Section: Ophthalmology

Systemic Review

ADVANCEMENTS IN GLAUCOMA TREATMENT: A REVIEW OF CURRENT AND EMERGING MODALITIES

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Received : 13/01/2023
Received in revised form : 20/02/2023
Accepted : 04/03/2023

Keywords:
Glaucoma, prevalence, traditional treatment approaches, anti-glaucoma medications, surgical options, emerging surgical techniques, implantable devices, neuroprotective strategies, combination therapies, and challenges.

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DOI: 10.47009/jamp.2023.5.4.362

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (4); 1809-1815

Abstract

Background: Glaucoma, a major cause of irreversible vision loss worldwide, poses significant challenges for healthcare providers due to its chronic and progressive nature. Recent advancements in glaucoma research have spurred the investigation of innovative treatment options. Although there have been notable strides in glaucoma management, obstacles persist, such as early detection, equitable access to advanced therapies, and cost concerns. Moreover, the potential neuroprotective role of ciliary neurotrophic factor (CNTF) and its implications in glaucoma management are being actively investigated. Emerging diagnostic technologies and imaging modalities are revolutionizing early glaucoma progression detection and monitoring. This article aims to explore the current and emerging modalities for managing glaucoma.

INTRODUCTION

Glaucoma is a multifaceted array of eye disorders that precipitates a gradual deterioration of the optic nerve's integrity—a vital channel transmitting visual information from the eye to the brain—thus engendering the plausible consequence of nerve tissue loss and eventual impairment of vision should intervention remain absent. The anterior segment of the eye contains a transparent fluid called aqueous humor, produced in the region behind the iris. It exits through channels at the junction of the iris and cornea, known as the anterior chamber angle. The cornea at the front of the eye covers the iris, pupil, and angle. Suppose the outflow of this fluid is impeded or hindered in any way, in that case, increased pressure inside the eye, called elevated intraocular pressure (IOP), may develop, and the individual experience optic nerve deterioration. Not every individual with elevated eye pressure will necessarily develop glaucoma; conversely, some people with normal eye pressure may still be at risk of developing the condition. An alternative hypothesis regarding the origin of this form of glaucoma suggests inadequate blood flow (perfusion) to the optic nerve.[1,2]

1. TYPES: It is classified as the following

a. Primary open-angle glaucoma

The prevailing type of glaucoma progresses gradually and typically remains asymptomatic. Many individuals are only aware of their condition once they experience substantial vision impairment. Glaucoma primarily impacts peripheral or side vision in the initial stages, but it can progress to central vision impairment. Failure to seek treatment for glaucoma can result in substantial vision loss in both eyes and potentially lead to blindness.

b. Acute angle-closure glaucoma:

An infrequently encountered form of glaucoma, also known as narrow-angle glaucoma, typically arises when the drainage angle between the cornea and the iris in the eye becomes obstructed or closed. Many individuals with this type of glaucoma have an exceptionally narrow drainage angle. As the eye ages, the lens thickness increases, pushing the iris forward and narrowing the space between the iris and the cornea. This narrowing of the angle obstructs the fluid's path to the drainage system, leading to a buildup of fluid and increased eye pressure.[3] Angle-closure glaucoma can exist in a chronic, gradual manner or acutely, appearing suddenly. It manifests suddenly due to a rapid elevation of intraocular pressure. Its indications may encompass intense eye pain, nausea, eye redness, perception of halos or colored rings around lights, and blurred vision. This constitutes an urgent

