft, it is either due to immunological rejection or endothelial decompensation. The latter is highly unlikely as the graft was recent and from a young donor. If immunological rejection is the cause for recurrent graft failure, long term immunosuppressive therapy in the form of systemic cyclosporine probably offers the best chance of graft survival after a re-graft. It is important to maintain adequate serum levels [trough levels of 120-150 ng/ml]. Co-administration of drugs like diltiazem can increase the serum levels by competitive protein binding and is a cost-effective way to do so without increasing the dose of expensive cyclosporine. If cost is still a major concern, azathioprine in combination with systemic steroid is a cheaper alternative. 2% topical cyclosporine is effective, without the side-effects of steroids, but difficulty in dispensing it in oil and incidence of superficial punctuate keratopathy makes it a less practical option. Considering his pseudophakic status I would like to maintain him on Prednisolone acetate eye drops once or twice a day after making sure that he is not a steroid -responder. Topical steroid therapy lowers the local population of immunologically active cells and reduces the expression of HLA class 2 antigens in the recipient cornea.

**Suggested management**

1] Blood – for genomic DNA analysis [a] for granular dystrophy [b] for GDLD

2] If no mutation is found in DNA analysis, medical consultation with an internist who is conversant with metabolic storage disorders to rule out mucopolysaccharidoses [MPS] or mucolipoidoses [MLS]. This assumes greater significance if the visual acuity is not explainable by corneal opacity.

3] Specific enzyme assay for MPS or MLS in blood or lacrimal fluid / conjunctival biopsy – if the internist suspects a storage disorder

4] If nothing emerges out of the aforementioned, further management will depend on the histopathologic study of the corneal button, which can give precious information, if the patient desires another keratoplasty. This needs to be done by an experienced ocular pathologist in an ophthalmic institute where facilities for immunohistochemical study and special stains are available. Polymerase chain reaction for HSV DNA from the corneal button may also be done considering the remote possibility of HSV keratitis.

The management paradigm, as discussed before depends on whether it is recurrence of primary disease or immunological rejection. If it is a keratoepithelin gene associated dystrophy [granular/ lattice], I would like to perform a routine keratoplasty with the same sized or a smaller graft. I would prefer to follow him up closely [once a month] and perform debridement of epithelium at the earliest sign of recurrence. In the case of immunological rejection, local and systemic immuno-suppression, as detailed before hold the key. In either scenario, being a high-risk graft, I would like to maintain him on topical steroids if the patient is not a steroid responder. Control of IOP and close follow up, monthly after the immediate postoperative period is desirable in this unfortunate patient.
***Editors Comments***

Graft failure following PKP is very common. Studies show that up to 30% of PKP patients have at least one episode of rejection with 5-7% of all grafts eventually failing because of rejection. Corneal graft failure can be primary due to donor endothelial damage or secondary, the most common cause of which being graft rejection.

The prognosis of keratoplasty depends on various factors like vascularisation, active corneal inflammation, glaucoma, immunological rejection, recurrence of the primary disease etc. Mucopolysaccharidosis (MPS) and certain corneal dystrophies are known to recur after keratoplasty.

Stromal vascularisation may be treated with photocoagulation with Argon blue-green or yellow dye laser either preop or postop.

Mucopolysaccharidosis in graft rejection

*Mucopolysaccharidosis* can be detected by urinary screening tests
- Toluidine blue spot test and
- Turbidity tests using (i) Cetylpyridium chloride and (ii) Acid-albumin.

The screening tests for mucopolysaccharidosis in urine are helpful indicators in predicting the chance for recurrence and rejection. The confirmatory test can be done with column chromatography.

High risk patients for recurrent graft rejection

According to *Collaborative corneal transplantation study*, high risk patients include those with
(a) 2 or more quadrants of stromal vascularisation and
(b) H/O previous graft failure

Approaches to prevent rejection in high risk patients are

(i) Making donor tissue less antigenic
- Central corneal graft
- Removal of donor epithelium
- Pretreatment of donor tissue with UV light, hyperbaric O2, heterologous antibodies, storage in organ culture
- Tissue matching-HLA & ABO

(ii) Suppressing host immune response
- Glucocorticoids- topical & systemic
- Azathioprine
- Cyclosporine A- topical & systemic (in monocular high risk patients)

It is important to start immunosuppressant in the immediate post op period itself in high risk patients.

**References**


(v) Metabolic basis of inherited diseases-Scriver

(vi) Clinical diagnosis by laboratory methods-Davidson & Henry

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Compiled by: Dr. Jayasree Menon.P, Dr. C.V.Andrews, Dr. Alex Joseph
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Searching the PubMed for Medical literature: Update for Ophthalmology

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Abstract

Efficient literature search is essential to the practice of Evidence-Based Medicine. PubMed provides free access to one of the largest searchable biomedical databases. Efficient literature search using PubMed requires a good understanding of the available search strategies and tools. In this article I will present a step-by-step approach for performing literature search using PubMed. Several PubMed tools including ‘Single Citation Matcher’, ‘Clinical Queries’, ‘Clipboard’ are highlighted using case based scenarios.

