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Review Article

Advanced trends in treatment of glaucoma

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ABSTRACT

Glaucoma is a slow escalating disease which causes the degradation of the retinal ganglionic cells (RGCs). It eventually results in irrevocable blindness if it is not diagnosed properly in time. The various important factors which are present in glaucoma are- increased intraocular pressure, increased glutamate levels, oxidative damage and changes in nitric oxide metabolism. The goal is to reduce the intraocular pressure which can be done by medications, laser procedures, surgical procedures and intraocular devices. The drugs used for the treatment of glaucoma are prostaglandin analogs, alpha-agonists, carbonic anhydrase inhibitors and cholinergic agonists. In ophthalmic formulations, emulsions, suspensions and soluble ophthalmic drug inserts (SODI) use of viscoelastic agents have been used in order to enhance the ocular drug delivery in patients as well as to provide a sustained release effect and better therapeutic action. It was observed that some patients are immune to medications and later have to resolve to laser procedures and surgical procedures. The future anti- glaucoma drug or technique should reduce intraocular pressure. It must also be neuroprotective and vasoprotective in nature and restore visual acuity.

Key Words: intraocular pressure, conventional medications, neuroprotective agents, IOP lowering devices

INTRODUCTION

Glaucoma or irrevocable blindness is accelerating and neurodegenerative in nature and is the second most prevalent eye disorder in the world [1]. It affects approximately 66.8 million people [2]. The characteristic feature is the death of the retinal ganglionic cells (RGC),optic nerve atrophy and degradation of the visual cortex and lateral geniculate nucleus, which causes resultant loss of axons and neurons [3][4]. The future research has opened up new vistas by helping us in the identification of various new factors which include glutamate excitotoxicity, Nitric oxide (NO) neurotoxicity, disruption of neurotrophic factor transport and aberrant autoimmune responses. As a result, novel targets for treatment are now in development with the primary objective of neuroprotection through anti-apoptotic mechanisms. Treatment interactions and their effects on other tissues are also being researched, especially since results from various experiments seem contradictory. For example, a lesser amount of NO might cause inhibition of apoptosis. Aberrant immune responses may lead to neuronal damage, but their absence might also promote neuronal death. While all current research is geared towards treatment options, the possibility of RGC regeneration should be explored to search for a glaucoma cure. There has been a remarkable development in the research and it is mainly focused on developing pre-existing drugs and new therapeutic molecules [5]. The ideal anti-glaucoma drug must be an entity that not only leads to the reduction of intra ocular pressure but also possesses and vasoprotective and neuroprotective characteristics. The aim of this review is to evaluate and understand the various recent advancements that are available in the treatment of glaucoma.

GLAUCOMA

Glaucoma is termed as an emergency. The important characteristic is a loss of visual acuity due to the degradation of the retinal ganglial cells. The factor which can be modified in glaucoma is intraocular pressure. Vascular insufficiency in the optic nerves and high intraocular pressure are the major factors of glaucoma [6]. The following **Table 1** explains the factors associated with glaucoma.

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TYPES OF GLAUCOMA

Glaucoma can be roughly differentiated into two categories- closed angle glaucoma and the open angle glaucoma. The paramount characteristic differentiating closed-angle glaucoma from open-angle glaucoma is that the angle which is formed due to the site of aqueous outflow, forms a closed angle due to the presence of the iris (defined if at least 270° of the angle is occluded).

Primary Closed-Angle Glaucoma: The individuals who acquire closed-angle glaucoma are generally unaware that they are suffering from the disease as it is an asymptomatic disease, however as the disease starts progressing there is a loss of visual acuity. It is characterized by very high IOP, unreactive pupil, effusion of the choroid, excessive accumulation of aqueous humor behind the iris which leads to increase in convexity, blurring of vision, vomiting, nausea, severe ocular pain, shallow anterior chamber and conjunctival hyperemia

Acute Primary Angle Closure: Patients having acute primary angle closure generally present the following symptoms- painful redness in the eye, nausea, headache, nausea, loss of visual acuity, unreactive and mild dilated pupil, increased IOP. It is regarded as an ocular emergency and if attention is not given immediately can lead to irreversible blindness.