ISSN (O): 2687-5365; ISSN (P): 2753-6556

situation wherein severe visual impairment can rapidly ensue. It poses a medical emergency as it can lead to vision loss within a day of its onset.[4]

c. Secondary glaucoma
   This form of glaucoma arises due to trauma or another ocular ailment. A range of medical conditions, medications, physical traumas, and eye anomalies can be potential causes of this type of glaucoma. In rare instances, secondary glaucoma can be a result of eye surgery. Factors such as using corticosteroids, eye diseases like uveitis (inflammation of the eye's middle layer), medical conditions such as diabetes, and eye injuries can contribute to this.[5] The symptoms typically correspond to the root cause of glaucoma. Depending on the underlying factors, the symptoms may resemble those of open-angle or angle-closure glaucoma.
d. Primary congenital glaucoma (PGC)
   It is an uncommon condition caused by genetically determined irregularities in the trabecular meshwork and anterior chamber angle. It leads to increased intraocular pressure (IOP) and is not associated with other ocular or systemic developmental abnormalities. It typically manifests within the age range of 3 to 9 months, with the most severe type present from birth. [6]. Increased intraocular pressure (IOP) is linked to the classic three symptoms (photophobia, epiphora, and blepharospasm) observed in children. These symptoms arise from the rapid enlargement of the child's eye, leading to buphthalmos, corneal enlargement, horizontal or oblique breaks in the Descemet membrane, and subsequent corneal edema and cloudiness.

2. PREVALENCE

Glaucoma stands as the primary cause of permanent vision loss worldwide. It has been approximated that a total of 60.5 million individuals were impacted by primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) on a global scale in the year 2010.[7] The risk and types of glaucoma differ across races and nations. In the United States, black individuals have a greater prevalence of primary open-angle glaucoma (POAG) than whites. On the other hand, East Asian populations exhibit a higher prevalence of POAG than primary angle-closure glaucoma (PACG), while Mongolians are more affected by PACG than POAG. The rapid rise in elderly populations worldwide makes it imperative to precisely determine the prevalence of glaucoma and forecast the future number of affected individuals.[8] Such accurate estimates are crucial for developing suitable health policies that serve diverse populations across the globe.

Traditional Treatment Approaches

Traditional treatment for glaucoma typically involves medications aimed at lowering intraocular pressure, a major risk factor for the disease. These medications reduce fluid production in the eye or enhance fluid drainage to maintain a healthy pressure level.

Anti-Glaucoma Medications

Common glaucoma medications include prostaglandin analogues, beta-blockers, alpha-adrenergic agonists, and carbonic anhydrase inhibitors.

Drug Class	Name of the Drugs	Formulation	Indications	References
α-adrenergic agonists	Dipivefrin, Apraclonidine, and Brimonidine	Eye drops	Used to treat chronic open-angle glaucoma.	[9]
β-adrenergic antagonists	Betaxolol (selective), Timolol, and Levobunolol (non-selective)	Eye drops	Recommended for the treatment of chronic open-angle glaucoma.	[9]
Carbonic anhydrase inhibitors	Brinzolamide, Dorzolamide, and Acetazolamide	Eye drops, Powder for injection (500 mg PO/IV, followed by 125-250 mg PO q4hr, Sustained-release: 500 mg PO q12hr)	Used in individuals with chronic open-angle glaucoma and acute angle-closure glaucoma before surgery and for secondary glaucoma.	[9,10]
Cholinergic agents	Pilocarpine, Aceclidine, Carbacholine (direct-acting agents), Demecarium bromide (indirect-acting agents)	Solution/drops	Used for the short-term management of some angle-closure glaucoma. Contraindicated for secondary glaucoma.	[9,10]
Prostaglandin analogues	Bimatoprost, Latanoprost, Travoprost, and Tafluprost	Eye drops	Prescribed to lower elevated intraocular pressure in individuals diagnosed with open-angle glaucoma.	[9]
Osmotic agents	Glycerol and Mannitol	Oral solution (1 to 2 grams per kg of body weight taken one time), Injectable solution (5%, 10%, 15%, 20%, 25%)	It can be utilized to terminate a sudden onset of glaucoma attack.	[9,10]

3. **SURGICAL OPTIONS**

a. Trabeculectomy
   When prescribed eye drops fail to effectively reduce intraocular pressure (IOP), your medical professional might suggest conventional glaucoma surgery. The prevailing surgical choice is trabeculectomy, which is also referred to as filtration surgery.[11] During this procedure, a