Key words: EBM; PubMed

Introduction

Evidence-based medicine (EBM) is ‘judicious application of the best research evidence integrated with individual physicians’ clinical expertise and patient values’ 1. Physician surveys suggest that most patient encounters generate one or more clinical questions that remain unanswered and need a quick and focused literature search 2-4. Thus, in an observational study at a university setting, an average of five unanswered questions were raised for every patient encounter 2. With biomedical information doubling every five years 5, the standard textbooks and reviews usually lag behind in their ability to provide the most current information on relevant clinical questions 6.

The practice of EBM can be summarized into four basic steps: 1) develop a focused clinical question; 2) search for the best evidence; 3) critically appraise the evidence; 4) apply the evidence and evaluate the outcome. In this review, I will present the techniques involved in formulating a well-built clinical question and searching the literature using the PubMed database. Interestingly, PubMed provides free access to one of the largest searchable biomedical databases.

Searching for Best Evidence: The electronic databases

Several electronic databases are available for searching citations. Most of these are subscription based and may not be freely available to the individual user. The source of biomedical information on the web can be divided into two major categories: 1) original published articles in the journals; and 2) synthesized information available as systematic reviews, synopses or decision support systems 7. However, a lack of experience with search techniques often leads to missing many relevant citations that may have an impact on patient care 8. MedLine is the U.S. National Library of Medicine’s premier bibliographic database. MedLine covers the fields of medicine, nursing, dentistry, veterinary medicine, health care system, pre-clinical sciences, and a few other areas of the life sciences. MedLine contains citations from over 4,600 journals, published in
70 countries. Over 14 million records are indexed in MedLine with most of the records from English language sources or having English abstracts.

The MedLine database can be searched with several search engines. The two most popular are Entrez and Ovid. Entrez is the life sciences search engine that is part of the National Center for Biotechnology Information's retrieval system. Entrez searches several databases including PubMed. PubMed includes MedLine, Old MedLine (1951 to 1965), articles from some non-MedLine journals and issues of journals published prior to their selection for MedLine indexing, and out-of-scope articles from ‘selectively indexed’ MedLine journals. Thus PubMed database is more comprehensive than MedLine. Furthermore, PubMed is more current and allows access to citations even prior to their indexing with MedLine.

Formulating the search question

The initial essential requirement for performing an effective search using PubMed is the ability to generate a well-built clinical question. The individual key components of this question can then be used as search terms in PubMed. Three basic steps are recommended for formulating the search question: 1) define the components of the search question; 2) identify the study design that will answer the search question; 3) identify the study type that will answer the search question.

Defining the components of the search question – Each search question has four components remembered best by the mnemonic-PICO.

1) Patient (P) – What is the patient group of interest e.g. diabetes mellitus.
2) Intervention (I) – What is the intervention of interest e.g. Tight blood pressure control.
3) Comparison (C) – What is the comparison intervention of interest e.g. Routine blood pressure control.
4) Outcome (O) – What is the primary outcome e.g. progression of diabetic retinopathy.

A search is usually started with two of the four components, usually patient and intervention. Depending on the question and retrieval, the search can be further focused by adding rest of the components of the question.

- Identify the study design that will answer the search question – The study design for most therapeutic interventions is likely to be a randomized double blind clinical trial (RCT). For clinical questions where several RCTs are reported in the literature, a systematic review or meta-analysis might be the most appropriate article to review. The optimal study design to assess prognosis and harm is likely to be a prospective cohort study.

- Identify the study type that will answer the search question – Most clinical questions can be answered by one of the four recognized study types i.e. diagnosis, prognosis, therapy and harm. Several databases including PubMed provide appropriate search filters to retrieve citations with the particular study design.

The rest of this article will cover the important features of PubMed. Clinical scenarios will be used to elaborate the search options. Readers are encouraged to conduct the searches as they go along in the article. All the actions that readers have to take are italicized, with the terms that they have to type placed in double quotes. Individual PubMed options are placed in single quotes.

Introduction to PubMed Homepage

Log on to www.pubmed.gov

The PubMed homepage has three key areas that are frequently used (Figure 1):

1. ‘Query box’ – The ‘Query box’ is used to enter the search terms as a free text entry area.
3. ‘Side bar’ – The blue ‘Side bar’ has some of the advanced PubMed features including the ‘MeSH Database’, ‘Single Citation Matcher’, ‘Clinical Queries’.

In addition PubMed homepage also has a black ‘Menu bar’ at the top that allows the user to link to other Entrez databases.

MeSH Database

It is important to have a basic understanding of the MeSH database prior to exploring actual search
strategies further. Medical subject headings (MeSH) database is the hierarchical library that is used to index citations. MeSH terms are arranged in a tree like structure with the more general terms representing the stem and narrower and more focused terms representing the distal branches. Each citation that is indexed with MedLine is assigned up to 15 MeSH terms based on the content of the article. An important feature of PubMed that increases search yield is ‘automatic term explosion’. This means that when a search term is entered in PubMed that matches with a MeSH term, PubMed automatically includes all the specific narrower terms that are associated with the search term.

Select MeSH Database from ‘Side bar’.

Type “macular degeneration” in the ‘Query box’ and select ‘Go’.

Look at the ‘Subheadings’, ‘Entry Terms’ and then scroll down to look at the MeSH tree associated with macular degeneration.

