

# insight

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## **Editorial**

The management of glaucoma, especially the medical management has undergone tremendous changes in the past decade. Newer, safer alternatives have evolved after years of research thus benefiting the patient. In fact newer medications continue to evolve and enter the arena at such a rapid pace that it is becoming increasingly difficult to keep one's knowledge updated. Hence this issue of Insight focuses on the current medical management of glaucoma in its Perspective section.

One leaves medical school after learning the 4 cardinal methods of examination - inspection, palpation, percussion and auscultation. However, we ophthalmologists most often use only one of these - inspection, to diagnose most intraocular diseases. In contrast to other specialties of medicine, a biopsy is rarely needed for diagnosis and it is also avoided to prevent potentially blinding complications associated with it. The other Perspective article in this issue of Insight details the indications, techniques and complications of intraocular biopsy in the rare event we need to perform one.

**Dr. Mahesh P Shanmugam**  
Editor

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Perspective:

# Current Therapeutic Options in the Management of Glaucoma

Vineet Ratra and Vijaya

The medical management of glaucoma is changing rapidly. Many more new therapeutic agents for the medical treatment of glaucoma have been introduced. Research is driving the development of safer and more effective therapies for lowering intraocular pressure (IOP). In addition, there have been advances in our understanding of glaucoma, though incomplete. Research is uncovering new agents, which may help preserve visual function in glaucoma. Some of our current therapies may have neuroprotective or vasoprotective qualities that may improve the outcomes of glaucoma management. Other agents designed to directly enhance neuronal survival also show promise in the treatment of glaucoma for the future

The **nonselective beta-adrenergic antagonists** have been the "gold standard" for glaucoma medical therapy since the introduction of **Timolol maleate** in the late 1970s. When introduced, these agents rapidly became accepted for first-line therapy due to their ocular comfort and efficacy. With the development of newer agents, the role of the nonselective beta-blockers as the automatic choice for first-line therapy is being reevaluated.

**Timolol maleate** is the prototype of the ocular beta-blockers used. It contains the maleate salt of the levo-isomer. It reduces IOP by 25-30 % and can be used in all types of glaucoma. In addition to timolol maleate, timolol hemihydrate is also available.

Table I : Beta-blockers

Class	Generic name	Trade Name	Concentrations	Dosing Regimen	Major Side effects	Mechanism(s) of IOP Reduction
1. Nonselective beta <sub>1</sub> -/beta <sub>2</sub> -adrenergic antagonists	Timolol maleate	lotim Glucamol Timoptic	0.25%, 0.5%	Two times a day	Bradycardia Bronchospasm Fatigue Impotence Hypotension	Decreases Aqueous humor Production
	Timolol maleate gel forming solution	Timolet GFS Timoptic XE	0.25%, 0.5%	One time a day		
	Levobunolol hydrochloride	Betagan	0.25%, 0.5%	One – Two times a day		
	Carteolol hydrochloride	Ocupress	1%	Two times a day		
2. Selective beta <sub>1</sub> -adrenergic antagonist	Betaxolol hydrochloride	lobet Optipress Betoptic	0.5%	Two times a day	Bradycardia Bronchospasm	Decreases aqueous humor production
	Betaxolol Hydrochloride Suspension	Betoptic – S Optipress- S	0.25%	Two times a day	Fatigue	

**Levobunolol** has the longest half-life of the currently available nonselective beta-blockers. This medication has an active metabolite, dihydrolevobunolol, which contributes to the long half-life of this agent.

**Carteolol** hydrochloride is a nonselective beta-adrenergic antagonist that also possesses intrinsic sympathomimetic activity (ISA). Pharmacologically, ISA may increase the systemic safety of this compound compared with the other beta-adrenergic antagonists because ISA minimizes some of the adverse effects that beta-blockers may have, particularly with respect to serum lipids. All beta-blockers tend to increase low-density lipoprotein cholesterol and reduce high-density lipoprotein cholesterol. Therefore, in patients at risk for cardiovascular disease, carteolol may be somewhat safer than other beta-blockers in this class.

**Betaxolol** - Within the beta-adrenergic antagonist class, only one beta-1 selective antagonist is available, betaxolol. In its present form as a racemic mixture, this compound is generally less effective in lowering IOP than the nonselective beta-adrenergic antagonists<sup>1,2</sup>. It also shows neuroprotective properties. Beta-1 receptors are located primarily in the heart and cardiovascular system; beta-2 receptors are in the lungs. Because of its selectivity, there is less likelihood of pulmonary side effects such as bronchospasm.<sup>3</sup> A newer formulation in development of only the l-isomer of betaxolol may offer improved efficacy.

**Mechanism of action** - Beta-blockers decrease IOP by reduction of aqueous humor production.

**Dosage and administration** - Timolol maleate is available in a 0.25% and 0.5% concentration, Betaxolol and Levobunolol in 0.5% concentration and Carteolol in 1% and 2% concentrations. Metipranolol, another nonselective beta-adrenergic antagonist, is available as a 0.3% concentration. Beta-blockers generally require twice daily therapy except levobunolol, which can be used once a day. More recently, new formulations of timolol have become available in a gel-forming vehicle, Timolet GFS in Xanthan gum gel and Timoptic XE in Gellan gum gel that has reinforced the concept of once daily dosing.

**Contraindications** - Bronchial asthma, obstructive pulmonary disease, heart block or cardiac failure, are major contraindications for nonselective beta-blockers and relative contraindications for selective beta-blockers.<sup>5</sup>

**Side effects** - The systemic side effects related to beta-blockers are dose related. Bradycardia, arrhythmia, heart failure, syncope, bronchospasm and airway obstruction, distal oedema, hypotension, depression, worsening symptoms of myasthenia<sup>6</sup> and masking of hypoglycemia in patients with insulin dependent diabetes mellitus, are the systemic side effects. Ocular side effects are uncommon but there may be instances of ocular irritation, redness and blurred vision. Beta-adrenergic antagonists are known to stabilize cell

membranes, and, therefore, may cause mild relative corneal anesthesia. This could potentially exacerbate dry eye symptoms.

**Washout** - The time needed for beta-blockers to lose their activity completely is 2-4 weeks.

Generally, a 25% to 30% reduction in IOP may be expected with initiation of therapy with a nonselective beta-blocker.<sup>7</sup> As with all glaucoma medications, a one-eye therapeutic trial is recommended. The beta-blocker should be instilled in one eye and allowed to reach steady state, which may require 3 to 4 weeks. Only one eye is treated and the other eye serves as a "control." On follow-up evaluation at 3 to 4 weeks, if the medication is effective, the IOP in the eye being treated should decrease compared with the untreated eye regardless of the absolute level of IOP. This helps to distinguish true effect from diurnal variation. If there is no difference or only little difference between the two eyes, the medication is probably not effective. With a one-eye therapeutic trial, there is a small effect in the fellow eye with usage of a topical beta-blocker. On average, the pressure in the fellow eye may be reduced 1 to 1.5 mm Hg, which may slightly mask the overall efficacy of the medication.

Once medical therapy is found effective and instituted in both eyes, it is necessary to assess the continued efficacy of the drug for the effects of short or long-term drift. In short-term drift, the pressure reduction may only be sustained for a matter of a few weeks or months. It has been suggested that, in response to beta-receptor antagonism, there is drug-induced up-regulation of beta receptors.<sup>8</sup> More commonly, long-term drift, or tachyphylaxis, may occur with the use of nonselective beta-blockers.<sup>9</sup> Therefore, it may be prudent to consider a reverse one-eye therapeutic trial if IOP control seems to be waning in a patient on a beta-blocker. In this circumstance, the medication is discontinued in one eye and the pressures are reexamined in 1 month. If the medication was still effective, the IOP in the eye where the medicine was discontinued should increase relative to the fellow eye. If the IOP does not increase, the beta-blocker should be discontinued and another medication should be substituted. Conversely, if the beta-blocker was proven effective, then it can be re-instituted in both eyes and adjunctive therapy should be considered.<sup>10</sup>

### **Adrenergic Agonists**

Nonselective adrenergic agonists such as epinephrine and dipivefrin are infrequently used today for the treatment of glaucoma and are being replaced by the alpha-2 selective agonists. **Epinephrine** is available in 0.25%, 0.5%, 1.0%, and 2.0% concentrations and is used twice daily. **Dipivefrin** is available in a 0.1% concentration and is also used twice daily. Dipivefrin is a prodrug of epinephrine, and, therefore, a much lower concentration is required topically.<sup>11</sup> Dipivefrin penetrates the cornea well, leading to intraocular concentrations that are similar to epinephrine compounds.