Primary Open-Angle Glaucoma: Inflammation of the eye followed by loss of the vision and increased IOP is the main characteristic feature of primary open angle. Glaucoma causes elevation of glutamate concentrations which are highly toxic in nature, which contributes to apoptosis of the optic axons [7] [8]. Selective perimetry and visual field testing can effectively identify changes to the peripheral field. There is an expansion which is very visible of the optic disc cup and lowering in the width of the neuro retinal rim [9]. An increase in the IOP that is greater than 21 mm Hg is an indication of glaucoma [10]. No single Mendelian mode of inheritance can give us an explanation regarding glaucoma [11]. Interactions of multiple genes can determine the risk factors for glaucoma. One can map specific genes which lead to the degradation of the anterior chamber of the eye [12]. Nitric oxide synthase-2 (iNOS-2) is an inducible form of NO Synthase which results in excessive production of Nitric oxide when it is present [13]. The presence of iNOS- 2 was observed in reactive astrocytes in the damaged tissues of the eye. One of the major factors which cause retinal ganglial cell apoptosis is the lack of neurotrophic factors. The presence of autoantigens in type 1 diabetes and glaucoma patients may provide a link between the two [14]. It has been observed that ischemia can lead to the activation of caspase [15].

TREATMENT

Avoidance of the progression of the disease, patient compliance and maintenance of the quality of life is the motto of prime importance in determining any treatment for a particular disease. In order to avoid the functional degradation or to decrease the rate of disease progression, it was observed that the most suitable treatment was to lower down the IOP. Initially, the target decreases the initial pressure to about 20-50% but, in order to maintain a target pressure, one needs to continuously monitor it. The general goal is to obtain better pressure control with topical and systemic medications to limit optic nerve damage.

CONVENTIONAL TREATMENTS

One must achieve the target IOP by less number of medications who have minimal side effects on the patients. **Table 2** explains, in brief, the various conventional medications that are used to lower the IOP. However, the choice of medication totally dependent upon the adverse effects, patient compliance, amount of doses and cost.

COMBINATION MEDICATION

In order to provide cheap and convenient usage, further developments were made to allow different pairs of drugs to be used. It also helps to maintain better dosing schedules. The combination therapy is mostly dependent upon the mechanism of action of the various components of the drug making up the combination. When selecting a drug as a component of combination therapy, one should be aware of the complementary mechanisms or the additive actions of the drug. Generally, a combination has an additive effect, patient compliant and has lesser side effects. For example, a carbonic anhydrase inhibitor and a beta-blocking agent provides good efficacy and reduces the IOP. Timolol 0.5% combined with brimonidine 0.2% is the newest combination available in the market. 0.005% latanoprost and 0.5% timolol produces an IOP reduction of 13-37%. The most commonly used combinations are Cosopt (timolol and dorzolamide), Xalacom (latanoprost and timolol) and Timpilo (timolol and pilocarpine) although this so far has been Government approved only for Veterans Affairs patients. The following table **(table 3)** explains the percentage reduction in IOP while using combination medications for treatment of glaucoma.

UNCONVENTIONAL METHODS

Lowering of the IOP is the most valuable and proven method to retard the progression of glaucoma. However, only IOP reduction is not sufficient to avoid glaucoma. The reasons for it can be- either there is rapid progression even when the IOP is decreased by any sort of conventional method of treatment, sometimes difficulties occur to lower the IOP in some patients because they don't respond to the medications and last reason is that the risks of IOP reduction are too great in some patients, e.g. endophthalmitis after trabeculectomy. Because of these reasons, the need for alternative methods to decrease or abort the progression of glaucoma is increasing rapidly. The methods can be divided into two major categories. The first includes unconventional methods to lower the IOP, e.g. drugs such as vitamins, marijuana. The second category includes treatments that do not affect IOP at all, but they help in the abortion of the progression of the disease. The health care professional wanted to convert all the marketed preparations into a preservative-free preparation which has high efficacy and better patient compliance. The following are the various marketed preparations that were discontinued on account of the above proposal.

