Medical Management of Glaucoma

Tanuj Dada, Vivek Dave, Neha Mithal
Glaucoma Services, Dr RP Center for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India

INTRODUCTION

Primary open-angle glaucoma is a pressure sensitive, progressive, chronic optic neuropathy characterized by acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. There are three major theories regarding the pathogenesis of glaucoma: (1) Mechanical (IOP related damage), (2) Vascular (decrease in blood supply to optic nerve head) and (3) Biochemical (decrease in neurotrophic factors/increased levels of neurotoxins) and therefore the three possible therapeutic options would be to (1) to decrease IOP, (2) to increase perfusion to the optic nerve head and (3) provide neuroprotection to retinal ganglion cells. As of today the only feasible option is to reduce IOP by medical, laser or surgical therapy. Several well-designed clinical trials have clearly established that lowering IOP is beneficial in slowing disease progression and helped to establish a clear relationship between IOP control and visual field preservation.

In addition one needs to address non-IOP dependant systemic factors such as blood pressure, diabetes, sleep apnea, lipids and vasospasm which can contribute to a worsening of glaucomatous optic neuropathy. This article outlines the essential work-up and follow-up protocol of POAG patients.

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Keywords: Pharmacotherapy of glaucoma, neuroprotection, target IOP.

Essential Work-up before Initiating Therapy

Medical therapy once initiated will be life long and the ophthalmologist must ensure that a correct diagnosis has been made and rule out medical conditions which could be adversely affected by glaucoma medications such as asthma, heart block, antihypertensive treatment, hypotension, diabetes, stroke, urinary stones, etc. Compliance to therapy, affordability of treatment and family history should be ascertained. In addition to routine ocular and systemic history taking, an assessment of the impact of visual function deterioration on activities of daily living should be done. Diurnal IOP variation, gonioscopy, stereoscopic disk evaluation/photographs and visual fields must be performed. The diurnal IOP measurement also helps in determining the timing of peak IOP spike in an individual patient and this information is used for setting an appropriate timing of glaucoma medication such that the peak IOP lowering effect of the drug blunts the IOP spike. If baseline IOP is ≥ 30 mm Hg, it is reconfirmed once and the patient should be started on therapy without the need for performing a diurnal IOP recording.

Glaucoma suspects require a case to case risk-to-benefit analysis regarding when to begin treatment. The ocular hypertension treatment study provides guidelines for risk stratification. Therefore, one should be more aggressive in treating patients who are older, have thinner corneas, higher baseline IOP, and larger baseline cup: disk ratios. For those patients who are similar to the OHTS cohort, a risk calculator can be used to estimate their 5-year risk of developing glaucoma.

Each treatment has its own inherent risks and benefits which must be clearly discussed with the patient before initiating therapy.

These include:

• Severity and type of glaucoma.
• Patient's compliance with treatment and his/her lifestyle.
Table 1: Goals of medical therapy for glaucoma

1. To achieve target IOP and reduce IOP fluctuations with minimal possible medications.
2. To administer glaucoma medication which have the least side effects on the quality of life of the patient.
3. To achieve this treatment at an affordable and sustainable cost for the patient.
4. Monitor the structure and function of the optic nerve for further damage and adjust the target IOP to a lower level if deterioration occurs.
5. To treat non-IOP dependant systemic factors [systemic hypertension, low diastolic perfusion pressures (diastolic blood pressure minus IOP), diabetes, hyperlipidemia, vasospasm] which may contribute to the development and worsening of glaucomatous optic neuropathy.
6. To educate and involve the patient and his family in the management of the disease process.

Antiglaucoma Medications

There are five classes of topical hypotensive medication: prostaglandins, β-blockers, selective (α-2) adrenergic agonists, carbonic anhydrase inhibitors (CAIs), and cholinergics (Table 2).

Systemic antiglaucoma medications include carbonic anhydrase inhibitors like oral acetazolamide and hyperosmotic agents like intravenous mannitol and oral glycerol. Carbonic anhydrase inhibitors are contraindicated in known allergy to sulfas drugs, acidosis, hyperkalemia, renal failure. Known side effects are numbness, paresthesia, nausea, depression, electrolyte disturbances and renal calculi. Hyperosmotic agents are indicated in short-term treatment of acute and marked elevation of IOP and for preoperative preparation before intraocular surgery. They are contraindicated in patients with anuria, severe dehydration, uncontrolled hypertension, pulmonary edema, cardiac decompensation.

How to Set Target IOP?

Target IOP is defined as “A range of acceptable IOP levels within which the progression of glaucomatous neuropathy will be halted/retarded”. It is the specific level of pressure that, if achieved, will prevent further Optic nerve damage and is the IOP where the rate of loss of ganglion cell will equal the age induced loss.12-15

The target IOP is dependant on several factors, the most important being the severity of glaucomatous optic neuropathy.