- Degeneration, Macular
- Degenerations, Macular
- Macular Degenerations

- Age-Related Maculopathy
- Age Related Maculopathy
- Maculopathy, Age-Related
- Maculopathy, Age Related
- Age-Related Maculopathies
- Age Related Maculopathies
- Maculopathies, Age-Related
- Maculopathies, Age Related

Typing any of these ‘Entry Terms’ in the ‘Query box’ leads PubMed to match that term to lung cancer. Selecting ‘Subheadings’ allows you to restrict search to the particular subheadings within the MeSH term.

Basic PubMed search features - ‘Boolean logic’, ‘Limits’, ‘Display options’

**Boolean logic** represents relationships between search terms. The three Boolean operators are ‘AND’, ‘OR’ and ‘NOT’. The operator ‘AND’ is used to retrieve citations that contain all the search terms, while the operator ‘OR’ is used to retrieve citations that contain at least one of the search terms. The operator ‘NOT’ is used to restrict citations containing a particular search
The use of ‘NOT’ is however confusing and should be avoided. While joining two search terms using Boolean logic, the Boolean terms should be typed in capitals (e.g. “AND” instead of “and”).

The ‘Limits’ option allows the user to narrow the search thereby retrieving fewer citations. The most commonly used ‘Limits’ are Publication Types, Ages, Publication Dates and Subsets.

Case # 1: A 56-year old male with new onset Type II diabetes mellitus consults you for discussion regarding decreasing his chances for retinopathy. He has been told by his physician that strict control of blood sugar and blood pressure can decrease his chances of developing retinopathy. Your question is: Do patients with diabetes and rigorous blood pressure have better ophthalmologic outcomes compared to regular management of blood pressure? Log on to www.pubmed.gov

Type in the search term, “diabetes AND antihypertensive AND retinopathy”. Look at the search results. You retrieve over three hundred citations.
Select ‘Limits’ and make the following selections within ‘Limits’:

- **Language**: English
- **Publication types**: Randomized controlled trials
- **Ages**: All Adult: 19+ years
- **Published in last**: Ten years
- **Subsets**: Core clinical journals (Core Clinical Journals is a list of 120 clinical journals that are likely to be available at most medical school libraries)

Click the box: *Link to free full text (connects to free articles available in entirety)*

The final screen appearance is shown in **Figure 2**.

Click **Go** and look at the output. You have much fewer articles that are more relevant.

The article by the UK Prospective Diabetes Study Group published in British Medical Journal in 1998 addresses the specific question that you are searching.

Now look at the way the citations are displayed. PubMed defaults to show citations in the summary format, in a set of 20, with the citations arranged in a chronologic order with the most recent citation shown first. The way citations are displayed, number of citations and how they are sorted can all be changed.

In the option ‘Display’ scroll down and select ‘Brief’.

In the option ‘Sort’ scroll down and select ‘Author’.

Click on ‘Display’.

Citations are now displayed in the ‘Brief’ format and arranged in an alphabetical order based on the author’s name.

Now select the ‘Back’ button to reach the previous screen.

Select the UKPDS article in BMJ by checking the box to the left of the citation.

Scroll down in ‘Display’ and select ‘Abstract’.

Click on ‘Display’.

The ‘Abstract’ format is now seen. You can also perform the same function by simply clicking on the authors’ names that is hyper-linked to the ‘Abstract’ format.

Looking for a specific article and expanding your search – The ‘Single Citation Matcher’ and ‘Related Articles’

‘Single Citation Matcher’ can be accessed from the ‘Sidebar’ and allows you to retrieve a single citation of interest. A simple fill-in-the-blank form allows you to enter the relevant information about the article of interest.

**Case # 2:** A 60-year old chronic smoker seeks your help for management of his moderate dry age-related macular degeneration. You counsel him about stopping smoking and plan on starting Zinc at a dose of 80 mg a day, along with other anti-oxidants. Patient wants to know the reported success of Zinc based on results from previous studies. You recall that the original randomized clinical trial was published in the Archives of Ophthalmology in the early 2000s and would like to pull up the citation.

Select ‘Single Citation Matcher’ from the ‘Sidebar’.

Enter the following information in search fields:

- **Journal**: “Archives of ophthalmology”
- **Date**: “2000:2003”
- **Title**: “Zinc”

(Note that a range of date is entered by putting a colon between the two years)

The final screen appearance is shown in **Figure 3**.

Select ‘Search’

The second article is the one we are interested in. ‘Single Citation Matcher’ is typically used to look for a specific citation but can also be used to search for multiple citations.

Now look to the right of the citation to find ‘Related Articles’. The ‘Related Articles’ tool helps you quickly identify articles related to the citation of interest. Several of the relevant articles are pre-selected and stored by PubMed. A pre-specified word-weighted algorithm that incorporates the assigned Medical Subject Headings (MeSH) and words from the title and abstract is used to choose the related articles. These articles are arranged from the most to the least relevant.

Select ‘Related Articles’.

Look at the citations that are retrieved. Assess their relevance to your search question.

Tools for systematic review – ‘Clinical Queries’ and ‘Clipboard’

‘Clinical Queries’ is accessed from the ‘Sidebar’. This tool gives the user an option to search using the ‘Clinical Queries Using Research Methodology Filter’ or the ‘Systematic Reviews’. ‘Clinical Queries Using
Research Methodology Filter’ incorporates validated search filters that are added to the search term. Search filters are available for four different study types i.e. therapy; diagnosis; etiology; and prognosis. Additionally, search can be specified as sensitive or specific depending on the question that is being asked. The ‘Systematic Reviews’ filter retrieves meta-analysis and systematic reviews for the search question.