**Mechanism of action** - The mechanism of action of non-selective adrenergic agonists is by decreasing aqueous production and increasing outflow.

**Side effects** - Because dipivefrin is a prodrug, systemic adverse effects are less likely. Ocular adverse effects of these agents include irritation, hyperemia, pupillary dilation precluding its use in occludable angles, follicular conjunctivitis, brittle angles, follicular conjunctivitis, brittle conjunctiva leading to subsequent filtration surgery failure, adrenochrome deposits, and the potential for cystoid macular edema in aphakic or pseudophakic eyes. Systemic adverse effects include hypertension, headaches, and cardiac arrhythmias.

**Table II : Adrenergic agonists**

Class	Generic name	Trade Name	Concentrations	Dosing Regimen	Major Side effects	Mechanism(s) of IOP Reduction
Nonselective alpha- and beta - adrenergic agonists	Dipivefrin Hydrochloride	Propine	0.1%	Two times a day	Allergy Conjunctival hyperemia Cystoid macular edema Headache Hypertension	Increases traditional outflow facility
Selective alpha <sub>2</sub> -adrenergic agonists	Apraclonidine	Iopidine	0.5%, 1%	Two - three times a day	Allergic blepharoconjunctivitis Dry mouth	Decreases Aqueous humor Production
	Brimonidine	Alphagan & Alphagan P	0.2% 0.15%	Two-three times a day	Dry mouth Fatigue Drowsiness	Decreases Aqueous humor Production and increases uveo scleral outflow

Within the adrenergic class, the alpha-2 adrenergic agonists are currently the primary therapeutic agents in use. Whereas effects of alpha-1 adrenergic agonists include vasoconstriction, pupillary dilation, and lid retraction, which are not advantageous in the treatment of glaucoma, alpha-2 adrenergic agonists are responsible for reducing IOP and providing potential neuroprotective properties.

**Apraclonidine** - This was the first alpha-2 selective agent available. This agent is only mildly selective for the alpha-2 over the alpha-1 receptors and is available in a 0.5% concentration for short-term therapy and a 1% concentration for post-laser use. Apraclonidine may be used two to three times daily.

This compound is associated with a high risk of follicular conjunctivitis and contact dermatitis and results in ocular irritation, hyperemia, and ocular discomfort. The most common systemic adverse effects include hypotension, dry mouth, and fatigue. It also has a high rate of tachyphylaxis. Hence it has limited use for chronic therapy.<sup>12</sup>

**Brimonidine** - Currently, brimonidine tartrate 0.2% (Alphagan) is the primary alpha-2 agonist used for glaucoma therapy. This agent has been shown to have similar efficacy in reducing IOP compared to Timolol.<sup>13</sup> Brimonidine also has a neuroprotective effect.

**Mechanism of action-** Initially, this agent suppresses aqueous production; with time, also leads to increased uveoscleral outflow.

**Dosage and administration-** Brimonidine 0.2% may be administered two to three times daily. Brimonidine's IOP reductions average 20% to 30%.

**Contraindication** - Oral monoamine oxidase (MAO) inhibitor users.

**Side effects** - Follicular conjunctivitis, contact dermatitis, ocular irritation, and hyperemia may occur in some patients. Most common systemic adverse effects include fatigue, hypotension, and sleepiness.

The washout period of brimonidine is 1-3 weeks.

### **Carbonic anhydrase inhibitors**

Carbonic anhydrase inhibitors (CAIs) are available in both oral and topical formulations. The oral medications are infrequently used for chronic therapy, but are useful for short-term elevations in IOP or acute glaucoma episodes. The primary oral CAIs are acetazolamide and methazolamide.

**Acetazolamide** - is available in 62.5 mg, 125 mg, 250 mg, and 500 mg strengths and is used four times a day. The lower dosages are primarily for pediatric use. The 500 mg strength is available in a sustained release capsule for oral administration once or twice a day, or as a powder, which may be reconstituted for parenteral administration.

**Mechanism of action** - is by decreasing aqueous production.

**Contraindications** - Hyponatremia, hypokalemia, hyperchloremic acidosis, kidney and liver disease and patients with adrenal gland failure. They are contraindicated in patients with allergy to sulfa medications, as there is a risk of Stevens-Johnson syndrome.

**Side effects** - Few ocular side effects are associated with these medications when administered orally. Systemic adverse effects include taste perversion, especially to carbonated beverages, acidosis, erythema multiforme, thrombocytopenic paraesthesias, lethargy, renal stones, loss of libido, hypokalemia, loss of appetite, frequency of urination, and bone marrow depression.

**Topical CAIs** - Currently available topical CAIs include **dorzolamide (Trusopt)** and **brinzolamide (Azopt)**. These medications have been found to have a modest effect on IOP, generally less than the effect of timolol.<sup>14,15</sup>

**Table III: Carbonic Anhydrase Inhibitors**

Class	Generic name	Trade Name	Concentrations	Dosing Regimen	Major Side effects	Mechanism(s) of IOP Reduction
Topical carbonic anhydrase	Dorzolamide	Trusopt	2%	Two -three times a day	Bitter taste	Decreases aqueous humor production
	Brinzolamide	Azopt	1%	Two –three times a day	Blurred vision	Decreases aqueous humor production.
Oral carbonic Anhydrase inhibitors	Acetazolamide	Diamox	125 mg, 250 mg	Four times a day	Anemias Electrolyte imbalance Fatigue Gastro-intestinal disturbances	Decreases aqueous humor production
		Iopar S R Diamox Sequel	250 mg 500 mg	Two times a day	Kidney stones Malaise Metabolic acidosis Paresthesias Polyuria Stevens-Johnson syndrome	

**Dosage and administration** - Dorzolamide is available in a 2% concentration and brinzolamide in a 1% concentration. These medications may be used two to three times daily.

**Side effects** - Ocular adverse effects include blurred vision, keratitis, ocular stinging and irritation, conjunctivitis, and transient myopia. In general, brinzolamide causes less stinging and irritation than dorzolamide because brinzolamide’s pH is more neutral. Systemic adverse effects of topical CAIs parallel those that may occur with the oral CAIs. However, the adverse effects associated with topical CAIs tend to be less common and less severe compared with oral CAIs, with the exception of the effects that are related to idiosyncratic reactions, such as Stevens-Johnson syndrome and bone marrow depression.

**Contraindications** - Topical CAIs are contraindicated in patients with corneal endothelial dysfunction as carbonic anhydrase 2 enzyme in the corneal endothelium when inhibited leads to corneal edema. Severe renal impairment and hypersensitivity to sulfa drugs are other contraindications.

### **Prostaglandin Analogue**

**Latanoprost 0.005%**- was the first available prostaglandin analogue introduced in the United States for glaucoma therapy in 1996. When used once daily, this medication has been demonstrated to have equivalent, or in some patients, superior efficacy when compared to timolol. Generally, IOP reductions of 25% to 30% may be expected.<sup>16</sup>



**Side effects** - Reported common ocular adverse effects include increased pigmentation of the iris, eyelash growth, hyperpigmentation, keratitis (which may at times be herpetic), cystoid macular edema, anterior uveitis, and conjunctival hyperemia and irritation.<sup>17,18</sup> In the clinical trials, the most common systemic adverse reactions were flu-like symptoms reported in one third of patients. Because latanoprost is a prostaglandin F-2-alpha analog, an inflammatory mediator, systemic absorption may result in joint and muscle inflammation leading to arthralgia and myalgia in some patients. This may be particularly noticeable in patients already prone to arthritis symptoms, such as those with rheumatoid arthritis. Hypertension may occur in some patients.