Unconventional medications: In February 2010, Allergan introduced a new lower strength of their prostamide bimatoprost. The original Lumigan, which contains bimatoprost 0.03% and benzalkonium chloride 0.005% was already in the market, however, prescribers were offered a new Lumigan containing bimatoprost 0.01% but with a higher concentration of benzalkonium chloride, 0.02%. In 2011, Alcon scrapped it's once a day pilocarpine 4% preparation, Pilogel. Patients using this product found it highly inconvenient to switch to a two- three times daily preparation. In 2012, another once a day preparation was discontinued, the Novartis product Nyogel contained the lowest dose of timolol 0.1%, this was used in glaucoma treatment for pregnant women and breast-feeding women in whom low dose products are preferred. In March 2013, Bausch & Lomb announced recently the discontinuation of another commonly used drug, Minims proxymetacaine hydrochloride with fluorescein and also the discontinuation of Fluorets, a fluorescein ophthalmic strips. In April 2013, Teva launched a licensed generic, preservative-free timolol and dorzolamide eye drop. Alcon changed the formulation of their prostaglandin analog, travoprost (Travatan) to travoprost with timolol (Duotrav) replacing the preservative benzalkonium chloride with another preservative Polyquad which was used in contact lens solution.

The new Travatan was the first eye drop classed as a medicine containing Polyquad. According to the studies the Polyquad-containing formulation of travoprost is as effective as that containing benzalkonium chloride. 2014 welcomed three new preservative-free glaucoma preparations bimatoprost 0.03% with timolol 0.5% preservative-free (Ganfort 0.3mg/mL + 5mg/ mL eye drops, solution, in single-dose container), latanoprost preservative-free 0.005% (Monopost) and bimatoprost preservative-free 0.03% (Lumigan 0.3mg/mL eye drops, solution, in single-dose container); bimatoprost 0.03% with timolol 0.5% preservative-free (Ganfort 0.3mg/mL + 5mg/ mL eye drops, solution, in single-dose container). In April 2013 Alcon's Simbrinza was launched and is the first combination therapy for glaucoma which contains brimonidine and brinzolamide. The various other chemical entities which are still in the pipelines are- Rho-kinase inhibitors (Aerie) – AR-12286; PG 286 (AR-12286 + travoprost), Rho-kinase inhibitors + norepinephrine transporter inhibitor (Aerie) – AR-13324; PG 324 (AR-13324 + latanoprost), NO-donating moieties in combination (Bausch & Lomb) – latanoprostene bunod (previously called BOL-303259-X and NCX-116) and Adenosine receptor analogues (Inotek) – Trabodenoson (previously called INO-8875 and PJ-875). Unoprostone isopropyl or Rescula (Sucampo Pharmaceuticals) is used for treating ocular hypertension and glaucoma, it is similar to latanoprost, a synthetic analog of dinoprost (prostaglandin F2α), it has to be administered twice daily. The main disadvantage of eyedrops is that it has to be self-administered and that sometimes people forget to use their medications. Patients with glaucoma and ocular hypertension are, therefore, likely to benefit from biodegradable ocular implants like a slow release punctal plug delivery system for longterm drug delivery of bimatoprost. In April 2014, Mirvaso launched brimonidine, a sympathomimetic is present in 0.33% concentration in a dermatological gel formulation. The side effects of prostanoid group of drugs were increase in the thickness and length of the eyelashes and hypertrichosis. However, Allergan launched bimatoprost as a cosmetic preparation.

Cannabis: Cannabis was used in the treatment of joint pains, constipation, joint pains, labor pain and also alleviates symptoms of nausea, vomiting, various types of pain as well as treating anxiety, depression, asthma, epilepsy, multiple sclerosis and loss of appetite with weight loss in patients suffering from severe chronic diseases [16] [17]. Delta-9-tetrahydrocannabinol (D9THC), the main psychotropic agent in marijuana, was responsible

for the IOP-lowering effects. D9THC, delta-8-THC and 11-hydroxy-THC produces significant short-term reductions in IOP while 8-beta-hydroxy-THC and cannabidiol were significantly less effective. A random study determined a dose-related and statistically significant acute reduction in IOP. A number of studies between the mid-1970's and early 1980's explored the therapeutic use of cannabis and its other components. Merritt *et al*., (1983) and found a significant dose-related reduction in IOP and mild systemic hypotension with no psychoactive effects when they used a topical form of cannabis [18]. However, Roth and Green (1979) reported that topical D9THC has no effect on IOP [19]. Jones *et al*., (1981) tested an oral formulation of D9THC and the drug did cause significant lowering of IOP [20]. Liu and Dacus (1987) observed that administration of D9THC by the IV route decreased IOP in rabbit eyes and administration of the compound via the cerebrum had no IOP effect thus, indicating that the central nervous system is not responsible for the reduction in the IOP [21].