Case #3: A 42-year old male with Type 1 diabetes mellitus presents to you with a history of progressive visual loss in the right eye. Examination reveals presence of proliferative and non-proliferative retinopathy in both eyes with advanced retinopathy in the right eye. He is seeking symptomatic relief and asks you if laser photocoagulation would improve symptoms. You would like to look up a systematic review on this topic.

Select ‘Clinical Queries’ from the ‘Sidebar’. Check the line ‘Systematic Reviews’.

In the search box enter the term, “diabetic retinopathy AND photocoagulation”

Look at the number of citations and see if your search retrieves relevant articles.

Now select the ‘Back’ button to reach the previous screen.

Check the box to the left of ‘Clinical Queries using Research Methodology Filter’.

In the ‘Category’, select ‘Therapy’ and in ‘Emphasis’, select ‘Specific search (narrow)’.

Your search term “diabetic retinopathy AND photocoagulation” should already be present in the ‘Query box’.

Select ‘Go’.

Look at the number of citations and see if your search retrieves relevant articles. Most of the articles retrieved would be clinical trials.

Now select the ‘Back’ button again to reach the previous screen.

Change the Emphasis to ‘Sensitive search (broad)’.

Select ‘Go’.

Look at the number of citations and see if your search retrieves relevant articles. You will retrieve a greater number of articles compared to the specific search and some of the articles will likely have lesser relevance.
‘Clipboard’ helps you temporarily store citations for up to 8 hours. This option is particularly helpful when you are doing several different searches and would like to select and save citations and work with them together. With the citations stored in the ‘Clipboard’, all the functions can be performed that are otherwise possible with a standard PubMed search.

Go back to the previous search just completed.

Select the first four citations by checking the box to their left.

Go to the ‘Send to’ button. Scroll down to ‘Clipboard’ and select ‘Clipboard’

Select ‘Send to’ button.

The message will appear on the left side of the window stating, ‘4 items were added to the Clipboard’ (Figure 4).

Select ‘Clipboard’ again from the ‘Features bar’. Look at the 3 citations.

You can change ‘Display’ or ‘Sort’ these items like any PubMed search output. Note that if you want to send all the citations obtained from a search to the ‘Clipboard’, do not select any of the citations and select the option ‘Send to’ ‘Clipboard’. All the citations up to a total of 500 will be sent to the clipboard.

While in the ‘Clipboard’, scroll down in the ‘Send to’ button and select ‘Clip Remove’.

Select ‘Send to’.

Select ‘Clipboard’ again.

‘Clipboard’ should now be empty.

Work with other options in the ‘Send to’ button including Text, File, E-mail and Order.

Conclusions

Physicians practicing Evidence Based Medicine will find it helpful to develop a well thought out literature search strategy. PubMed is one of the most comprehensive biomedical database, is available for free and offers several tools for performing a focused literature search. Familiarity with these search tools will help users perform efficient citation retrieval. PubMed provides an online tutorial that might be helpful for both new and experienced users.

References


Effects of Ruboxistaurin on Visual Loss in Patients With Diabetic Retinopathy

PKC-DRS2 Group, Ophthalmology 2006; 113; 2221-2230

Patients with diabetes mellitus have an increased risk of vision loss despite current therapies. Severe loss of vision from PDR and moderate loss of vision from Diabetic macular oedema (DME) can be reduced by laser photocoagulation, however the main goal of therapy is to prevent further visual loss, and it is associated with many complications.

Hyperglycemia induced synthesis of diacylglycerol results in the activation of protein-kinase C beta (PKC), which plays a central role in mediating the ocular complications of diabetes. VEGF also activates PKC beta. Diabetes-induced activation of PKC increases both retinal vascular permeability and neovascularization in animal models.

Ruboxistaurin, an orally administered PKC beta isozyme selective inhibitor, ameliorates the adverse effect of high glucose and diabetes induced blood flow abnormalities in patients.

PKC DRS2 was a 36-month multicentre double masked parallel placebo controlled study. Patients were randomized to either a placebo or ruboxistaurin (32 mg) administered orally once daily. 685 patients participated in this study which was conducted in 70 centers, under the supervision of Dr. Lloyd Paul Aiello, Beetham Eye Institute, Joslin Diabetes Center, Boston. Patients were eligible if they had Best corrected visual acuity score of >45 letters(20/125) measured by Early treatment diabetic retinopathy study visual acuity (ETDRS VA) protocol, retinopathy level > 47A and < 53E,(ETDRS retinopathy severity scale) and no prior pan retinal photocoagulation in at least one eye.

Ophthalmologic examination and VA assessment were performed at screening and at each 3-month visit. Retinopathy status was assessed every 6 months with (ETDRS) standard 7-field 30° colour stereoscopic fundus photography.

Effect of oral ruboxistaurin (32mg/day) on reduction of sustained moderate visual loss (SMVL) (>15-letter decrease in ETDRS VA score maintained > 6 months or VA sustained from month 30 to 36) in patients with moderately severe to very severe non proliferative diabetic retinopathy was taken as the main criteria for success.