**Bimatoprost 0.03% (Lumigan)** – Bimatoprost is also derived from cell membrane bound lipids. However, this agent has no demonstrable binding to any of the known prostaglandin receptors and is derived from anandamide, rather than arachidonic acid from which typical prostaglandins such as latanoprost are derived. This agent, may therefore, represent a new class of compounds that have been termed prostamides. Early published reports suggest that this agent is superior to timolol in reducing IOP, offers potentially better diurnal control than latanoprost, and has less prostaglandin-like side effects than latanoprost.<sup>19</sup>

**Mechanism of action** - Preliminary studies suggest that IOP lowering effect occurs as a result of increase in outflow facility by reduction in resistance to outflow of the pressure sensitive pathways.<sup>19</sup>

**Dosage and administration** - It is available in 0.03% concentration. Once daily administration has been seen to provide good 24 hrs IOP control.

**Side effects** - Conjunctival hyperaemia is seen to be more common. Otherwise the side effects are similar to those with latanoprost.

**Unoprostone 0.15% (Rescula)**- A second prostaglandin-related analogue is unoprostone. This agent has low affinity for prostaglandin receptors and may be considered a docosonoid derivative. In addition to lowering the IOP, this agent may inhibit the activity of endothelin-1 and may improve ocular blood flow.<sup>20</sup> However, a beneficial effect on human ocular blood flow remains unproven.

**Mechanism of action** - It is believed to increase the aqueous outflow although the exact mechanism is still unknown.

**Dosage and administration** - The recommended dosage for Unoprostone 0.15% is twice daily.

**Side effects** - The most common ocular adverse effects reported are burning/stinging, itching, dry eyes, hyperemia, increased eyelash length. Abnormal vision, eyelid disorders and lacrimation disorders have also been reported. It causes permanent change in pigmented tissues and thus can lead to change in the iris color over a long period. The most commonly reported systemic

adverse effects were flu like syndrome, allergic reactions, bronchitis, pharyngitis, rhinitis, sinusitis, hypertension and insomnia.

**Contraindications** - It should be used with caution in patients with active intraocular inflammation, renal or hepatic impairment.

**Travoprost 0.004% (Travatan)** - is a selective FP prostanoid receptor agonist that appears to have efficacy and side effects similar to latanoprost.

**Mechanism of action** - It reduces IOP by increasing the uveoscleral outflow, however the exact mechanism is still unknown.

**Dosage and administration** - The recommended dosage is once daily in the evening.

**Side effects** - The common ocular adverse effects are conjunctival hyperemia, dry eye, foreign body sensation, subconjunctival haemorrhage and tearing, permanent darkening of the iris and periorbital tissues, increase in the number and length of eyelashes and reduced vision. The systemic side effects are angina, arthritis, anxiety, bronchitis, hypertension, bradycardia, depression, dyspepsia and prostate disorder.

**Contraindications** - It should be used with caution in patients with active intraocular inflammation, hepatic impairment. It should not be used in women who are pregnant or planning a pregnancy as it interferes with maintenance of pregnancy. (Information brochure of Travatan.)

#### **Parasympathomimetic (miotic)**

A variety of parasympathomimetic (miotic) agents are available for the treatment of glaucoma.<sup>21</sup> However, the use of these agents is decreasing as newer therapeutic agents have been developed. The parasympathomimetic agents are either direct acting cholinergic agonists or indirect acting anticholinesterase agents.

**Direct acting cholinergic agonists** - These include **pilocarpine** solutions, pilocarpine gel, and carbachol. These agents are available in a variety of concentrations and their dosage varies from once daily for the pilocarpine gel to four times daily for the pilocarpine solutions. Typical IOP reductions of direct acting cholinergic agonists are 15% to 20%.

**Side effects** - Ocular adverse effects include posterior synechia, miosis, brow ache, cataract, myopia, retinal detachment, dermatitis, and ocular irritation. Systemically, these agents may cause increased salivation, gastric secretion, and abdominal cramps, particularly with overdosing.

**The anticholinesterase inhibitors** - include **echothiophate iodide**, **physostigmine**, and **demecarium**. These agents are administered once to twice daily and result in an average of 15% to 20%

**Table V : Parasympathomimetics**

Class	Generic name	Trade Name	Concentrations	Dosing Regimen	Major Side effects	Mechanism(s) of IOP Reduction
Parasympathomimetics	Pilocarpine Hydrochloride	Pilocarpine	0.5%, 1%, 2%, 3%, 4%, 6%	Four times a day	Brow ache Dimming of vision	Increase traditional outflow facility
		Ocusert	Insert 20mg/hr 40 mg/hr	Four times a day for 5 to 7 days	Fluctuating vision Gastro intestinal disturbance	
	Pilocarpine nitrate	Pilogan	1%, 2%, 4%	Four times a day	Headache Induced myopia Miosis	
	Pilocarpine gel	Locarp gel Pilo-Hs gel	4%	At night	Retinal detachment	

reductions in IOP. Ocular adverse effects of the anticholinesterase inhibitors are similar to the direct acting cholinergic agents, including pseudopemphigoid. Systemic side effects are also similar. The anticholinesterase inhibitors may cause considerable ocular inflammation following ocular surgery and prolonged paralysis may occur following the use of certain muscle relaxants during general anesthesia. Therefore, it is advisable to discontinue these agents at least 1 to 2 weeks before general anesthesia is anticipated.

### Fixed Combination Agents

Fixed combination agents are gaining popularity. Historically, combinations of pilocarpine and epinephrine compounds were used but are rare now. More recently, a **timolol/dorzolamide (Cosopt)** combination therapy has been available. This fixed combination is used twice daily and results in pressure reductions of 25% to 30%.<sup>22</sup> It is important to remember that the ocular and systemic adverse effects are a combination of the side effects of both medications. In addition, as with any fixed combination medication, it is

prudent to first use the components of the fixed combination independently to ensure they are effective and well tolerated before using the fixed combination. Fixed combination therapies such as **latanoprost/Timolol (Xalacón)**, **timolol/brimonidine**, and others are being evaluated in clinical trials.

### General Approach to Medical Therapy

Currently, when initiating medical therapy for glaucoma, three agents or classes of medications are primarily considered as first-line therapy: nonselective beta-blockers, brimonidine, and latanoprost. A one-eye therapeutic trial should be performed to ensure efficacy and to assess tolerance of any medication. If one medication does not reach the desired therapeutic threshold of reducing pressure by 20% to 25%, discontinuing that agent and trying another should be considered before considering adjunctive therapy. Of these three agents, brimonidine and latanoprost have the most favorable systemic safety profiles and least risk of systemic drug interactions. In addition, the adverse effects of brimonidine and latanoprost, when they occur, are generally easy to diagnose and are thought not to cause serious potential sequelae. However, some of the long-term adverse effects of a prostaglandin analogue remain unknown, because these agents have been available for only 4-5 years. Many more years of follow-up may be required before the implications of some of these adverse effects, such as iris pigmentation, related to these agents, are understood. Beta-adrenergic antagonists are associated with the lowest risk of topical adverse effects; however, there are many potential systemic adverse effects.