ISSN (O): 2687-5365; ISSN (P): 2753-6556

tiny opening is created in the sclera (the white part of the eye), covered by a thin trapdoor. This allows the excess aqueous humour (the clear fluid between the eye's lens and cornea) to drain through the trapdoor into a small reservoir just beneath the eye's surface, concealed by the eyelid. As a result, intraocular pressure is lowered, and glaucoma progression is slowed. Following trabeculectomy, approximately half of the patients do not need glaucoma medication for a significant period after the surgery. While the procedure effectively reduces intraocular pressure, it is essential to note that it is not a cure, and individuals may still experience vision loss even after the surgery.[12]

I. MINIMALLY INVASIVE GLAUCOMA SURGERY (MIGS): A BREAKTHROUGH IN GLAUCOMA TREATMENT

Minimally invasive glaucoma surgery (MIGS) offers a safer and less invasive method to lower intraocular pressure (IOP) compared to conventional surgery, with the potential to reduce the need for topical medications. It is commonly performed in conjunction with cataract surgery using phacoemulsification, as observed in various clinical trials. Currently, these procedures are focused on treating patients with mild-to-moderate glaucoma. It achieves IOP reduction through four primary methods: bypassing the juxtacanalicular trabecular meshwork (TM) to enhance trabecular outflow, facilitating uveoscleral outflow through suprachoroidal pathways, decreasing aqueous production from the ciliary body, and establishing a subconjunctival drainage pathway.[13]

1. Increasing trabecular flow:

Five MIGS procedures, namely Trabectome, iStent, Hydrus, gonioscopy-assisted transluminal trabeculectomy (GATT), and excimer laser trabeculectomy (ELT), target the juxtacanalicular portion of the trabecular meshwork. They are designed to address the primary site of aqueous outflow resistance in most patients with open-angle glaucoma (OAG). Occasionally, postoperative scarring at Schlemm's canal can hinder the procedure's effectiveness. Furthermore, while these procedures lower juxtacanalicular resistance, they do not address other sites of outflow resistance, such as elevated episcleral venous pressure, which may be more critical for certain patients.[13]

2. Increasing uveoscleral outflow by suprachoroidal shunt

   Uveoscleral outflow contributes to about 50% of the normal human eye's aqueous drainage, and there appears to be a negative pressure gradient of 3-4 mmHg that facilitates aqueous outflow into the suprachoroidal space. Opening the uveoscleral pathway through prostaglandin analogs or cyclodialysis cleft leads to a significant reduction in intraocular pressure.[14]

3. Reducing aqueous production:
4. It is done by endocyclophotocoagulation. Cyclophotocoagulation, primarily performed through the transscleral approach, has been a longstanding treatment option for refractory glaucoma. Similar to other minimally invasive glaucoma techniques, it is conjunctival-sparing and can be performed in conjunction with cataract surgery.
5. Establishing a subconjunctival drainage pathway

   Subconjunctival filtration establishes an unnatural pathway for aqueous outflow and is the foundation for traditional trabeculectomy and aqueous shunt glaucoma surgeries. For this procedure to be effective, the eye should not have pre-existing conjunctival scarring, and it is yet to be determined whether disuse trabecular atrophy might impact intraocular pressure (IOP) outcomes in this surgical approach.[15]

II. LASER-BASED THERAPIES

1. SELECTIVE LASER TRABECULOPLASTY (SLT)

   It has sparked a renewed interest in using laser trabeculoplasty to lower intraocular pressure (IOP) in glaucoma-affected eyes. SLT's safety profile includes mild and temporary inflammation, ocular pain, and a slight possibility of moderate IOP elevation post-procedure. The exact mechanism of SLT remains unknown, but it delivers lower energy to the trabecular meshwork, causing less damage to angle tissues. This procedure is a safe and effective method for reducing intraocular pressure (IOP) in glaucoma-affected eyes and can be used as either primary or additional therapy. [16]