Sustained moderate visual loss occurred in 9.1% of placebo-treated patients versus 5.5% ruboxistaurin-treated patients(40% risk reduction, P=0.034). Mean VA was better in the ruboxistaurin-treated patients after 12 months. Baseline-to-end point visual improvement of >15 letters was more frequent (4.9% vs. 2.4%) and > 15-letter worsening was less frequent (6.7% vs. 9.9%) in ruboxistaurin-treated patients relative to placebo (P=0.005). When clinically significant macular edema was > 100 micrometer from the center of the macula at baseline, ruboxistaurin treatment was associated with less frequent progression of edema to within 100 micrometre (68% vs. 50%, P=0.003.) Initial laser treatment for macular edema was 26% less frequent in eyes of ruboxistaurin treated patients (P=0.008).

To put in a nutshell, according to the study, oral ruboxistaurin treatment reduced vision loss, need for laser treatment and macular edema progression, while
increasing occurrence of visual improvement in patients with nonproliferative retinopathy. It is the first pharmacological agent demonstrated to reduce vision loss from diabetes over an extended period. Given that it is well tolerated, nondestructive, and beneficial even after prior laser treatment, ruboxistaurin represents a novel therapeutic approach that might be used along with optimal metabolic control and current ophthalmic therapies to reduce the likelihood of vision loss in patients with diabetes.

The International Classification of Retinoblastoma Predicts Chemoreduction Success

Carol L. Shields et al, Ophthalmology 2006; 113; 2276-2230

The international classification of retinoblastoma (ICBR) was finalized by a group of retinoblastoma experts in April 2003 at Paris. The primary goal for development of this new classification was to create a simpler, more user-friendly classification that would be quick to recall and more applicable to current therapies such as chemoreduction (CRD). The previously used Reese-Ellsworth classification was created in the 1960s when external beam radiotherapy (EBRT) was the most popular conservative (non enucleation) treatment. In fact, it became apparent that tumor location, multifocality, and size were not of major concern because CRD was effective despite these variable. The aim of the study was to evaluate the reliability of the International Classification of Retinoblastoma (ICRB) for predicting treatment success with chemoreduction. The study was designed as a Non comparative interventional study. 249 patients participated in this study which was done at ocular oncology service Wills Eye Hospital. The eligibility criteria for treatment with CRD were children with RB in whom either eye ordinarily would require enucleation or EBRT for cure of disease based on published indications. All eyes were treated with CRD and were classified according to ICRB; group A included those eyes with retinoblastoma ≤3mm; group B included those eyes with retinoblastoma >3mm, macular location or minor subretinal fluid; group C included those eyes with retinoblastoma with localized seed; group D included those eyes with retinoblastoma with diffuse seeds; group E included those eyes with massive retinoblastoma necessitating enucleation. The CRD regimen included vincristine, etoposide and carboplatin for 6 cycles plus local consolidation with thermotherapy or cryotherapy. Each case was classified according to Reese-Ellsworth classification also.

Chemoreduction success, was defined as avoidance of external beam radiotherapy or enucleation. Of the 249 eyes 23 (9%) were in-group A, 96 (39%) were in-group B, 21 (8%) were in group C and 109 (44%) in-group D. In this series, group E were managed with enucleation. Treatment success was achieved in 100% group A, 93% of group B, 90% of group C and 47% of group D eyes. ICRB showed consistent predictability for CRD success with in major categories. The authors claim that ICRB can be of assistance in predicting CRD success for retinoblastoma. Additional treatment methods are necessary to salvage more group D eyes.
Keratoconus is a degenerative non-inflammatory disease of the corneas with onset generally at puberty. It is progressive in 20% of cases and can be treated by lamellar or penetrating keratoplasty. Changes in corneal collagen structure organization and intercellular matrix as well as apoptosis and necrosis of keratinocytes prevalently or exclusively involving the central anterior stroma and the Bowman's lamina, are documented in the literature.

The technique of corneal collagen cross-linking consists of photo polymerization of stromal fibers by the combined action of a photosentizing substance (riboflavin or vitamin B2) and ultraviolet type A rays (UVA) from a solid-state UVA source. Photopolymerization increases the rigidity of corneal collagen and its resistance to keratectasia.

The method of corneal cross-linking using riboflaving and UV light is technically simple and less invasive than all other therapies proposed for keratoconus. Unlike other mini-invasive methods, such as intrastromal rings (INTACS) and excimer laser surgery, that do not block keratectasia but merely treat the refractive effects of the disease, Riboflavin UV Type A rays treats and prevents for underlying pathophysiological mechanism.

The main aim of this study was to assess the effectiveness and safety of riboflavin-UV induced cross-linking of corneal collagen in reducing the progression of keratoconus and in improving visual acuity. This was a prospective nonrandomized open study. Staring in September 2004, 10 eyes of 10 patients (mean amen 31.4 years) with bilateral keratoconus were treated by combined riboflavin-ultraviolet type- A rays (UVA) collagen cross-linking. Radiant energy was 3mW/cm² or 5.4 joule/cm² for a 30-minute exposure at 1 cm form the corneal apex. A complete ophthalmologic examination (uncorrected visual acuity (IUCA), sphere spectacles corrected visual acuity (SSCVA), best corrected visual acuity (SSCVA) best spectacle-corrected visual acuity (BSCVA) was performed. Patients had corneal computerized topographic examination, linear scan optical tomography, endothelial cell count, ultrasound pachemetry, intraocular pressure (IOP) evaluation, and HRT II system confocal microscopy at 1,2,3 and 6 months. After treatment, eyes were medicated and dressed with a soft contact lens.