Patients should be carefully queried at each visit regarding potential side effects. The

**Table VI : Combination Product**

Class	Generic name	Trade Name	Concentrations	Dosing Regimen	Major Side effects	Mechanism(s) of IOP Reduction
Combination product	Dorzolamide-timolol	Cosopt	Dorzolamide 2%- Timolol 0.5%	Two times a day	Bitter taste Fatigue	Decreases aqueous humor production
	Latanoprost Timolol	Xalacón	Latanoprost 0.005% Timolol 0.5%	Once a day		Decreases Aqueous humor production and increases outflow

scope of this questioning may be tailored to uncover the adverse effects most likely to be associated with the use of a particular compound. One must be cognizant that patients, as well as their general physicians, may not associate adverse effects or difficulties with medical conditions to the use of their glaucoma drops, particularly where cardiac, pulmonary, or central nervous system side effects are concerned. It is important to ensure that patients understand the proper dosing requirements of the different agents and are able to demonstrate that they can instill their medications successfully. Often, patients fail medical therapy because they are unable to use their medications properly. If the medications can be used according to the recommended dosing regimens, they would most likely be effective. When a patient seems to be losing pressure control, one must consider that the current agents may be no longer effective. Adding other medications may complicate the therapeutic regimen, decrease compliance, and increase the cost and risk of adverse effects. Therefore, reverse therapeutic trials should be considered to ensure the medications are effective before adding additional medications.

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**Perspective:**

# Intraocular Biopsy Techniques

**Ajeet Madhav Wagle And Mahesh P Shanmugam**

## **INTRAOCULAR BIOPSY TECHNIQUES**

Unlike most other disciplines of medicine ocular tissues usually allow direct examination of the pathology aiding in diagnosis. Biopsy is an invasive procedure and is infrequently performed in intraocular diseases. It is usually indicated only in specific situations of diagnostic dilemma after all possible non-invasive investigations are inconclusive or when the result of the biopsy is likely to alter the management significantly. The advantage lies in a possible tissue diagnosis and/or identification of the causative microbiologic agent.  
prerequisites

An ocular biopsy should be minimally invasive, with a low complication rate and should attempt at preserving vision if possible. A team of skillful surgeon, pathologist and a microbiologist with good co-ordination is a must for best results. Equally important is a well-equipped laboratory facility. The specimen is very sparse and delicate and needs proper handling.

The patient must be well informed about goals of treatment, likely management options, anticipated pathologies and possible risks and complications. An informed consent for the procedure is a must.

Indications

### 1. Intraocular mass lesions/tumors –

Masquerade syndromes – e.g. suspected intraocular lymphoma.  
To differentiate an amelanotic melanoma from ocular metastasis.  
Suspected ocular metastasis with unknown primary malignancy.

Atypical presentations – e.g. retinoblastoma in adults.

Excision biopsy of anterior segment tumors – especially iris and ciliary body.  
Patient insisting on histopathological diagnosis prior to recommended therapy.

### 2. Infections – etiologic diagnosis (Bacterial/Viral/ Fungal/Protozoal)

Endophthalmitis

Nonresolving/ Vision threatening chorioretinitis

Subretinal abscess – non-resolving/atypical presentation.

### 3. Degeneration's –

!Amyloidosis

## **Contra-indications**

1. Typical clinical presentation and diagnosis possible noninvasive investigations.
2. Friable tumors- e.g. retinoblastoma, for risk of dissemination.
3. Biopsy unlikely to alter management/ prognosis.

## **Biopsy techniques**

1. Aqueous tap
2. Vitreous tap/ Diagnostic vitrectomy
3. Fine Needle Aspiration Biopsy
4. Chorioretinal Biopsy
5. Incisional/Excision Biopsy

Vitreous biopsy for acute endophthalmitis is probably the most common ocular biopsy performed<sup>1,2</sup>. Fine needle aspiration biopsy is used mainly for mass lesions while chorioretinal biopsy is indicated in non-resolving inflammatory disorders. Excision biopsies are performed for anterior segment tumors, rarely though for posterior segment lesions.

### **Aqueous Tap <sup>1</sup>**

#### **indications**

1. Endophthalmitis
2. Masquerade syndromes
3. Nonresolving/ Atypical anterior chamber inflammation with hypopyon.

#### **Procedure**

Anterior chamber tap is an outpatient procedure. Asepsis is ensured with 5-10% povidone iodine. With patient in supine position, eye speculum is used to separate the lids and topical anaesthetic agent is instilled into the cul-de-sac. A 27 – 30 gauge needle mounted on a 1cc/2cc disposable syringe is used. The globe can be stabilized with a forceps. An entry into the anterior chamber is made at the temporal limbus, 180° away from the mass. The needle is gently advanced parallel to the iris plane, avoiding the pupillary area in a phakic eye. 0.1-0.2 ml of aqueous is gently aspirated. The needle is withdrawn in the same fashion and a sterile cotton bud is applied at the site. The eye is patched with topical antibiotics and patient is reviewed after 1 hour. Specimen is promptly transported to the laboratory in the syringe after inserting the needle in a cork for further processing.



## **Complications**

1. Flat anterior chamber - usually reforms within an hour.
2. Hyphema.
3. Infection
4. Corneal / lens injury.

## **vitreous tap <sup>1</sup>**

A specimen of vitreous can be obtained by vitreous tap or a diagnostic vitrectomy. Vitreous tap is an out patient procedure while a diagnostic vitrectomy is performed in an operation theatre. The latter provides a larger sample of the vitreous, besides applying lesser traction on the vitreous. It also helps in clearing the ocular media, decreasing the bacterial load.

## **Indications**

1. Endophthalmitis
  2. Masquerade syndromes – esp. intraocular lymphoma.
  3. Ocular metastasis with vitreous involvement and unknown primary malignancy.
  4. Nematode infections.
  5. Myiasis.
  6. Amyloidosis
- Procedure

### **1. Vitreous tap-**

The periorbita is cleaned with povidone iodine. Under topical anesthesia, with a lid speculum, a parsplana approach is used. The globe is stabilized with a cotton tip applicator/ toothed conjunctival forceps. A 2cc disposable syringe with a 23-25 G needle is used to obtain the specimen. The parsplana entry is in the superior or inferior temporal quadrants at 3 mm from limbus in aphakes/ pseudophakes and 3.5mm in phakic eyes. The direction of the needle is towards the center of the globe. Under direct visualization, 0.1-0.2cc of vitreous fluid is aspirated from the mid-vitreous cavity.

Automated self-sealing vitrectomy<sup>1</sup> either with 23G (Peyman) or 25G (deJuan) disposable vitreous cutters can be performed in the outpatient department. A small peritomy is made at the desired site. Parsplana entry with a Ziegler knife is made. Manual aspiration under indirect ophthalmoscopic control is used to obtain a 1-2cc vitreous aliquot. Sterile air may be injected through a separate 30G needle entry to maintain intra-ocular volume.

### **2. Diagnostic/ Therapeutic vitrectomy-**

It involves a standard 3-port parsplana vitrectomy. An undiluted specimen is obtained in suspected endophthalmitis

using separate aspiration tubing with a 3-way stopcock and a 5cc disposable syringe for manual aspiration prior to starting the main infusion line. The suction may be manual or automated. The diluted specimen collected in the cassette can also be utilized if needed.

### **Complications**

1. Subconjunctival hemorrhage
2. Vitreous hemorrhage
3. Lens damage
4. Endophthalmitis – in previous sterile inflammation.
5. Retinal detachment – rare.

### **Fine needle Aspiration Biopsy (FNAB) <sup>1,3,4,5</sup>**

Jacobiec et al<sup>3</sup> first proposed FNAB of intraocular tumors in 1979. The advantage of FNAB is that it allows histopathological correlation in atypical presentations of intraocular tumors, avoiding the need for an open biopsy or sacrificing the eye. It is a safe procedure in trained hands and in spite of a theoretical risk of dissemination through the needle track; no such case has been documented yet<sup>6</sup>. A sensitivity and specificity of 84% and 98% respectively has been reported<sup>7</sup>. False negative results are known; hence do not rule out a malignancy if negative.