The following factors govern the setting of a target IOP for an individual patient.14

- Optic nerve head and visual field damage
- Life expectancy
- IOP level at which damage occurred
- Rate of progression
- Family history
- Systemic diseases (Diabetes, HT, CAD, CVD).

There is no a way to determine the pressure below which further optic nerve damage will be prevented in any particular patient, therefore the initial target pressure is an estimate towards the ultimate goal of protecting the optic nerve. The target pressure is different among patients, and even in the same patient it may require recalculation in the course of the disease.

When initiating therapy, it is assumed that the measured pretreatment pressure range resulted in optic nerve damage, so, the initial target pressure selected is at least 20% lower than the pretreatment IOP.

As a general guideline the IOP in any established case of glaucoma should always be kept below 18 mm Hg. The specific target IOP can be set by classifying the disease based on severity of glaucomatous damage as follows:

**Mild:** Glaucomatous optic nerve abnormalities with normal visual fields.

20% IOP reduction from baseline values, keep IOP < 18 mm Hg.

**Moderate:** Visual field abnormalities in one hemifield but not within 5° of fixation.

30% IOP reduction, set IOP below 15 mm Hg.

**Severe:** Visual field abnormalities in either hemifields or field loss within 5° of fixation. 50% IOP reduction, set IOP below 13 mm Hg.
### Table 2: Summary of ocular hypotensive medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Efficacy</th>
<th>Local side effects</th>
<th>Systemic side effects</th>
<th>Peak effect, washout period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostaglandin analogues:</strong> latanoprost, bimatoprost, travoprost, unoprostone</td>
<td>Increases uveo scleral outflow by remodeling the extracellular matrix between the ciliary musculature</td>
<td>Most efficacious of all topical antiglaucoma medications. Decrease IOP about 30 to 35% from baseline. Worldwide the first line drug</td>
<td>Conjunctival hyperemia, stinging, hypertrichosis, trichomegaly, periocular skin pigmentation, uveitis, cystoid macular edema in pseudophakes and aphakes</td>
<td>No known serious side effects. Some reports of transient flu like symptoms, joint pains</td>
<td>2 weeks, 6 weeks</td>
</tr>
<tr>
<td><strong>β-blockers:</strong> timolol, betaxolol (cardioselective), levobunolol,</td>
<td>Act on β-adrenergic receptor on the ciliary body and decrease aqueous production</td>
<td>Decrease IOP from 25 to 30% from base line. Efficacy decreases over a period of time called as long-term tachyphylaxis</td>
<td>Ocular stinging, ocular hypesthesia, epitheliopathy.</td>
<td>Side effects common on long-term instillation. Bradycardia, heart block, bronchospasm, hyperglycemia, depression, psychosis,</td>
<td>4 to 6 weeks, 4 to 6 weeks</td>
</tr>
<tr>
<td><strong>α-adrenergic agonists:</strong> brimonidine, apraclonidine,</td>
<td>Act on alpha adrenergic receptors on ciliary vasculature and decrease aqueous production and also increase uveo scleral outflow</td>
<td>20 to 25% decrease in IOP from base line. Very efficacious as a prophylaxis to decrease postlaser IOP spike</td>
<td>Follicular conjunctivitis, associated periocular contact dermatitis, blepharoconjunctivitis, lid retraction.</td>
<td>Brimonidine crosses blood brain barrier to cause systemic hypotension and drowsiness. It is thus contraindicated in children (&lt; 6 years, &lt; 6 kg)</td>
<td>2 weeks, 2 weeks</td>
</tr>
<tr>
<td><strong>Cholinergic agonists:</strong> pilocarpine</td>
<td>Increases trabecular outflow</td>
<td>Decreases IOP by 20 to 25%</td>
<td>Headache, brow ache, induced myopia, miosis, conjunctival hyperemia, iris cyst, uveitis, cystoid macular edema, retinal detachment</td>
<td>Abdominal cramps, sweating, bronchospasm, diarrhea</td>
<td>3 hours, 1 week</td>
</tr>
<tr>
<td><strong>Carbonic anhydrase inhibitors:</strong> dorzolamide, brinzolamide</td>
<td>Decreases aqueous production by inhibiting carbonic anhydrase enzyme in the ciliary processes</td>
<td>Decreases IOP by 20 to 25% from baseline</td>
<td>Stinging and burning sensation, corneal decompensation in Fuch’s cornea and postkeratoplasty eyes</td>
<td>Bitter taste in the mouth, rarely drug hypersensitivity</td>
<td>72 hours, 1 week</td>
</tr>
</tbody>
</table>

The adequacy of the target pressure is periodically reassessed by comparing optic nerve status (quantitative assessments of the disk and nerve fiber layer, and visual field tests) with previous examinations. If progression occurs at the set target pressure, the target IOP should be lowered.\textsuperscript{12-18}