Comparative preoperative and postoperative results showed increases of 3.6 lines for UCVA (P=.0000112), 1.85 lines for SSCVA (P=.00065), and 1.66 lines for BSCVA (P=.00071). Topographic analysis showed a mean K reduction of 2.1 ± 0.13 diopters (D) in the central 3.0 mm. Statistical analysis of IOP and endothelial cell count did not show significant differences. Topo-aberrometric analysis findings of corneal symmetry showed a trend toward increasing corneal symmetry with major reduction in asymmetry between vertical hemi meridians. Refractive results showed a reduction of about 2.5D in the mean spherical equivalent, topographically confirmed by the reduction in mean K. Result of surface aberrometric analysis showed improvement in morphologic symmetry with significant reductions in comatic aberrations. Although this study was limited in terms of follow up and number of patients, it confirms that UV rays emitted by Light Emitting Diodes is perfectly calibrated in energy density to produce apoptosis, hence, necrosis of unhealthy activated keratocytes in addition to being completely absorbed by riboflavin beyond the programmed dose and necessary thickness. The results of the pilot study of riboflavin UV induced corneal collagen cross linking were encouraging as far as safety and effectiveness are concerned.

Reviewed by: Dr. Alex Baby DO, DNB., Little Flower Hospital and Research Center, Angamaly
Dry Eye

Book Preview A practical Guide to Ocular Surface Disorders and Stem Cell Surgery
Edited by Amar Agarwal, MS, FRCS, FRCOphth
Publisher SLACK INCORPORATED
NJ USA. 2006, Price: $ 60/-

Dry eye and ocular surface disorders are complex conditions with multiple modes of treatment. Navigate your way through the perplexities with Dry Eye: A practical Guide to Ocular Surface Disorders and Stem Cell Surgery.

Dr. Amar Agarwal has arranged a comprehensive and easy-to-read text focusing on this emerging and hot topic. With contributions from more than 30 of the world’s leaders in ophthalmology, Dry Eye explains all there is know about dry eye disorders and management, as well as information on stem cell surgery.

The four sections inside Dry Eye cover every aspect of ocular surface disorders.

- Section one presents an introduction to the anatomy.
- Section two provides Clinical assessment of a dry eye case and various specific conditions.
- Section three takes on the critical role of management and procedures.
- Section four details special situations.

Main topics covered:
- Stem cell surgery
- Amniotic membrane transplantation
- Cataract and refractive surgery in a dry eye case
- Autologous serum
- Drugs used to treat and manage dry eye
- Punctual occlusion
- Computer vision syndrome

With this text, Dr. Agarwal and his contributing authors have provided well-organized and timely information to guide us to a better understanding of the causes of tear loss and recent breakthroughs in treatment alternatives.

Dr. Agarwal has provided ophthalmologists with the right information to better understand and manage patients afflicted by problem dry eye, a condition that continues to affect more people worldwide.

Ophthalmic Lasers

Charles M. Wormington
Publisher: Butteworth Heinemann.
Philadelphia USA-2005, Price $ 59.95

The field of ophthalmic lasers is constantly evolving-more sophisticated types of lasers plus new and better applications of those lasers are emerging for the diagnosis and treatment of many ocular diseases. These advances are changing the way ophthalmologists use many of these techniques or refer patients to specialists who use them.

This comprehensive, practical guide is designed to help you determine when and how to use lasers for ophthalmic applications and how to manage ophthalmic laser patients before, during, and after laser surgery.

Inside the book you’ll find

- Complete coverage of the basics of lasers-how they work, what components are necessary, how their output is described, characteristics of laser radiation the way lasers and tissues interact and damage mechanisms that account for the clinical uses.
- Important new diagnostic uses of lasers for both the anterior and posterior segments and the therapeutic uses for the anterior segment, including vision correction, laser posterior capsulotomy, glaucoma treatment laser iridotomy, and laser trabecuoplasty.
Corneal Transplantation Surgery has undergone tremendous advancements over the last few decades. This book has been designed as a practical guide to the various aspects of corneal grafting surgery. It elucidates the basic aspects in preoperative evaluation, investigations, established surgical procedures and the advanced techniques in special situations as well as the newer technology in corneal grafting. Theoretical as well as research aspects of corneal grafting have been dealt in a practical manner. An extensive and well-illustrated section provides up-to-date knowledge of complications in corneal transplantation and their management. This should be of particular assistance to ophthalmologists practicing in remote areas and involved in the postoperative care of the grafted patients.

This book provides a comprehensive knowledge and information about the various aspects of Corneal grafting surgery. World-renowned corneal transplantation surgeons from the developed and the developing countries have come together to address the complex issues of corneal transplantation surgery in a simple and effective manner. These stalwart corneal surgeons enlighten the readers with their knowledge and vast experience in both basic and advanced surgical skills in a lucid and practical style.

Topics include:

- Key aspects of the ophthalmologists role in laser applications, such as referrals and post-procedure complication management.

Chapter 1 covers the basics of lasers: how they work, what components are necessary, how their output is described, and the characteristics of laser radiation.

Chapter 2 covers the different types of ophthalmic lasers available. Chapter 3 provides fairly comprehensive coverage of the new ophthalmic diagnostic uses of lasers. Chapter 4 through 9 are devoted to therapeutic uses of ophthalmic lasers in the anterior segment.