### **Indications**

1. Suspected intraocular lymphoma
2. Metastatic disease of choroid with unknown primary.
3. Metastasis Vs amelanotic melanoma of choroid.
4. Mass lesion- Malignant Vs benign/ infective pathology.
5. Atypical presentations – e.g. retinoblastoma in adults.

### **Prerequisites**

1. Clear media for good visualization.
2. Skilled surgeon and cytopathologist.
3. Well-equipped laboratory facility.
4. Availability of possible treatment options.
5. Prompt treatment of the malignancy once the diagnosis is established.

### **Materials**

20-25 G, 1-1.5 inch disposable needle  
10cc disposable syringe  
Extension silicon tubing with luer lock (to allow safe aspiration without needle movement)  
Indirect ophthalmoscope/ Wide angle viewing system

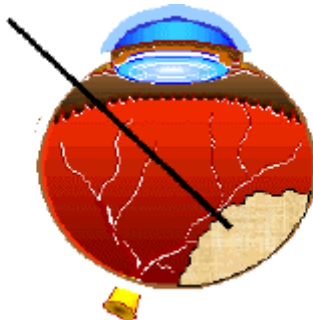
## Procedure

FNAB is usually performed in an operation theatre under local anesthesia. Routine cleaning and draping is done. The approach to the lesion depends on the site and type of lesion, visualization, and lens status.

1. Limbal
2. Clear corneal
3. Direct – trans-scleral/ subretinal
4. Parsplana - trans-vitreous

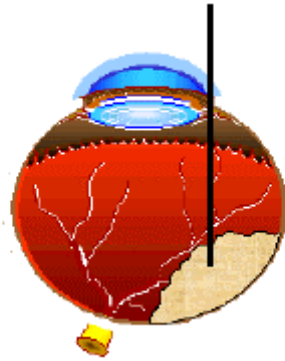
## Parsplana approach

A limited peritomy may be made at the proposed site. The globe is stabilized with a traction suture/ forceps. An indirect ophthalmoscope or an operating microscope with a wide angle viewing system may be used. The latter has the advantage of a bimanual approach if needed. The needle is inserted into the mass lesion and proper needle placement is ensured. Areas with large retinal vessels are avoided. The retinal hole at the entry site is usually self-sealing because of the associated blood clot. Once within the mass, abrupt aspiration is applied. The needle is advanced further into the mass and the suction is gently released. The procedure is repeated with the needle in place. It is important to know that the sample will not be visible in the silicon tubing because of the small quantity. It is usually present in the needle lumen. The needle is gently withdrawn only after the suction has been equilibrated. A higher suction is needed for solid tumors. Retinopexy may be done to the retinal break with laser photocoagulation but it is not mandatory. A 23-25 G entry is self-sealing. The eye is patched with topical antibiotics.



## Parsplana Approach

It is especially indicated in friable tumors like retinoblastoma to decrease the chances of tumor dissemination. The needle is inserted through the peripheral clear cornea, 2-3mm within the limbus, through the iris root, zonules, and vitreous into the mass. The multiple interphases are believed to 'wipe off' the needle and restrict the seeding of tumor cells along the needle tract.



**Clear Corneal Approach**

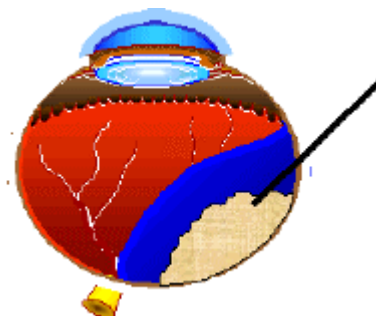
### **Transscleral approach**

1. Direct - For anterior tumors in ciliary body or anterior choroid region the needle is inserted under a partial thickness scleral flap.



**Direct Trans-scleral Approach**

2. Subretinal - In case of mass lesions with associated bullous retinal detachment the needle can be inserted through the subretinal space into the mass.



**Subretinal Approach**

### **Complications - (Posterior segment FNAB)**

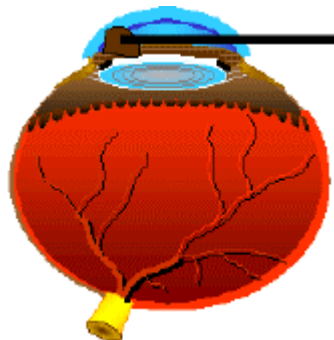
1. Hemorrhage – tumor and vitreous hemorrhage are the most common complications and usually do not need any intervention. Rarely choroidal and subretinal bleed can occur.

2. Retinal tear and Retinal detachment with PVR – retinal break almost never leads to a retinal detachment and gets sealed with a blood clot.

3. Infection

4. Tumor seeding along the needle tract, especially in friable tumors like retinoblastoma can occur. However dissemination of tumor has not been reported in the literature as yet.

Limbal approach - It is used for anterior segment mass lesions. The needle is inserted from the limbus opposite to the mass, avoiding the pupil. It is performed under visco-elastic cover.



**Limbal Approach**

### **Complications - (anterior segment FNAB)**

1. Hyphaema
2. Increased intraocular pressure
3. Tumor seeding

### **Chorioretinal biopsy <sup>1,2</sup>**

Specimen handling - 2cc of normal saline is aspirated through the needle and the silicon tubing into the syringe. A rubber cork is applied to the needle tip and the specimen is promptly delivered to the pathologist.

Peyman et al<sup>9</sup> first described the technique of chorioretinal biopsy in 1975. It is employed in cases of diagnostic dilemma with atypical or refractory intraocular inflammatory lesions, which may be vision or life threatening, especially if the result is likely to alter the management significantly. In patients with bilateral involvement biopsy is performed on the eye with the worse disease.

### **Indications**

Non-resolving, refractory, vision threatening, intraocular inflammation.  
Aqueous and vitreous tap negative.

To rule out malignancy e.g. lymphoma.  
To look for specific microbiologic etiology.  
To avoid potentially toxic, empiric treatment.  
To help treat life threatening systemic condition in immunocompromised individuals.

### **prerequisites**

In addition to those criteria mentioned for FNAB, hypotensive general anesthesia is preferable.

### **Procedure**

The approach depends on the location of the disease process.

1. External - lesions anterior to equator
2. Internal - lesions posterior to equator

### **External approach**

The two methods described in literature are-

#### **Peyman et al <sup>1,3</sup>**

Under local or general anaesthesia, limbal peritomy is performed. The rectus muscles are tagged. The proposed site is identified. Peyman eye basket is sutured around the site. A 8mm corneal trephine is used to mark a half thickness scleral groove. Infusion cannula is placed followed by two superior sclerotomies. Partial thickness hinged scleral flap is raised with a 64 no. Baeyer blade. 4mm skin trephine is used to mark the area of biopsy within the bed. Surface diathermy followed by penetrating diathermy is applied to the margins of the biopsy site. Sharp scissors are used to excise the specimen. Partial vitrectomy is done through the biopsy site and the flap is sutured with 9'0 nylon. Infusion is turned on and a parsplana vitrectomy with endolaser around the biopsy site is completed.

#### **Martin et al <sup>8</sup>**

Preoperative laser photocoagulation around the lesion is performed. Initial standard 3-port parsplana vitrectomy is performed and a vitreous sample is obtained. A near full thickness scleral flap is raised 6mm posterior to the limbus. 2 rows of penetrating diathermy are applied in the bed. Two parallel incisions are made 4mm apart with a 75 no. blade and completed with vanna's scissors. A 0.12mm forceps is used to hold the biopsy tissue. A papsplana vitrectomy with endolaser, fluid gas exchange with a gas tamponade is performed.

## **Internal / Endoretinal approach**

Freeman et al<sup>10</sup> described this approach for lesions behind the equator with a primarily retinal disease. A standard 3-port pars plana vitrectomy is performed. Diathermy is performed around the biopsy site. Biopsy site is usually at the junction of healthy and diseased retina. A retinotomy with a blade of a vertical scissors is followed by gentle injection of fluid in the subretinal space. Initial retinotomy is extended 3-6mm along the posterior border of the site and then extended anteriorly 2-4mm on both sides to obtain a hinged flap. The tissue is removed with a fine 0.12mm forceps. A fluid gas exchange with endolaser and gas or silicon oil tamponade follows.