The disadvantages of cannabis were the variety of systemic side effects, psychoactive effects and short duration of action which was followed by a typical rebound effect. According to the recent research, cannabinoids can have a high potential in lowering the IOP. Hodges *et al.,* (1997) observed that WIN55212-2, a synthetic cannabinoid which has a strong affinity for the CB1 (cannabinoid receptor 1) receptor, did not affect the IOP when given systemically to normotensive rabbits [22]. Pace *et al*., however, proved that there is a relationship between IOP reduction and CB1 receptor when it was demonstrated that rabbits pretreated with an injection of CB1 receptor antagonist followed by a topical administration showed no IOP reduction, but when the same two cannabinoids not pretreated and the drug was topically applied showed a significant IOP reduction [23]. It was observed that due to the use of systemic cannabinoid administration Hodges et al studies opposed the cannabinoid- CB1 receptor-induced IOP reduction relationship. Pocella *et al*., developed strong evidence into determining the exact mechanism by which cannabinoids cause IOP reduction in eight human glaucoma subjects using a synthetic cannabinoid WIN55212-2. It was observed that there are large amounts of CB1 receptor in the ciliary body and it plays a direct role in the reduction of IOP [24]. But the exact nature of IOP reduction is still unknown and would require further investigation. A non-psychoactive synthetic cannabinoid IV administration of HU-211 produced a drop in IOP, with a remarkable IOP reduction at four hours post-administration. The systemic use of this cannabinoid showed no effects on blood pressure, heart rate or pupil dilation [25]. The authors believe that an increase in the aqueous humor outflow is the main mechanism of action.

Neuroprotective agents: Neuroprotection is antiapoptosis of retinal ganglial cells. One must take into consideration the site of protection in designing a vaccine. The target should be in the retinal ganglial cells because the cell death is induced by increased IOP which generally occurs in the retinal ganglial cells [26].T-cell induced neuroprotection helps in the vaccination of retinal ganglial cells from apoptosis. Copolymer-1 is an antigen that causes a cross reaction with a wide range of Tcells, which provokes a protective immune response, This is used as a vaccine and provides protection to the retinal ganglionic cells from cell death which is caused by increased IOP or toxins[27]. iNOS-2 Inhibitors like aminoguanidine can have a neuroprotective effect and prevent the death of retinal ganglionic cells[28]. Nipradilol usually releases a small amount of NO, it is a unique drug as it can decrease both IOP and is neuroprotective in nature. Ginkgo biloba extract (EGb 761) is used as a nutritional supplement for vasodilation, reduction of platelet aggregation and reduction of blood viscosity [29]. It contains 6% terpenoids and 24% flavonoid glycosides which lead to inhibition of toxicity and NO free radical accumulation by inhibition of iNOS [30]. It was observed that EGb 761 improved the visual impairment in a significant number of patients. However, a continuous administration is need as a discontinuation of EGb 761 lead to a reversion of visual acuity [31]. The effects of EGb 761 are dicey. Interleukin-10 also has neuroprotective activity through the STAT-3 pathway [32]. Caspase Inhibitors can also reduce apoptosis by inhibiting caspase. Baculoviral IAP (BIRC-4) and minocycline can lead to the inhibition of apoptosis of optic nerve axons [33] [34]. Geranylgeranylacetone (GGA) is an acyclic polyisoprenoid and a heat shock protein, has neuroprotective effects In particular, HSP72 seems to act as an anti-apoptotic chaperone protein that interferes and activates Heat Shock Factor 1 (HSF-1), a transcription factor for heat shock protiens (hsps) , which oligomerizes and translocates when exposed to stress [35]. NMDA antagonist acts on the receptor and provides neuroprotection. It avoids the increase of glutamate production, which leads to apoptosis by allowing entry of calcium into the cell. Memantine, is an N-methylD-aspartate glutamate receptor inhibitor, it is in clinical trials [36]. Eliprodil provides protection from glutamate assisted cytotoxicity. Riluzole decreases apoptosis of primary mix retinal cells and is neuroprotective in nature. R16, a peptide (interphotoreceptor-retinoid binding protein) derived from the retinal

