GLAUCOMA: CURRENT AND DEVELOPING CONCEPTS FOR DIAGNOSING AND TREATMENT – A REVIEW

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ABSTRACT
Glaucoma is a condition that involves distinctive changes in the optic nerve and visual field. It is marked by functional and structural abnormalities in the eye in which optic nerve damage can ordinarily be alleviated and inhibited by sufficiently reducing intraocular pressure (IOP). A detailed interview is indispensable in diagnosing glaucoma and determining the proper course of management. Advances in glaucoma treatment are desperately needed. This is because proven medical and surgical therapies are limited in their capacity to stop glaucoma progression. Both work by reducing IOP, a risk factor for glaucoma but not necessarily the sole cause for disease progression.

KEYWORDS: Glaucoma, Intraocular pressure, Laser surgery.

INTRODUCTION
Glaucoma is a condition that involves distinctive changes in the optic nerve and visual field. It is marked by functional and structural abnormalities in the eye in which optic nerve damage can ordinarily be alleviated and inhibited by sufficiently reducing intraocular pressure (IOP).

Basically, the disease can be classified into primary glaucoma, in which there is no other cause of elevated IOP, secondary glaucoma, in which the elevation in IOP results from other ocular disease, systemic disease, or drug use, and developmental glaucoma, in which the elevation in IOP results from developmental anomalies in the anterior chamber.

Primary glaucoma is divided into primary open angle glaucoma (broad definition) (a disease concept that encompasses both conventional primary open-angle glaucoma and normal-tension glaucoma) and primary angle-closure glaucoma.^[1-3]
I. Primary glaucoma
1. Primary open-angle glaucoma (broad definition)
   A. Primary open-angle glaucoma
   B. Normal-tension glaucoma, normal-pressure glaucoma

2. Primary angle-closure glaucoma
   A. Primary angle-closure glaucoma
   B. Plateau iris glaucoma

3. Mixed glaucoma

II. Secondary glaucoma
1. Secondary open-angle glaucoma
2. Secondary angle-closure glaucoma

III. Developmental glaucoma
1. Early onset developmental glaucoma
2. Late onset developmental glaucoma
3. Developmental glaucoma accompanying other congenital anomalies

1. Early onset developmental glaucoma
In this disease type, congenital anomalies are limited to the trabecular meshwork. Frequently, however, this is combined with mild hypoplasia resulting from developmental anomalies of the iris. Moreover, pathologies such as increased corneal diameter, conventionally referred to as buphthalmos, and corneal opacity are also frequent.
2. Late onset developmental glaucoma
Such cases involve hereditary abnormalities in anterior chamber angle formation, but the onset is delayed because the abnormalities are minor.

3. Developmental glaucoma with other congenital anomalies
This category encompasses a wide variety of conditions, including aniridia, Marfan syndrome, Axenfeld-Rieger syndrome, Peters’ anomaly, Sturge-Weber syndrome, and neurofibroma.\textsuperscript{[4,5]}

**DIAGNOSIS**
The initial interview is of essential and fundamental importance in the treatment of glaucoma. A detailed interview is indispensable in diagnosing glaucoma and determining the proper course of management.

In order to take into account the possibility of secondary glaucoma, in addition to taking a history for ocular trauma, inflammation, surgery, infection, etc., it is also important to determine the patient’s history of systemic disease and medication.

- Moreover, it is also important to interview the patient concerning subjective symptoms, with symptoms such as blurred vision, irisopsia, eye pain, headache, and hyperemia indicating a possible history of acute glaucoma attacks.
- Moreover, it is also important to ask about the patient’s family history, and patients with a family history of glaucoma in particular should be asked about visual function damage in blood relatives.

If information from other physicians is available concerning diagnosis and treatment with respect to IOP, the eye grounds, or the visual field, such information should be used whenever possible.

1. **EYE PAIN**
In cases of markedly elevated IOP due to acute glaucoma attacks, etc., the patient will frequently experience sudden and severe eye pain. Generally speaking, the patient will experience severe eye pain when IOP rises markedly from a normal value to a high value. Eye pain may also be caused by factors such as irritation to the ciliary body resulting from corneal epithelial damage or uveitis.
2. HEADACHE
In acute glaucoma attacks, accompanying sudden elevation of IOP, the patient may experience headache accompanied by nausea and vomiting, as well as symptoms such as reduced visual acuity, photophobia, and irisopsia.

3. BLURRED VISION
The patient may experience blurred vision in the event of secondary glaucoma resulting from corneal edema and uveitis accompanying a marked increase in IOP.

4. VISUAL FIELD DEFECTS
In the initial stage of glaucoma, even in cases where anomalies have been detected by visual field testing, the patient frequently has no subjective symptoms of such anomalies. If a patient complains of visual field anomalies, this frequently means that optic nerve damage or visual field damage has already progressed to a considerable degree.

5. HYPEREMIA
Bulbar conjunctival hyperemia is experienced not only in acute glaucoma attacks, but also in various forms of secondary glaucoma such as glaucoma secondary to uveitis, neovascular glaucoma, and phacolytic glaucoma.