## **Complications**

Choroidal bleed  
Vitreous hemorrhage  
Tractional/rhegmatogenous retinal detachment  
Cataract

## **Excision biopsy**

An excision biopsy is sometimes performed for anterior segment mass lesions of the iris and ciliary body, but rarely so for posterior segment lesions. The human eye can tolerate up to 2.5 clock hours of ciliary body excision although up to 6 clock hours of ciliary body has been safely excised in primates<sup>2</sup>. A full thickness resection of up to 15x7mm can be tolerated as well<sup>2</sup>.

## **Anterior segment tumors**

External approach - may involve one of the following

1) Iridectomy – With a limbal incision, a wedge shaped resection of the iris tissue is performed. An attempt is made to resuture the iris and achieve a round pupil.

2) Iridocyclectomy - As described by Zirm et al<sup>1</sup> (1911), a T shaped scleral incision is placed over the mass lesion. After dissecting the partial thickness scleral flaps, an entry is made at the limbus and the mass lesion is excised beginning at the pupillary margin. Flieringa used a partial thickness scleral flap hinged at the limbus. The limbal incision is extended on both the sides. Incision is made at the pupillary margin and extended around the tumor. Peyman et al<sup>2</sup> described the use of hypotensive anaesthesia to decrease the chance of bleeding, if not contraindicated due to the associated systemic status. A 360-degree limbal peritomy with tagging of the recti is done. The tumor is localized with a transilluminator or an indirect ophthalmoscope. The margins are marked with diathermy. Peyman cyclectomy C shaped wire is sutured around the margins. 3 port sclerotomies are made away from the tumor site. Preoperative laser photocoagulation is done around the tumor if it

extends into the anterior choroid. The mass is excised beginning at the pupillary margin under a partial thickness scleral flap. The scleral flap is sutured with 7'0 Dacron. This is followed by a parsplana vitrectomy, fluid gas exchange, 360-degree encirclage and a gas or silicon oil internal tamponade.

3) Penetrating sclerouveoretinovitrectomy (full thickness eye wall resection)<sup>1,7,9,11</sup>- It was described by Meyer Schwikerath and extensively studied by Peyman et al<sup>1, 11</sup>. It is indicated in anterior mass lesions with suspected scleral involvement. Under hypotensive anaesthesia, a 360-degree limbal peritomy is made and the tumor is localized. The margins of the tumor are marked with diathermy. 3 sclerotomies are made away from the tumor. A donor scleral graft is kept ready. A full thickness scleral incision is made 2mm beyond the margins of the tumor. Diathermy is applied to the uveal tissue and the tumor is excised. Scleral graft of the same size is sutured with 7'0 dacron. A parsplana vitrectomy, fluid gas exchange, endolaser and gas/silicon oil tamponade follows.

### **Internal approach**

Peyman et al<sup>1,7,9</sup> have described internal approach for anterior segment lesions. A trans-scleral diathermy is performed around the tumor. 3 port sclerotomies are made. Intraocular diathermy is applied around the mass. The mass is excised with intraocular scissors. A parsplana vitrectomy with fluid gas exchange and gas/silicon oil tamponade is done.

### **posterior Segment tumors**

#### **External approach**

Peyman et al<sup>1,7,9</sup> described full thickness/ partial thickness eye wall resection. The procedure is similar to that described for anterior segment lesions. Preoperative laser photo-coagulation can be done around the mass lesion 3-4 weeks prior to the excision. The sclera or retina may be spared, if not involved, with a partial thickness resection.

#### **Internal approach**

Indicated in cases of suspected malignant melanoma choroid with-

No extrascleral extension / scleral involvement.

No metastasis

Posterior margin of the tumor more than 10 disc diameters from the optic disc

Good general health

#### **Internal retinchoroidotomy**

Preoperative laser photocoagulation around the mass is done. A 360-degree peritomy is followed by examination of all the quadrants for evidence of extraocular spread. Standard 3-port parsplana vitrectomy is done. With a wide angle viewing system extensive laser photocoagulation is applied to the tumor. The tumor is excised under hypotensive anaesthesia with an increased



intraocular pressure to decrease the chance of bleeding. Fluid gas exchange with endolaser and gas/silicon oil tamponade is done.

### **Retina sparing internal resection <sup>1</sup>**

Peyman et al<sup>1</sup> described this procedure for tumors at the posterior pole close to the optic nerve/ fovea. Preoperative laser photocoagulation is done around the tumor. A 3 port partial vitrectomy is done. Contiguous diathermy is applied in an arcuate fashion for 130-180 degrees away from the fovea. A 160-degree retinotomy is made and the retinal flap is reflected to expose the tumor. Diathermy is applied to the tumor margins and it is excised with intraocular scissors. Laser photocoagulation is applied to the scleral bed and margins of the retinotomy. A parsplana vitrectomy, fluid gas exchange, encirclage and gas/silicon oil tamponade follows.

### **Complications**

Vitreous hemorrhage

Cataract

Retinal detachment

Raised intraocular pressure

Hypotony

Intraocular biopsy is a valuable tool in the armamentarium of an ophthalmologist. Although not frequently performed, it provides us with an opportunity for resolving diagnostic dilemmas. The indications for intraocular biopsy are limited by the possible complications associated with this invasive procedure.

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# Phacoemulsification with Trabeculectomy using 5 Fluorouracil - A Retrospective study

**L Vijaya, B. Shantha, Arun Kumar Narayanaswamy and M. Baskaran**

## **Introduction**

Cataract often is the cause for visual deterioration, which necessitates intervention in patients with co-existing glaucoma. Management of cases with unsatisfactory control of intraocular pressures inspite of maximal medical therapy and co-existing cataract confronts us with a situation where in a combined cataract extraction with a filtering surgery would be the ideal management option. With the advent of small incision cataract, minimal conjunctival manipulation and decreased postoperative inflammation seems to enhance the success of a filtration procedure<sup>1</sup>. The standard extracapsular cataract extraction with trabeculectomy has the disadvantages of a large limbal incision with poorly formed blebs and varied grades of intraocular pressure control<sup>2</sup>. The resultant scarring prevents subsequent surgery if required while this is preserved in patients undergoing a phacotrabeculectomy.

The use of anti-metabolite as an adjunct seems to play an important role in achieving a good postoperative bleb. We used a single application of 5-fluorouracil (5-FU) intraoperatively with no supplementary postoperative subconjunctival injections of 5-FU and report our results in this study.

## **Patients and Methods**

We reviewed the medical records of 41 consecutive patients with minimum follow-up of six months at Medical Research Foundation, Chennai, who underwent phacoemulsification with posterior chamber intraocular lens implantation and trabeculectomy with 5-FU. Patients were chosen for the combined procedure on the basis of their degree of intraocular pressure control, extent of visual impairment and optic nerve damage. All surgeries were performed using a standard approach by a single surgeon. Preoperatively pupils were dilated with 5% Phenylephrine and 1% Tropicamide. All procedures were performed under peribulbar anaesthesia with 2% Lignocaine and 0.5% Bupivacaine mixture. A fornix based conjunctival flap (40%) was dissected. Good hemostasis with light cautery attained. A triangular merocel sponge soaked in 5-FU (50mg/ml) was placed on the bare sclera for one minute duration. The sponge removed and ocular surface was well irrigated. Scleral tunnel measuring 5mm x 4mm was fashioned 1.5-2 mm from limbus extending 0.5mm into the clear cornea using a crescent knife. Anterior chamber was entered with slit knife to creating 2 side ports at 10 and 2'O clock. A continuous curvilinear capsulorhexis was completed under viscoelastic cover. Phacoemulsification and cortical

aspiration completed via the superior tunnel created using a 3.2 keratome. Entry was widened to 5.5mm permit placement of intraocular lens in the bag. A trabeculectomy was performed under the scleral flap using a Kelly's descemet punch followed by a peripheral iridectomy. The scleral flap was closed with a single releasable 10-0-nylon suture. The Tenons and conjunctiva were closed in a single layer using 10 '0' nylon in the form of wing sutures. Anterior chamber was formed via the side port. Postoperative topical Betamethasone was prescribed 6-8 times/day in tapering doses over 6 weeks. Patients were seen on day one and subsequently on day 3 and at varied intervals until final review at 6 weeks. No sub conjunctival injections of 5-FU were given in the postoperative period.