2. LASER PERIPHERAL IRIDOTOMY (LPI)

   This procedure is employed as a treatment for patients with angle-closure glaucoma and as a preventive measure for individuals at risk of angle-closure glaucoma. It involves using laser energy to create a tiny opening in the iris (the colored part at the front of the eye) to aid in opening the drainage angle and managing or preventing angle-closure glaucoma. This opening is not detectable to the naked eye. This treatment aims to prevent elevated intraocular pressure and minimise the likelihood of vision loss due to glaucoma. When the procedure is conducted in the early stages of the disease, there is a 66–75% chance of "curing" the condition. If applied later in the disease progression, it can aid in slowing or halting the condition's advancement. Medication and/or surgery may be required alongside laser treatment in severe cases.[17]

3. NOVEL DRUG CLASSES AND DELIVERY SYSTEMS

   Available marketed formulations of anti-glaucoma drugs need help crossing the blood-retinal barrier or achieving sufficient systemic bioavailability. Consequently, drugs with lower therapeutic indexes require frequent administration, accumulating concentrated solutions in the eye and causing toxic effects and cellular damage. To address these issues, novel

ISSN (O): 2687-5365; ISSN (P): 2753-6556

drug delivery systems such as in-situ gels, liposomes, niosomes, hydrogels, dendrimers, nanoparticles, solid lipid nanoparticles, microneedles, or ocular inserts play a crucial role in enhancing the therapeutic effectiveness of anti-glaucoma drugs.

IN-SITU GELLING SYSTEM

The ocular in-situ gelling system refers to a formulation that starts as a liquid when administered to the eye but transforms into a thin gel layer in response to physiological changes. These in-situ gels are initially in a solution form, and upon exposure to eye conditions, specific stimuli activate their conversion into a gel, facilitating drug delivery. Different types of polymers are utilized to create in-situ gels to achieve such phase transitions. Polymers that respond to stimuli are becoming increasingly intriguing for ocular drug delivery. These macromolecules undergo physicochemical changes in response to the surrounding environment, wherein the stimulus triggers chemical alterations and induces structural changes in the polymers. Carbopols and polycarbophils are among the frequently employed polymers for formulating in-situ gels.[18]

LIPOSOMES

These are vesicles composed of natural or synthetic lipid materials featuring phospholipid bilayers with an inner aqueous core and an outer lipid layer. This unique structure allows liposomes to deliver hydrophilic and hydrophobic drugs to the eye. Additionally, they are highly biocompatible, biodegradable, and non-toxic. It has shown remarkable efficacy in delivering drugs to the eye's anterior and posterior parts.[19]

NIOSOMES:

Niosomes, similar to liposomes, are bilayer vesicles comprised of amphiphilic non-ionic surfactants.[20] They consist of two essential components, cholesterol, and non-ionic surfactants, making them non-immunogenic, biocompatible, and biodegradable. These are preferred over other drug delivery systems like liposomes due to their lower toxicity levels when using non-ionic surfactants. They offer advantages such as better physicochemical stability and enhanced drug permeation.

HYDROGEL

It can regulate the flow of aqueous humor in the anterior chamber, effectively controlling intraocular pressure (IOP). The restricted outflow of aqueous humor is achieved through the properties of the hydrogel. It has demonstrated promising potential in enhancing drug retention in the cornea and prolonging the reduction of intraocular pressure (IOP) over an extended duration.[21]

EMERGING SURGICAL TECHNIQUES

NON-PENETRATING DEEP SCLERECTOMY (NPDS):

It is also known as non-penetrating trabeculectomy, a filtering surgery involving excising the internal wall of Schlemm's canal to allow subconjunctival filtration without entering the anterior chamber. This surgical technique was developed to reduce the complications associated with traditional trabeculectomy.[21] The two primary intraoperative complications during NPDS are difficulty locating Schlemm's canal and TDM (Trabeculo-Descemetic Membrane) perforation. Difficulty in finding Schlemm's canal is usually due to inadequate depth in the scleral canal dissection, often stemming from concerns about dissecting too deeply into the choroid. In such cases, creating a third deep scleral flap can help achieve the correct plane necessary to identify Schlemm's canal. Intraocular hemorrhage is an infrequent complication of NPDS, as the reduction in intraocular pressure (IOP) occurs gradually and with more predictability when compared to penetrating surgeries. NPDS is among the latest and frequently employed filtration surgery techniques for treating glaucoma. It is recommended for managing both primary and secondary open-angle glaucoma.[23]