ganglial cells. [37] Activators of transcription and signal transducers of protein-3 (STAT-3) play a paramount role in cell growth and cell differentiation. Ciliary neurotrophic factor (CNTF), has neuroprotective activity, which promotes survival of retinal cells, due to interleukin-10 signaling through the pathway of STAT-3[38] [39]. Erythropoietin (EPO) is a hematopoietic factor and is neuroprotective aborts apoptosis [40]. EPO receptors are usually found on cell bodies and dendrites of Retinal ganglionic cells. Intravitreal injection in rats leads to enhancement of the RGC survival by 92%. A dosage less than 4 µl of 0.1M EPO does not have the toxic effects [41]. The mechanism of neuroprotection is by the PI-3kinase/Akt pathway. EPO decreases the depolarization in the membrane potential which causes due to NO production [42]. The injection of EPO does not generate the production of news cells but it aborts the progression of the disease. MRZ-99030 (Merz Pharmaceuticals GmbH), reduces b-amyloid aggregation and is currently the subject of clinical trials to assess the safety of a topical formulation. One of the most attractive approaches for the treatment of eye diseases- Gene therapy. Apoptosis protein inhibitors not only block the apoptosis protein but also inhibit caspase. Ocular administration is better as compared to IV route as they have a lesser chance of side effects. In a study intravitreal injections of AAV-CBA vector coding for human baculoviral IAP repeat-containing protein-4 (BIRC4) were given to rats and it was found that there was inhibition of caspase along with the survival of retinal ganglionic cells. This explains that by using caspase inhibitors one can block the apoptosis and thus brings about an efficacious therapy for glaucoma [43].

Other alternative treatments: Various alternative and complementary methods to either slow down or stop glaucomatous progressions have come in picture and are being reviewed for its role in treatment. However, it was interesting that ophthalmologists were unaware that their patients take complementary and alternative medications. But there is a need for ophthalmologists to be aware of various complementary therapies so that they can understand their patients better. Herbal medications might have a role in the reduction of IOP. Vitamin C (ascorbic acid) at high doses provides a short-term IOP lowering effect, but has a reversible and short duration effect. The role of acupuncture on IOP reduction was studied by Meira-Freitas *et al*; (2010) [44]. There is insufficient evidence that thiamine, vitamin B12, vitamin A, or vitamin E are helpful for glaucoma, they can be used to treat severe macular degenerative diseases but they do cause some serious adverse effects. Ginkgo biloba and bilberry can be used in the treatment of glaucoma but there is less evidence in support of their role in therapy. Palmitoylethanolamide is a drug that has some of the same effects of cannabinoids. Exercise can lower the IOP whereas, squeezing and pushing of the eyes can lead to lowering of IOP. Passo et al observed nine glaucoma patients before and after three months of exercise training and 20% decrease in IOP was observed. However, once the exercise was stopped there was a reversal in three weeks. Patients with glaucoma who play brass or woodwind instruments are at high risk of glaucoma. Valsalva not only raises the IOP but also raises intra-cranial pressure. According to various reports, there is a strong relation between glaucoma and obstructive sleep apnea, but this is a controversial topic. Stein et al surveyed a database and found no difference between the incidence of glaucoma with or without sleep apnea. It was observed that the Asian are at a greater risk of angle closure than the Caucasians. It is thus unclear whether the treatment of sleep apnea would be helpful in glaucoma, and might be significant only in certain individuals. The Latino Eye Study did not show an association between smoking and glaucoma, but the confidence limits were wide and a small effect could have been present but not detected. With this evidence, preventing glaucomatous progression does not a justify telling patients to stop smoking, but should be recommended for the value to their overall health.
Forskolin is a diterpene derivative has a specific action on adenylate cyclase which increases intracellular cAMP. Alpha lipoic acid, a very powerful antioxidant, avoids nerve damage wich is caused because of oxidative stress and can be used in the treatment of glaucoma.The plants like-erycibe (Erycibe obtusifolia; dinggongteng aka baogongteng), pueraria and areca seed can be used for the treatment of glaucoma. Salvia miltiorrhiza a solution of the herb when injected intravenously, provides the improvement in the microcirculation of the retinal cells.