## Results

41 patients (41 eyes) underwent phacoemulsification combined with trabeculectomy with 5-FU with IOL implantation. Mean age at presentation was  $65 \pm 8.65$  yrs (50-89 yrs). There were 32 males and 9 females. Mean follow-up was  $12.41 \pm 6.22$  months (6-30.3 months). Primary open angle glaucoma was the major indication of surgery (32/41 eyes - 78%). The mean number of preoperative medications in 34 patients was  $1.65 \pm 0.54$ . Mean preoperative intraocular pressure was  $23.08 \pm 7.41$  mm of Hg (14-50 mm Hg). IOP was less than 18 mm Hg in 82.5% patients at last follow-up. Mean spherical equivalent at 6 weeks was  $-1.31 \pm 1.30$  DS and mean cylindrical error was  $-1.17 \pm 1.31$  DS. Postoperative visual acuity was more than 20/40 (6/12) in 95.1% patients. Releasable sutures were removed in 39 patients. Postoperative medications were needed only in 3 patients ( $2.67 \pm 0.58$ ). Re surgery was done in one patient after failed needling procedure with 5-FU during late postoperative follow-up. Bleb was elevated in 25 eyes (61%); low in 11 eyes (26.8%); flat in 5 eyes (12.2%). Complications included: Cystoid macular edema - 2 eyes; choroidal detachment -1; Central retinal vein occlusion- 2, recurrent vitreous haemorrhage and retinal detachment -1.

## Discussion

Treatment of the patient with co-existing cataract and glaucoma is a common situation, which the glaucoma specialist often faces. If the IOP is well controlled with low doses of well-tolerated medication and minimal glaucomatous damage, cataract surgery alone is performed. On the other hand, if the IOP is uncontrolled with maximum tolerable medical/laser treatment, with advanced glaucomatous damage, a filtering surgery alone has been advocated. In most patients, where the IOP is under borderline control with 2 or more medications, or if there is moderate to severe glaucomatous damage in association with a cataract, combined surgery would be appropriate.<sup>1</sup> However, the refinements associated with phacoemulsification and the pharmacological modulations of wound healing with the use of antimetabolites have altered the indications for combined surgery<sup>1</sup>.

Various studies comparing phacoemulsification with trabeculectomy and extracapsular cataract extraction with trabeculectomy have shown that the former is a safe and effective technique to control postoperative IOP in

patients with glaucoma.<sup>2,3</sup> In phaco-emulsification, the smaller conjunctival and scleral incisions reduce ocular inflammation and therefore, wound healing stimuli. Therefore, the chances of long-term success of filtering surgery are improved. Thus, combined cataract and filtering surgery using phacoemulsification is associated with greater IOP reduction than combined surgery using extracapsular cataract extraction.<sup>4</sup> The procedure is also effective in those patients with high pre-operative IOPs.<sup>5</sup> Patients undergoing phacoemulsification in conjunction with trabeculectomy have the benefits of earlier visual rehabilitation, less postoperative astigmatism, less postoperative IOP spikes and fewer complications postoperatively as compared to those undergoing extracapsular cataract extraction with trabeculectomy.<sup>6</sup>

Over the last few years, antimetabolites have been used in conjunction with trabeculectomy to improve the chances of achieving a good IOP control. Studies have shown that with the use of intra operative mitomycin the IOP's are lower and fewer postoperative medications needed for IOP control.<sup>7,8</sup> However, the rate of complications associated with Mitomycin-C, especially wound leaks, hypotony and resultant maculopathy makes us wary of using it in a combined surgery. Our surgical results using intraoperative 5-FU (50mg/ml) for 1 minute has not only shown promise regarding the success in terms of bleb formation and IOP control also has been effective in terms of reducing the incidence of corneal epithelial toxicity associated with the use of postoperative sub conjunctival injections. Only 3 patients in our study needed additional medication for IOP control.

In conclusion, phacoemulsification with IOL implantation and trabeculectomy with 5-FU combines the advantages of small incision cataract surgery and in achieving good control of intraocular pressures with very minimal postoperative complications.

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# Whether Retinitis Pigmentosa could be due to defective metabolism of Transthyretin

**S. Ramakrishnan, K. N. Sulochana and R. Punitham**

The degeneration of photoreceptor is presumed to be the primary cause for retinitis pigmentosa (RP). This disease affects about 1.5 million people worldwide every year. Though the disease is mainly hereditary, sporadic or non-hereditary cases are also seen in population. It is generally felt, vitamin A supplementation would slow down the rate of retinal degeneration in adult onset RP although controversies to this opinion exist. Association of several mutations in genes coding for functional proteins of neural retina such as Rhodopsin, Phospho diesterase, cGMP gated channel, Arrestin, Rhodopsin kinase, Peripherin with RP has been reported.<sup>1</sup> Recently an association between mutation in the gene coding for RPE 65 protein in the chromosome 1p 22-p31 region<sup>2</sup> and RP has been reported. This gene is expressed in retinal pigment epithelium.

A mutation in this gene could manifest in the form of defective RPE 65 protein. Although the precise biochemical function of RPE 65 is not known, it is believed that this protein is involved in vitamin A transport and metabolism. Therefore mutation of this gene may cause defective transport of retinol from RPE to rod outer segment. It is justifiable to think that patients who are identified with RPE 65 gene mutation, can be supplemented with Vitamin A as a mode of treatment. Increasing vitamin A load could improve the availability of this vitamin at the target tissue through increased complex formation.

Another protein of our interest is transthyretin (TTR), which is also involved in vitamin A transport. We have reported the presence of TTR in retina and vitreous<sup>3</sup>. This protein carries vitamin A (retinol) from liver along with retinal binding protein delivers retinol to RPE and returns to blood. Recent studies have identified gene coding for TTR in retina<sup>4</sup>.

If RP is due to defective vitamin A metabolism due to quantitative and qualitative impairment in TTR, it would also affect normal physiology of retina. Such cases can also be supplemented with vitamin A for visual improvement. Hence we under took present study to know the levels of TTR in-patients with RP.

## **Materials and Methods**

Serum samples from 19 patients of clinically proven RP and 2 families of four patients with RPE 65 mutation was analyzed for vitamin A by carr-price reaction<sup>5</sup>. The TTR was analyzed in the serum samples received from patients with RP by poly acrylamide gel electrophoresis (PAGE)<sup>6</sup>. 20 mg of serum protein was loaded on to 7.5% page and after running for 1 hour, the



proteins were stained with Coomassie brilliant blue to get the protein profile. Standard TTR from Sigma chemical company USA was used for identification of this protein in serum samples. The protein content was estimated by method of Lowry et.al<sup>7</sup>.

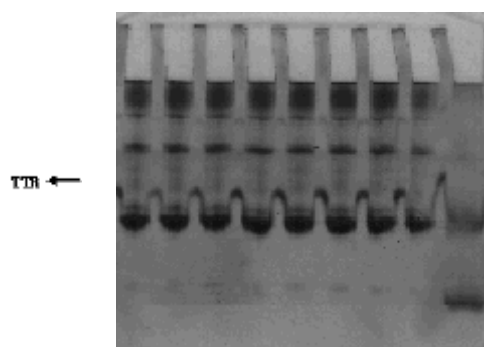
TTR of serum was also subjected to immuno electrophoresis using microscopic slides with 1% agar gel. 5ml of serum was loaded and 28 mg antihuman TTR (Sigma Chemical Company, USA) was taken for assays<sup>8</sup>. At the end of electrophoresis, a well with 30 mm length x 3 mm breadth was set, and then anti-human TTR was loaded. The slides were kept in a moist chamber for 24-36 hours. At the end of the incubation period, slides were removed, dried at 60° C for 1 hr. and stained for protein using Coomassie brilliant blue R-250 and destained by acetic acid, methanol and water mixture.