The intent is that the book will be useful for both the novice and the experienced eyecare practitioner as well as for students and residents in training programs. This book will be especially useful for those practitioners who refer patients for laser treatment. The book will help practitioners decide which type of system will be useful for their practice, their patients, or referral of their patients. This book is up to date with the latest advances in ophthalmic laser technology.
Welcome to KSOS

All new members to this community are welcome to use the KSOS website that is feature rich and informational. The website address is

www.ksos.in

How to register as in the website?

All members are requested to provide the webmaster of KSOS, their details such as

1. First Name     2. Last Name     3. email id

What the webmaster will do:

The webmaster will add these details into the member list. The system will generate the User Id and Password, which will then be emailed to you.

Once the members receive their user ids and passwords, they are requested to visit the website and log in using the Member Login area (top right of the website). Then use the “View My Account” link to see your account details. Please update your details in that section. You are also allowed to change your User Id and Password, to your liking. Please use names that you can always remember, for your user id. If you change your password, do memorise the new password.

Online facilities for the Members

KSOS members have access to very good online resources. All members can then take advantage of the advanced facilities provided such as

1. KSOS journals: Members alone can access the KSOS journals online. You have to login to access the journals.
2. Message Board Members alone can feed messages into the message board for the rest of the KSOS members.
3. Discussion Forum for members All members are also requested to take part in the discussion forum (a new feature) in the website. For this, you are requested to register separately. The instructions for this have been given in the “News Update” section of the website.
4. Video Streaming has been added to the website
This feature has been added to the KSOS website, making the website even more vibrant. It features streaming video content of medical surgeries and procedures.
5. Useful links The KSOS Website provides links to useful and important websites across the world.
6. Member search KSOS members can access the contact details of any other member, using the website. All members are requested to visit the website and see the features in the website and get accustomed to the online system.
CME Programmes

STATE CONFERENCES

“Practical tips in Cataract Surgery”
22nd April 2007
Chaithanya Eye Hospital, Trivandrum.
Dr. K G R Nair
Ph: 0471-2447183

CME on Cataract
20th May 2007
Malappuram Ophthalmic Society
Dr. Muhammed Swadique
Ph: 9447117722

CME “Anathanayanam 2007”
27th May 2007
Regional Institute of Ophthalmology, Trivandrum
Dr. Simon Geroge
Ph: 9847228448

“POT POURRI”
8th July 2007
Chakrabarti Eye Care Centre, Trivandrum
Dr. Meena Chakrabarti
Ph: 0471-2555530

NATIONAL CONFERENCES

7th All India Uveitis Conference
1st & 2nd December 2007
Venue: International Convention Centre,
Sumanti Shankaradeva Kalakshetra
Organising Secretary: Dr. Dipankar Das
E-mail: usissn2007@sify.com

INTERNATIONAL CONFERENCES

ASCRS Symposium on Cataract, IOL and Refractive Surgery
April 27th – May 2nd 2007
Venue: San Diego Convention Centre, California

ASOA Congress on Ophthalmic Practice Management and the Clinical and Surgical Staff Programme.
April 28th – May 1st 2007
Venue: San Diego Marriott Hotel & Marina
E-mail: www.ascrs.org, www.asoa.org
Mail: ASCRS, ASOA 2007
C/o Convention Data Services
107 Waterhouse Road
Bourne, MA 02532

XXV Congress of the European Society of Cataract & Refractive Surgeons (ESCRS)
September 8-12, 2007
Venue: Stockholm
E-mail: www.escrs.org
## List of Award Winners of DRISHTI - 2006

<table>
<thead>
<tr>
<th>Award</th>
<th>Winner</th>
<th>City</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Sankara Menon Award</td>
<td>Dr. GIRIDHAR A.</td>
<td>Kochi</td>
</tr>
<tr>
<td>Dr. Siva Reddy Award</td>
<td>Dr. MEENA CHAKRABARTI</td>
<td>Trivandrum</td>
</tr>
<tr>
<td>Dr. Tony Fernandez video award</td>
<td>Dr. ANJU RAJU</td>
<td>Kochi</td>
</tr>
<tr>
<td>KSOS Free paper award</td>
<td>Dr. MEENA C.K.</td>
<td>Hyderabad</td>
</tr>
<tr>
<td>Scientific poster award</td>
<td>Dr. MEENA CHAKRABARTI</td>
<td>Trivandrum</td>
</tr>
<tr>
<td>Dr. Subramaniam award for P.G. students</td>
<td>Dr. ANU ANNA PAUL</td>
<td>Chaithanya, Trivandrum</td>
</tr>
<tr>
<td>TACO Quiz for PG students</td>
<td>Dr. BINDU APPUKUTTAN</td>
<td>Dr. BUSHRA T. Regional Institute of Ophthalmology Trivandrum</td>
</tr>
</tbody>
</table>
The Role of Antioxidants in Age Related Macular Degeneration

**AMD : THE NEMESIS OF THE AGED**
- Leading cause of Irreversible Blindness
- Affects population > 85 Years: 100% in 2020?
- Epidemic of AMD, increasing prevalence age
- 9.2% of all types of AMD

**OXIDATIVE STRESS & AMD**
- Morphological changes in Ageing & Disease associated with Oxidative Stress
- Harmful Reactive Oxygen Intermediates (ROI) includes Free Radicals, Singlet Oxygen, Hydrogen Peroxide