SURGICAL METHODS

There has been a great development in new surgical approaches which can reduce complications related to the conventional surgery. The following approaches are used in the advanced surgeries. The Trabectome is a device which removes tissue using an electro-surgical handpiece, this is used for the disruption of the tissue. Canaloplasty involves the dilation of the Schlem's canal and reduces the pressure in the eye. The Ex-Press mini-shunt generally avoids eye pressure getting too low in the immediate post-operative period. The limitations are – questionable procedures and less efficacy and development. Laser surgery is a

secondary choice of treatment of glaucoma. The primary strategy involves "burning" holes in various areas within the eyes. The advantages include noninvasive and less possibility of infection and bleeding. The IOP in combination with timolol, the two-year IOP lowering success rate is 70%, compared with the laser alone (44%) and timolol alone (30%) [45]. Trabeculectomy is can lower the IOP and it is one of the most common surgical procedure. It consists of cutting off a small portion of the trabecular meshwork in order to provide a drainage route for aqueous humor. Antiscarring agents are used to decreasing fibroproliferative response and increase success rates of the surgery. Surgical management is designated when there is inadequate lowering of IOP or there is persistent progression leading to damage of the optic cells in spite of surgical and laser treatments.

FUTURE TREATMENTS

The apt treatment for glaucoma is something which provides better efficacy, patient compliant, 100% bioavailability, sustained effect and has negligent side effects. Glaucoma drainage devices were in demand when trabeculectomy did not provide the necessary actions or there were too many side effects generated by the conventional trabeculectomy [46]. The success rates of devices range from 25- 94% [47]. Taking this into consideration, scientists have developed various devices to provide optimum health care to the patients suffering from glaucoma. The following are the list of future treatments for glaucoma.

IOP-lowering Drugs: Relaxation of the tension in the trabecular meshwork is an approach that can be used to enhance aqueous humor outflow via the physiological pathway, it is a tissue that is physiologically similar to the muscle and the myosin-actin complexes within the cells are highly dynamic, and Rho GTPase kinase (ROCK) is generally responsible for their regulation. ROCK phosphorylation generally acts in three ways to increase contractile tension- indirectly through inhibition of MLC phosphatase and activation of Lim kinases and directly, via phosphorylation of myosin light chain. ROCK inhibitors AMA0076, (Amakem Therapeutics), LM7101, a Lim kinase 2 inhibitor (Lexicon Pharmaceuticals), (AR12286 plus latanoprost) and AR12286, (Aerie Pharmaceuticals) are in clinical development. Some class of drugs affects the adenosine receptors like- adenosine R1 agonist INO-8875 (Inotek) has shown a positive response in Phase I and Phase II clinical trials for IOP reduction in patients suffering from glaucoma. By stimulating the secretion of various enzymes, the remodeling of the connective tissue occurs and finally enhances the outflow of the aqueous humor through the pathway. These drugs target the adenosine A3 receptor- ACN-1052 (Acorn Biomedical) and CF-101(Can-Fite BioPharma). These compounds are consumed by the oral route of administration, which provides less IOP fluctuation and greater duration of action. Two other additions to the development pipeline are in early-phase clinical trials are- mixed prostaglandin agonist ONO-9054 (Ono Pharma) and SYL040012 (Sylentis). SYL040012 is an RNAi-based compound aborts the pathway which is responsible for the receptor protein production.

New Delivery Systems: Amorphex Therapeutics developed a type of contact lens which has its residence on the lid and can deliver drugs in a controlled and sustained release fashion. Travoprost punctal plugs (Ocular Therapeutix) are currently in clinical trials. In a recent Phase II study, Norbert Pfeiffer observed that the plugs provided a sustained reduction in the IOP. Polymerized collagen gels (Euclid Systems) which are a type of biodegradable matrix and is suitable for depot delivery. Icon Bioscience is developing various nanoparticles which will be seen as a potential drug delivery system in the future.