## Result and Discussion

The clinical condition, demographic details and the serum vitamin A levels of these patients are given in table 1. Figure 1 shows the electrophoretic profile of serum proteins which was normal in all the cases studied.

Figure 2 shows the immuno-electrophoresis of serum samples against antibodies of TTR, samples showed normal precipitation line indicating TTR from all RP patients and controls were immunologically identical.

Among 19 patients studied only 3 were on vitamin A treatment at the time of investigation. These three patients had normal levels of vitamin A. Among the remaining 16 patients, 10 were found to have lower (10.6 to 24.6 mg/dl) than normal level of 25 to 75 mg/dl. Perhaps diet supplementing with vitamin A may be beneficial to them in controlling retinal degeneration. Besides this may also protect them against other systemic disorders of vitamin A deficiency. Hence it may be important to measure the levels of vitamin A in cases of RP.



**Figure 1 — Electrophoretic pattern of serum samples from RP patients showing TTR band.**

**Table: 1**

No.	Age/Sex	Vitamin A	Clinical diagnosis	Inheritance
		µg/dl IU/dl		
1.	60/F	16 48.6	Atypical – RP	Sporadic
2.	44/M	37.8 114.0	Typical RP – myopia, macular – degeneration,difficult in night vision. On vitamin A therapy	Autosomal recessive
3.	26/F	16.3 49.5	Typical – RP Tubular vision	Autosomal recessive
4.	46/M	54.8 166	? RP, macular degeneration On vitamin A therapy	Sporadic
5.	31/M	37.8 114.5	Typical RP On vitamin A therapy	Autosomal recessive
6.	33/M	40.3 122	Typical RP, difficult vision – 10 yrs . On vitamin A therapy	Autosomal recessive
7.	43/M	26.7 80.9	Typical RP – 16-18 yrs	Autosomal recessive
8.	45/M	51.5 156	Typical RP.	Autosomal recessive
9.	34/M	46.7 141.0	Atypical RP	Sporadic No consanguinity
10.	26/M	35.7 108	Retinitis punctata albescens.	Autosomal recessive
11.	14/F	10.6 32.2	Suggestive of RP	Parental consanguinity
12.	28/M	17.5 53.3	Typical RP Macular degeneration	Autosomal recessive, Consanguinity
13.	14/M	35.7 108	RP typical	Consanguinity
14.	54/F	Low	RP,Day and night blind vision	Autosomal dominant, consanguinity
15.	46/M	17.6 53	Night blindness from childhood	Sporadic, Consanguinity
16.	43/M	17.4 52.7	Typical RP	Autosomal recessive
17.	16/M	20.0 62	Typical RP – RP 65	Autosomal recessive
18.	27/M	18.9 57.3	Typical RP – RP 65	Autosomal recessive
19.	26/M	24.6 74	Typical RP – RP 65	Autosomal recessive

*Figure 1 — Electrophoretic pattern of serum samples from RP patients showing TTR band.*

to measure the levels of vitamin A in cases of RP.

The levels of TTR in all the cases studied were normal in this series. Perhaps looking for changes in TTR in large number of patients with RP would throw some light. The limitation of this study was the analysis of TTR was done only in blood, but not in ocular tissues. Despite the fact that these two proteins (from retina and blood) are immunologically identical, one does not know their subtle, chemical and structural differences. Hence it is important to study the TTR of retina to have clear understanding of the subject.

Analysis in vitreous would be ideal, as vitreous is considered as repository of retinal metabolism. The sample of it may not be available unless these people undergo surgery.

Animal models can also be used to make such studies, by mutating TTR gene in order to produce defective TTR protein and looking at the details of changes in vitamin A metabolism in eye.

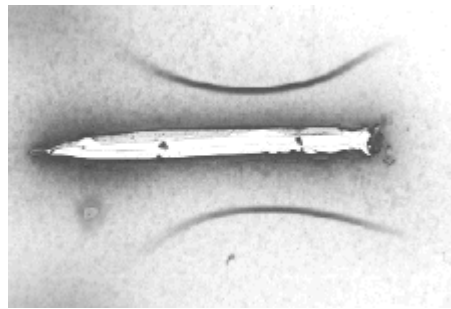


Figure 2 — Immuno electrophoresis of serum showing precipitins for TTR.

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## COME, GIVE THE GIFT OF SIGHT

# Intravitreal Steroid Implants in Chronic Recalcitrant Uveitis

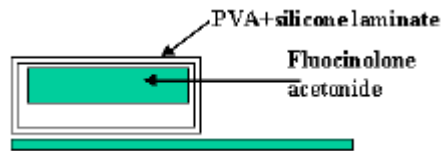
Kannan M Narayana and Jyotirmay Biswas

Conventional treatment of non-infectious intraocular inflammation, especially those involving the intermediate and posterior segments mainly involves management with corticosteroids administered through different routes like topical, periocular and systemic. Complications like steroid-induced cataract, steroid-induced glaucoma are seen with all routes of administration of steroids. Topical route, though associated with only local complications, may fail to achieve desired results in majority of intermediate and posterior uveitis. Periocular steroids better serve the purpose, but need to be repeated frequently. Systemic steroids are the best alternative in terms of inflammation control, but have the well recognized systemic complications attached to them. Hence the search is on for an ideal agent with best inflammation control, least local and systemic side-effects. Intravitreal drug delivery system is probably the next logical step as a route of drug administration. It allows therapeutic levels of the drug to reach the target site, without causing the systemic toxicity. Intravitreal ganciclovir was one of the first drugs to be administered through this route clinically, with useful results. This has encouraged this route of delivery.

## **Sustained release Implants**

Sustained release technology basically involves design of a surgically inserted drug delivery system into the vitreous cavity, which contains the drug of interest that is slowly delivered into the vitreous. Various drugs have been experimentally tried including dexamethasone<sup>1</sup> and cyclosporine.

<sup>2</sup> In preliminary human studies done by Jaffe et al <sup>3</sup> fluocinolone acetonide was found to be useful in the management of severe uveitis in seven eyes of five patients. There was improvement or stabilization of vision in all treated eyes. There was a significant decrease in inflammation and reduced requirement for systemic steroids and immunosuppressive agents. However, four eyes had increased Intraocular pressure 6 weeks to 6 months following implantation. This implant is currently being evaluated in a large ongoing multicentric trial. The implant is composed of a central core consisting of the active drug, compressed into 1.5 mm diameter tablets, overlaid with multiple polymer coatings including polyvinyl alcohol and silicone laminate. The device releases 2mg/day and is designed to release efficacious levels of the drug substance over an extended period of time (up to 3 years).



The limitations of this route of administration stem from the fact that it is as yet an unestablished route and it involves an intraocular surgical procedure. The large list of exclusion criteria include the presence of only anterior uveitis, uveitis of infectious etiology, known steroid responsiveness, presence of toxoplasma scar in the eye and significant media opacities. In addition to these, there are the associated risks of post-implantation infectious endophthalmitis and vitreous hemorrhage, making one eyed patients unsuitable for this implant.

This implant may be helpful in the management of long standing severe uveitis, particularly in reducing the need for systemically administered corticosteroids and immunosuppressive agents. The other advantage is the expected long-term achievement of inflammation control. However need for careful case selection cannot be overemphasized as this involves all the potential surgical complications of intraocular surgery. The current trial may be able to provide with the final answers.

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