Spectral domain OCT
Optical coherence tomography (OCT) in glaucoma offers the opportunity to objectively measure the retinal nerve fibre layer and its associated change with time. It is an attractive tool in glaucoma assessment due to its ability to take non-contact, objective high-resolution measurements. Newer generation OCT scanners, referred to as spectral or Fourier domain (SD) OCT, are 200 times faster than the older time-domain (TD) OCTs, reducing patient movement artefact and increasing axial resolution. The new SD OCTs are able to achieve a resolution of 3-6 microns compared with a 10-micron resolution previously achieved with TD OCT.\[6\]

DARC (Detection of apoptotic retinal cells)
The ability to detect glaucoma at the earliest stages before field loss, where approximately 40 per cent of ganglion cells have already been lost, has been a goal in clinical glaucoma management for several decades.
A new technique which utilizes the unique optical properties of the eye to directly visualize retinal ganglion cell (RGC) death may now be a realistic option and for the first time may give glaucoma physicians the opportunity to detect glaucoma earlier and monitor the response to treatment in a visual and quantifiable manner.[7]

The technology relies on the unique properties of annexin V, a protein which has the ability to bind to negatively charged phospholipids in the presence of Ca2+. A technique termed “Detection of Apoptotic Retinal Cells” (DARC) has been developed which utilizes non-radioactive fluorescent labelled annexin V and high-resolution imaging to enable real-time detection of apoptosis in the RGCs.[7]

**IOP telemetry**

The evidence in support of peak IOP and IOP fluctuation points to the importance of targeted IOP strategies. This is particularly so given evidence that the timing and type of current IOP lowering therapies can effect IOP fluctuation in different ways.[8-10]

Measurements are taken every 5 min for duration of 30 sec, giving a total of 288 measurements (each of which is a mean of 300 readings) over a 24 h period. The results obtained are presented in an arbitrary unit and not millimetres of mercury[11] Using 24 h tracing, there has been identification of individual circadian IOP patterns.[12]

**TREATMENT**

**PRINCIPLES OF GLAUCOMA THERAPY**

1. **Objective of therapy is to maintain the patient's visual function**

The purpose of glaucoma therapy at the present time is to maintain the patient’s visual function. Visual function damage severely impairs patients’ QOL. However, in providing treatment, one must not only bear in mind possible adverse effects and complications of treatment, but also the social and economic burden imposed by hospital visits and/or hospitalization and the impairment to QOL caused by worry about blindness.

2. **The most reliable method of treatment is reduction of intraocular pressure**

At present, based on the evidence, the only reliable treatment for glaucoma is to decrease IOP. Improvement of ocular blood flow and direct neuroprotection have attracted attention as new therapeutic methods involving factors other than IOP, and these may become innovative therapeutic options in the future.
3. **Causal therapy must be provided for all treatable causal factors**
   If it is possible to treat a causal factor in elevation of IOP, this factor must be treated in conjunction with therapy to reduce IOP. Types of causal therapy include iridotomy in types of glaucoma in which pupillary block causes elevation of IOP, such as primary angle-closure glaucoma, anti-inflammatory treatment in glaucoma due to uveitis, retinal photocoagulation in neovascular glaucoma, and discontinuation of steroid administration in steroid glaucoma.

4. **Early detection is vital**
   At present, once visual function has been lost in glaucoma, there is no way to regain it. It is also known that in the late stages of glaucoma, the disease may continue to progress even when treatment is provided. Accordingly, early detection and treatment of glaucoma are of primary importance.

5. **Achieving the maximum effect with the minimum required drugs**
   There are many antiglaucoma drugs available but the principle of drug treatment of the disease lays in obtaining the maximum effect with the minimum required drugs and the minimum adverse effects. For this reason, the mechanism of action, adverse effects, and contraindications of the drugs used must be understood. In addition, factors such as QOL, treatment costs, and compliance must also be taken into consideration.

6. **Selecting among drugs, laser treatment, and surgery**
   As the therapeutic options in glaucoma include drug treatment, laser treatment, and surgical treatment, the appropriate therapeutic modality must be selected based on the individual patient and the disease stage and type. Concomitant use of multiple drugs may increase adverse effects and reduce compliance. Generally speaking, when three or more drugs are required to control IOP, other therapeutic options such as laser treatment or invasive surgery should be considered.\[^{13}\]

**CURRENT TREATMENT OPTIONS**

The goal of treating glaucoma lies primarily on preventing or delaying the loss of visual field. Since neuronal cell death is irreversible, no cure is available once the visual field is lost. However, since IOP is the primary risk factor causing the loss of RGCs, the strategies of treatment mostly involve lowering IOP.\[^{14}\] Other important factors such as cost, convenience and safety should also be considered.\[^{15}\]
Current treatments for glaucoma include

- Medication
- Laser use and surgery

MEDICATIONS

Medications involve inhibiting the inflow of aqueous humor, enhancing the outflow of aqueous humor, protecting the optic nerves\textsuperscript{[16]} and manipulating the osmotic pressure between plasma and the eyes.\textsuperscript{[13]}