IOP Monitoring Devices: Variations in the IOP has been one of the parameters to understand the progression pattern of glaucoma. Triggerfish (Sensimed AG) is an alternative technology which is a contact lens with an embedded strain gauge that records the continuous changes happening 24-hours a stretch in ocular surface tension. Implandata Ophthalmic Products uses implantable micro-sensors that communicate the data to a handheld external device. iSense (AcuMEMs), another implantable device is also in development. These two systems would require surgery for implantation in order to access the anterior chamber. These devices not only measure but also determine the fluctuations in pressure thus, having a significant impact on the treatment.

IOP-lowering Devices: Patients are generally less compliant to surgical procedures and are more comfortable to medications. One can also use an alternative therapy which not only maintains patient compliance but it is also efficient in the maintenance of therapeutic concentration in the targeted tissue. Implantation of devices are relatively low risk and are implanted during cataract. These are devices which are in the developmental stages or they are just launched in the market. The Cypass (Transcend Biomedical), is a thin polymer tube is inserted under the scleral spur into the supraciliary space which creates another outflow pathway for the aqueous drainage.

The Hydrus microstent (Ivantis) has a design of a cardiac stent and is placed in the canal of Schlemm, it maintains a canal which helps in the aqueous drainage. In a current trial, the patients experiencing the device maintained an IOP of 21 mmHg or less without medication for six months. AqueSystems developed an implantable device which forms a path for the drainage of the aqueous humor. The main property of this device is that it is hard in the dehydrated form but gets converted into a soft gel when it comes in contact with the fluid. The most advanced implant is Glaukos iStent (June 2012). It is a titanium tube which provides a direct connection between Schlemm's canal and the anterior chamber, it provides an outflow of the aqueous humor. This device showed an immense reduction in the IOP in various clinical trials. The iStent has its own set of limitations, the patient has to undergo cataract surgery, five-year monitoring of the patient is necessary.

List of marketed preparations: The following table **(table 4)** is the list of various medications that are available In the market for the treatment of glaucoma

CONCLUSION

Glaucoma is a medical emergency and if not treated properly can lead to irreversible blindness. However, with early diagnosis and treatment, one can restore their visual acuity and lead a better life. Though there is a wide variety of anti- glaucoma agents they can produce systemic and local adverse effects. Many drugs are still in the developmental stage. An ideal anti- glaucoma drug candidate should have a better IOP lowering capacity along with less number of side effects. Despite having various advancements, IOP is still sometimes uncontrollable. Various research has been conducted and advanced antiglaucoma medications along with various devices are still in the developmental or the clinical stages. Examples of various advanced drugs that are available are - the Rhokinase inhibitors, microtubule-disrupting agents, serotonergics and cannabimimetics. Research has been directed to a better pathway where the application of various molecular, cellular and polymer techniques can help induce ways that not only help in the regeneration of the retinal cells but also stop the progression of glaucoma thus, building up visual acuity.

Table 1. Factors Associated with Glaucoma

FACTOR	INFORMATION
Corneal thickness	Patients with corneal thickness lesser than 588 mm are can be diagnosed with Primary Open Angle Glaucoma (POAG).
Elevated IOP	High IOP is the most important factor for the development of glaucoma.
Sex	Females are at greater risk of chronic angle closure glaucoma and normal tension glaucoma.
Systemic hypertension	Increase in blood pressure causes increase in IOP
Race	The risk of developing glaucoma is higher in blacks than in white Americans and Indians.
Migraine	May be at higher risk for the development of NTG.
Diabetes	Micro-angiopathy is one of the factors observed in the pathogenesis of glaucoma.