**How to Start Therapy?**

Once the diagnosis of glaucoma has been confirmed, ocular hypotensive medications can be started, starting with one drug at a time. Therapy is usually started in worse eye (usually with higher IOP/more structural and functional damage) first.\textsuperscript{5} This is known as the one eye therapeutic trial. A drug with atleast 20% IOP lowering efficacy is chosen as the first line therapy (usually a β-blocker or prostaglandin analog). After the peak IOP reduction ability of that drug is reached, diurnal variation of IOP (IOP reading at every 3 hours from early morning to late night, e.g. 7 am and 10 am, 1 pm, 4 pm, 7 pm, 10 pm) is evaluated to look for
reduction in IOP and fluctuation. In eyes with ocular hypertension—if a decision has been made to treat and in cases with early glaucoma, topical β-blocker therapy may be initiated as the first line therapy provided there are no systemic contra-indications. Once there is moderate/severe visual field damage, a prostaglandin analog is preferred as it is more likely to achieve desired target IOP. In eyes with normal pressure glaucoma, prostaglandin analogs are the preferred choice to start therapy and β-blockers should be avoided as they are absorbed systemically and can lead to a decrease in optic nerve head perfusion pressure. In eyes with primary angle closure glaucoma, the first step is to do a laser peripheral iridotomy, and then start with medical therapy as mentioned above.

When to Switch or Add Therapy?

If the drug achieves the desired target IOP, it is continued and started in the second eye. If drug fails to reduce IOP by at least 20% IOP from baseline or produces severe side effects, we switch to another class of drugs. However, if the first drug does reduce IOP more than 20% from baseline but target IOP level is not reached, a second drug is added. A time interval of at least 5 minutes should be given before administering the second drop. In case IOP does not reach target IOP by three topical antiglaucoma medications, laser/filtering surgery should be considered.

Combination Therapy

If IOP is not at target with a single drug, a second drug is added. These two drugs should have different mechanism of action and the best combination is a prostaglandin analog (which increases outflow) with a β-blocker (which decreases inflow). Using combination eye drops with two drugs in the same bottle is a good choice if more than one drug is required as it decreases number of eye drops to be instilled into the eye, decreases preservative induced conjunctival toxicity and increases compliance. The most important benefits of fixed-combination therapies are that they provide equivalent IOP reductions with the potential benefits of improved compliance, patient convenience, and cost savings. Also, fewer drops per day mean decreased exposure of the ocular surface to preservatives.

Improving Compliance

Noncompliance is a serious issue which leads to therapeutic failure and progression of optic neuropathy. It has been estimated that approximately 10% of all visual loss from glaucoma can be attributed to nonadherence to therapy. The major reason for noncompliance is that glaucoma is a chronic disease that requires lifetime therapy and is slowly progressive, therefore, patients do not notice immediate consequences if they do not comply with treatment.

Therefore a proper patient counseling about the disease process, the rationale for treatment and how drugs act, and the need of life long medication and follow-up cannot be over emphasized. At each follow-up, the patient should be questioned about possible systemic side effects which may lead to a discontinuation of medication by the patient. It is good to have printed cards for medication schedules, demonstrate the eye drop administration technique and tailor dosing schedule to daily events.

How to Instill Eye Drops?

The patient should be instructed to wash both hands, sit down on a chair or lie in bed. If seated, the head is tilted slightly backwards while gazing upward. The lower lid is gently pulled down with the nondominant hand to form a small concavity in which the drops will be placed. With dominant hand, the dispenser is held above this concavity. The bottle should be near enough to make sure that the drop will enter the eye and far enough so as not to touch it (2 to 5 cm). Avoiding blinking and the body of the bottle is pressed so that a single drop falls into the eye. After application, lids should be kept closed (or digital compression be applied to the punctum) for 1 to 2 minutes to minimize systemic absorption. The bottle cap should be replaced and any excess fluid wiped from the skin, especially when using prostaglandin medications that may darken the skin color.

Follow-up

In general a patient with established glaucoma should be followed up every six months, however the frequency of follow-up can be increased or decreased depending on the severity of disease and whether there is any progression or no over time. In stable patients with early disease, an yearly follow-up may be adequate, while in advanced cases or documented progression, a 3 to 4 monthly follow-up would be advised.

In addition to treating the ocular condition, the ophthalmologist should also focus on educating the patient to adopt a healthy life style and take care of any systemic disease factors. Such measures include asking the patient to stop smoking, wear a loose tie, regular exercise, decrease weight if obese, and meditation to decrease the stress associated with disease and improve the quality of life. For primary prevention and early detection, a check-up of other family members of the glaucoma patient is recommended.

Tanuj Dada
(tanujdada@hotmail.com)

“To put the world right in order, we must first put the nation in order; to put the nation in order, we must first put the family in order; to put the family in order, we must first cultivate our personal life; we must first set our hearts right.”

—Confucius