**WHAT ARE FREE RADICALS**
- Contains 1/More Free Electrons (Unstable)
- Attracts Electrons From Other Mols (stable)
- Damage To Lipids, Proteins, & DNA

**OXIDATIVE STRESS & AMD**
- High Level of Light Irradiation,
- High O2 Consumption, Phagocyossed
- Photoreceptor Outer Segments Rich in Polyunsaturated Fatty Acids,
- Increased Lipid Peroxidation, Build Up Of Oxidised Pufa,
- Basal Laminar Deposits As Drusen,
- Insufficient Waste & Nutrient Transfer To & From Choroid

**Zinc & Antioxidants Plus Zinc Significantly**
- Reduced the risk of Developing Advanced AMD in the high risk category 3 & 4.
- Antioxidants Alone: 17%
- Zinc Alone: 21%
- Antioxidants Plus Zinc: 25%

**AMD : THE INDIAN STORY**
- AGE > 50 years: 10%-30%
- AGE < 50 years: 1.39% - 2.25%
- (Andhra Pradesh Eye Disease Survey 1996-2000)

**AMD : NUTRITIONAL FACTORS**

**DIETARY INTERVENTION WITH INCREASED CONSUMPTION OF ANTIOXIDANT NUTRIENTS COULD BE**
- A PRIMARY PREVENTIVE MEASURE For Controlling Oxidative Damage That May Lead To AMD

**AREDS : DESIGN**
- A Randomised Placebo Controlled Trial of High Doses of Vit C, Vit E, α CAROTENES, & Zinc For AMD.
- 11 Centres, Double Masked Clinical Trial on 3640 patients, F/u: 6.3 Years,
- 2.4% Lost To F/U, (ARCH OPHTHALMOL 2001; 119;1417 – 1436 AREDS REPORT : 8)

**AREDS STUDY DESIGN 4R**
- CATEGORY 1& 2 PARTICIPANTS
- Extensive Small Drusen, Non Extensive Intermediate, Drusen, Pigment Abnormalities In One Or Both Eyes
- CATEGORY 3 & 4
- Large Druse, Non Central Geographic Atrophy, Advanced AMD In One Eye

**AREDS : REPORTS**
- Zinc & Antioxidants Plus Zinc Significantly reduced the risk of Developing Advanced AMD in the high risk category 3 & 4.
- Antioxidants Alone: 17%
- Zinc Alone: 21%
- Antioxidants Plus Zinc: 25%

**AREDS : REPORTS**
- Statistically Significant Reduction in Risk Of Moderate Visual Loss in Category 3 & 4 No Serious Adverse Effects Associated with Any of the Study Medications

**CONCLUSIONS OF AREDS**
- All Patients > 55 yrs Should Have A Dilated Fundus Examination to Determine
- RISK OF DEVELOPING AMD
- Consider Supplements on A Long Term Basis In Large Drusen, Non Central Geographic Atrophy In One Or Both Eyes
- Advanced AMD In One Eye/Visual Loss Due To AMD In One Eye
- No Contraindications Such As Smoking

**BILATERAL ADVANCED AMD ???**
- No Clear evidence that Supplements are Beneficial Long Term Supplements: How Long ???

**AREDS REPORT**
- Treatment Benefits & Visual Outcomes maintained through 7 Yrs in participants at risk of progression of AMD
- A Word Of Caution !!!
- The Treatment Benefit Is Modest & Participants In All Treatment Arms Continue To Progress To Advanced AMD & Loose Vision

**UNANSWERED QUESTIONS**
- Choice of supplement, Financial implication of long term supplementation, toxicity, schedule: daily /alt days /skip,
- how long ???, reformed chronic smoker - can it be safely given?
### ANTIOXIDANT SUPPLEMENTS: THE CURRENT SCENARIO

<table>
<thead>
<tr>
<th>Criteria</th>
<th>AREDS Recommendation</th>
<th>V.Ret</th>
<th>Vitalux Plus T</th>
<th>I.site</th>
<th>I.site Forte</th>
<th>Retinokare</th>
<th>Antoxid</th>
<th>Antoxid HC</th>
<th>Ocugold</th>
<th>Glacex</th>
<th>Eye Vital</th>
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<tbody>
<tr>
<td>Beta Carotene / Vit A</td>
<td>(β) 15mg</td>
<td>(β) 5mg</td>
<td>(A) 10000 lu</td>
<td>6000 lu</td>
<td>(A)2500 lu</td>
<td>(β) 10mg</td>
<td>(β) 30mg</td>
<td>(β) 1.2 Mg</td>
<td>(A)2500 lu</td>
<td>(A)5000lu</td>
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<tr>
<td>Vit C</td>
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<td>300mg</td>
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<td>100mg</td>
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<td>3.2mg</td>
<td>6.4mg</td>
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<td>256mcg</td>
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**COMPARISON OF CURRENTLY AVAILABLE ANTIOXIDANT PREPARATION WITH THE RECOMMENDED AREDS SUPPLEMENTS**
GENERAL INSTRUCTIONS TO AUTHORS

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: Give 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 communication, 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: Authors(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 copyright 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.

The manuscripts are to be sent to The Editor by Courier Mail or by Registered post. The corresponding author will receive communication from the Editor within two weeks of receiving the manuscript.

11. All manuscripts are subjected to editorial board review.

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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