\(\alpha_2\) adrenoreceptor agonists and \(\beta_1\) receptor antagonists lower IOP by inhibiting the inflow of aqueous humor to the eye. Timolol, which is the most prescribed drug, and betaxolol, which has the fewest systemic side effects, are both \(\beta_1\) receptor blockers.\textsuperscript{[16]} A third type of drug that inhibits the inflow of humor is carbonic anhydrase inhibitors, such as acetazolamide and dorzolamide. Such drugs are often formulated together as in Cosopt (dorzolamide hydrochloride and timolol maleate).\textsuperscript{[15]}

Another method of reducing IOP is by enhancing the outflow of humor from the eyes through the use of muscarinic acetylcholine receptor agonists. This mechanism is indirect, but involves a muscarinic acetylcholine receptor (M3)-mediated contraction of the ciliary muscle.\textsuperscript{[16-17]} The contraction causes the widening of the spaces in the trabecular meshwork. The newest class of drugs using this strategy is the prostaglandin F2\(\alpha\) derivatives which enhance the uveoscleral outflow. Bimatoprost falls under this category and is considered the most effective anti-glaucoma drug.\textsuperscript{[18]}

Points to be borne in mind in drug combination

- In cases where the drug is not effective or not effective enough, or if tachyphylaxis occurs, change the initial therapy rather than adding an additional drug.
- The additional drugs should be used only if the effect of monotherapy is insufficient.
- Increasing the recommended dosage will not enhance, the IOP -lowering effect and will increase adverse effects.

Guidance in administration

In order to increase efficacy by improving intraocular penetration, while minimizing adverse effects by reducing systemic absorption of eye drops, and also in order to improve compliance, it is important to guide patients in the proper administration method as follows.
✓ Wash hands prior to administration.
✓ Be careful not to allow the tip of the eye drop bottle to touch the eyelashes.
✓ Administration should be conducted one drop at a time.
✓ After administration, gently close the eye and compress the lacrimal sac.
✓ Wipe away any eye drops that have overflowed around the eye and wash off any eye drops adhering to the hands.
✓ When multiple eye drops are used, the administration interval should be 5 minutes or longer.

LASER SURGERY
A. Laser iridotomy
1) Purpose
To relieve pupillary block, equalize pressure differential between the anterior and posterior chambers, and open the anterior chamber angle.

2) Indications
This procedure is the first choice therapy in primary or secondary angle-closure glaucoma due to pupillary block. It may also be performed in patients with suspected plateau iris syndrome in order to eliminate the factor of pupillary block.

3) Preoperative preparation
a) In order to stretch/tighten the iris and facilitate perforation, 1%-2% pilocarpine is instilled one hour before surgery.
b) In order to prevent postoperative elevation of IOP spike, apraclonidine is instilled one hour before and immediately after surgery.
c) If the cornea is edematous, drugs such as carbonic anhydrase inhibitors or hyperosmotics are administered to make the cornea transparent prior to surgery.
d) The procedure is carried out under topical anesthesia.

4) Postoperative management
1) IOP is monitored for 1-3 hours after surgery in order to determine whether or not transient elevation has occurred.
2) Carbonic anhydrase inhibitors or hyperosmotics are administered as needed. Postoperative inflammation is usually self limiting, but depending on the extent of the inflammation, it may be necessary to administer topical steroids.
Surgical devices
All surgical devices aim to reduce IOP in a way that is predictable and associated with fewer side effects compared to established techniques. Current challenges faced with new devices will be applicability to glaucoma subtypes, cost and training required.

B. Laser trabeculoplasty
1) Purpose: The trabecular meshwork is irradiated with a laser in order to improve aqueous outflow.

2) Indications: Primary open-angle glaucoma (broad definition), exfoliation glaucoma, pigmentary glaucoma, primary angle-closure glaucoma following laser iridotomy, mixed glaucoma, etc. However, it is known to be difficult to normalize IOP in eyes in which this pressure is 25 mmHg or above. Rather than a replacement for invasive surgery, IOP should be considered an adjunct to drug treatment. Moreover, the IOP -lowering effect of this procedure is known to recede over time.

3) Preoperative preparation
1) In order to prevent postoperative IOP spike, topical apraclonidine is given one hour before and immediately after surgery.
2) The procedure is carried out under topical anesthesia.

4) Postoperative management
1) IOP is monitored for 1-3 hours after surgery in order to determine whether or not transient elevation has occurred.
2) Carbonic anhydrase inhibitors or hyperosmotics are administered as needed.
3) Postoperative inflammation frequently resolves spontaneously, but depending on the extent of the inflammation, it may be necessary to administer topical steroids. [19-21]

CONCLUSION
Recent exciting developments in glaucoma management hope to, in part, address these concerns. These include the development of a new class of IOP lowering medications (Rho-kinase inhibitors), newer and safer techniques for surgically reducing IOP and the development of non-IOP dependant therapies such as neuroprotection.

Advances in glaucoma treatment are desperately needed. This is because proven medical and surgical therapies are limited in their capacity to stop glaucoma progression. Both work by
reducing IOP, a risk factor for glaucoma but not necessarily the sole cause for disease progression.

REFERENCES