TRABECTOME

This surgery enhances fluid drainage from the eye by removing the trabecular meshwork, which acts as a strainer, restricting flow into the natural drainage system. This procedure has been performed through the same small corneal incision used for cataract surgery. It can be performed as a standalone procedure without cataract removal during the same session, but it is more commonly combined with cataract surgery. [24]. This combination can be applied in two typical scenarios such as:

When glaucoma is the primary concern, and it is not adequately controlled with eye drops or laser treatment and also used in cataracts causing blurry vision or glare.

When the main issue is a symptomatic cataract resulting in glare or blurry vision, reduce the use of eye drops for glaucoma.

INNOVATIONS IN IMPLANTABLE DEVICES

The development of glaucoma drainage devices offers an alternative pathway for efficient aqueous humor drainage from the anterior chamber, reducing intraocular pressure (IOP).

CONVENTIONAL GLAUCOMA DRAINAGE DEVICES

The purpose of glaucoma drainage devices is to redirect aqueous humor from the anterior chamber to an external reservoir. Following surgery, a fibrous capsule will form in approximately 4-6 weeks, regulating the flow of aqueous humor. These devices have proven effective in managing intraocular pressure (IOP) in eyes with trabeculectomy failure and those with limited conjunctiva due to scarring from previous surgeries or injuries. Additionally, they have successfully treated complex glaucoma, including uveitic glaucoma, neovascular glaucoma, and pediatric and developmental glaucoma.[25] These drainage devices can be linked to different postoperative complications. Early postoperative complications resemble those seen in other filtration procedures,

ISSN (O): 2687-5365; ISSN (P): 2753-6556

such as shallow chambers, hypotony, and suprachoroidal hemorrhage. These devices come in various sizes, materials, and designs. Selecting a specific type of drainage device depends on a patient's preoperative intraocular pressure (IOP) and optic nerve condition, the desired long-term IOP control, and the surgeon's comfort and preference. Careful preoperative screening, planning, and precise surgical techniques are essential in reducing postoperative complications.[26]

MICROSTENTS

Hydrus Micro stent

The micro stent is composed of nitinol, a nickel-titanium alloy with super-elastic properties, enabling it to regain its original shape after deformation. When inserted, the microstent can expand Schlemm's canal up to four to five times its natural width, preventing the collapse of the canal caused by elevated intraocular pressure (IOP). The FDA approved the Hydrus micro stent in 2018 for its utilization alongside cataract surgery to lower intraocular pressure in adult patients diagnosed with mild to moderate primary open-angle glaucoma. The Hydrus stent is contraindicated in angle-closure glaucoma, traumatic glaucoma, malignant glaucoma, uveitic glaucoma, neovascular glaucoma, and congenital anomalies of the anterior chamber angle.[27]

Trabecular bypass stent

This is a heparin-coated titanium stent designed to be inserted through the trabecular meshwork (TM) into Schlemm's canal. In primary open-angle glaucoma, the juxtacanalicular TM is believed to be the primary source of outflow resistance. By facilitating unimpeded access of aqueous to Schlemm's canal, drainage into collector channels and more distal aqueous veins should improve, reducing intraocular pressure (IOP).[28]

NEUROPROTECTIVE STRATEGIES

Neuroprotection in glaucoma pertains to interventions aimed at safeguarding the optic nerve or preventing the death of retinal ganglion cells (RGCs). These interventions can influence cellular factors within the optic nerve or address external risk factors (e.g., reducing intraocular pressure) that may impact the nerve's health.[29] It differs from lowering intraocular pressure (IOP) and is an additional strategy for treating glaucoma. While reducing IOP is considered an indirect approach to neuroprotection, supplementing with other neuroprotective agents may be essential. These interventions can involve neutralizing the toxicity of risk factors, such as using glutamate receptor antagonists or inhibitors of nitric oxide synthase, offering different approaches to neuroprotection. These processes include the production of external nerve-derived risk factors like glutamate and nitric oxide, the deprivation of internal trophic factors in nerve cells, the loss of intracellular self-repair mechanisms, and the generation of intracellular destructive processes. The rationale behind using neuroprotective agents is to act as pharmacological antagonists, restoring the balance between cellular death and survival signals, thereby preventing RGC death and optic nerve damage. Since RGC loss is a critical step in glaucoma's pathophysiology, neuroprotection may help preserve visual function.