Table 2. Classes of Conventional Medications Used to Lower IOP

NAME	MECHANISM OF ACTION	ADVERSE EFFECTS	EXAMPLES
Prostaglandin analogues	Increased uveoscleral outflow of aqueous humor	Darkening and lengthening of eyelashes and pigmentation of the iris.	Latanoprost
Cholinergic agonists	Increased aqueous outflow	Ocular irritation, dry eyes, myopia, ciliary spasm	Carbachol
Carbonic anhydrase inhibitors	Decreased level of aqueous humor production	Ocular irritation, dry eyes, burning sensation, nausea, diarrhea, loss of appetite, paresthesia	Acetazolamide
β-adrenergic blockers	Decreased level of aqueous humor production	Ocular irritation, dry eyes, burning sensation, bradycardia, chronic pulmonary diseases	Betaxolol
α-adrenergic agonists	Decreased level of aqueous humor production and Increased uveoscleral outflow of aqueous humor	Ocular irritation, dry eyes, burning sensation, allergies, CNS effect, respiratory effect, renal failure	Aparaclonidine

Table- 3: Percent reduction in IOP with various combinations of drugs

COMBINATION	% REDUCTION IN IOP
Latanoprost- carbonic anhydrase inhibitors	15- 24.1%
Latanoprost-pilocarpine	7- 14%
Latanoprost- dipivefrin	15-28%
latanoprost-timolol	13- 37%

Table 4: List of marketed preparations

Name	Concentration	Route of Administration	Side Effects	Mechanism of Action
Timolol	0.25 and 0.5%	eye drops	Systemic: Brochospasm, headache, dizziness, bradycardia, hypotension Ocular: Superfi cial punctate keratitis, ocular pain, corneal anesthesia, diplopia, ptosis	Decreases the Aqueous humor production
Carteolol	1%	eye drops	Systemic: Brochospasm, headache, dizziness, bradycardia, hypotension Ocular: Superfi cial punctate keratitis, ocular pain, corneal anesthesia, diplopia, ptosis	Decreases the Aqueous humor production
Betaxolol	0.25 and 0.5%	eye drops	Systemic: Brochospasm, headache, dizziness, bradycardia, hypotension Ocular: Superfi cial punctate keratitis, ocular pain, corneal anesthesia, diplopia, ptosis	Decreases the Aqueous humor production
Levobunalol	0.5% to 1%	Eye drops	Stinging, bradycardia, hypotension	Decreases the Aqueous humor production
Pilocarpine	0.5 to 8%	eye drops	Salivation, urination Ocular: Miosis, follicular conjuctivitis, induced accommodation, retinal detachment, iritis	Increases Aqueous outflow
Epinephrine	0.25-2%	eye drops	Blurred vision, conjunctival hyperemia ↑ Uveoscleral outfl ow, Headache, palpitations, high blood pressure, anxiety	Increases Aqueous outflow
Dipivefrin	0.1%	eye drops	Burning, stinging, follicular conjunctivitis, blurry vision, headache	Increases Aqueous outflow
Acetazolamide		tablets	Paresthesia of fi ngertips and toes,	Decreases the Aqueous humor

			fatigue, depression, kidney stones, (125 mg and 250 mg four times daily thrombocytopenia, agranulocystosis, aplastic anemia	production
Apraclonidine	0.5% and 1%	Eye drops	Tachyphylaxis, allergic blepharoconjuctivitis ↑ Minor increase in aqueous outfl ow Brimonidine 0.2 and 0.5% applied twice daily ↓ Aqueous production & Irritation, dry mouth, drowsiness ↑ Minor increase in aqueous outfl ow	Decreases the Aqueous humor production
Methazolamide		tablets	Paresthesia of fi ngertips and toes, fatigue, depression, kidney stones, (25 and 50 mg) 2-3 times daily thrombocytopenia, agranulocystosis, aplastic anemia	Decreases the Aqueous humor production
Dorzolamide	2%	ophthalmic solution	Corneal edema, stinging, burning and itching three times daily	Decreases the Aqueous humor production
Brinzolamide	1%	ophthalmic suspension	Blurred vision, tearing; bitter, dry eyes; headache three times daily	Decreases the Aqueous humor production
Latanoprost	0.005%		Iris pigmentation, mild conjunctival hyperemia, local irritation, cystoid macular edema, increase in the evening growth eyelashes	Increases Uveoscleral outflow
Bimatoprost	0.03%	ophthalmic solution	Mild conjunctival hyperemia, Iris pigmentation daily in the evening	Increases Uveoscleral outflow
Travaprost	0.004%	ophthalmic solution	Macular edema, cystoid macular edema	Increases Uveoscleral outflow

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