BRIMONIDINE

It is frequently employed as an anti-glaucoma agent to lower intraocular pressure (IOP) by acting as an alpha-2 adrenergic agonist. It also offers protection to retinal ganglion cells (RGCs) from somatic, axonal, and dendritic degeneration in various optic injuries, including those related to ischemia, NMDA-induced neurotoxicity, ocular hypertension, optic crush, and optic neuritis. Its neuroprotective effects are believed to result from several mechanisms, including the activation of neurotrophic factors, vasomodulation, inhibition of glutamate, upregulation of cell-survival signals, and downregulation of apoptosis. Studies have demonstrated that Brimonidine not only safeguards the retina from ischemic damage in a dose- and time-dependent manner but also promotes neural regeneration following injuries.[30]

STEM CELL THERAPY

Mesenchymal Stromal Cells (MSCs)

These cells have also been associated with neuroprotection in glaucoma. Researchers are currently exploring the therapeutic potential of MSC secretome, which includes neurotrophins and exosomes derived from MSCs capable of carrying various cell signaling molecules.[31]

NEUROTROPHINS

Ciliary Neurotrophic Factor

The hypothalamic neuropeptide, a ciliary neurotrophic factor (CNTF), can provide neuroprotection in glaucoma as a neuronal survival factor.[32]

COMBINATION THERAPIES IN GLAUCOMA

When monotherapy fails to achieve the target pressure in glaucoma or when there is a progression of glaucomatous damage or conversion from ocular hypertension to glaucomatous optic neuropathy, a combination of antiglaucoma medications is recommended. Recently, numerous fixed combinations containing two active compounds have become available for the medical management of glaucoma. These fixed combinations offer greater convenience for patients compared to non-fixed combinations, as they require less frequent application, potentially improving adherence. Additionally, they are likely to contain lower amounts of toxic preservatives than non-fixed combinations.[33] The available fixed-combination medications with their mechanism include:

B-blocker/CAIs have a synergistic effect in reducing overall aqueous production.

B-blocker/alpha agonists also act synergistically as aqueous suppressants. Additionally, alpha agonists can enhance outflow through the uveoscleral pathway, potentially further reducing IOP.

CAI/alpha agonists decrease aqueous production and increase uveoscleral outflow. They can be a

ISSN (O): 2687-5365; ISSN (P): 2753-6556

favorable alternative treatment for individuals who cannot take B-blockers or prefer to avoid PGAs due to ocular effects like hyperemia, eyelash growth, and iris or periorbital hyperpigmentation, particularly with monocular treatments.

B-blockers/PGA lower IOP by decreasing aqueous production and increasing outflow.[34]

CONCLUSION

The future of glaucoma trends holds promise and potential, but it also presents certain challenges that must be addressed. Advancements in research and technology offer new possibilities for early detection, improved diagnostic tools, and novel therapeutic interventions that could enhance patient outcomes and quality of life. Fixed-combination medications offer greater convenience and potentially better patient adherence, with their combined mechanisms of action providing more effective IOP control. However, despite these promising developments, challenges persist in glaucoma management. Ensuring early and accurate diagnosis and comprehensive and continuous monitoring remains crucial to prevent irreversible vision loss. Collaborative efforts among clinicians, researchers, and healthcare policymakers are essential in tackling these challenges. With sustained dedication to research, innovation, and patient care, the glaucoma community can pave the way for a brighter, more successful future in combating this sight-threatening disease.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556

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ISSN (O): 2687-5365; ISSN (P): 2753-6556