Review on Commonly used Medical Therapies for Glaucoma

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ABSTRACT

Glaucoma is a multipart disorder which leads to continuous degeneration of the optic nerve leading to partial or total blindness. Topical medications are the most common form of therapy to patients. All medication used in glaucoma acts either decreasing the production of aqueous humour and/or by enhancing its outflow, which aids in reducing intraocular pressure. Medications that cause a decline in aqueous humor secretion are beta-blockers, a2 agonists, and carbonic anhydrase inhibitors. While medications that enhances aqueous drainage include Cholinergic agonists, prostaglandin analogues and adrenergic agonists. Amongst all the drugs, latanoprost and its combinations offer the highest reduction in intra-ocular pressure, but its instability at room temperature is a major drawback to patients. All types of alternative therapy are still at an initial stage, and there are various scopes of development, and further clinical studies will provide more insight. And surgical procedures, which are mainly Argon laser trabeculoplasty and Selective laser trabeculoplasty, are currently preferred, which provides effective results for the patients, but it is not very suitable for all the patients, and there are a few postoperative complications. Thus, modern research on the reduction of dose, precise drug delivery and sustained reduction of IOP shall help in improvising the medications of glaucoma and help mankind from this serious vision-threatening disease.

INTRODUCTION

Glaucoma is a multipart disorder which leads to continuous degeneration of the optic nerve leading to partial or total blindness. There are about 67 million patients of glaucoma worldwide, out of which 14 million glaucoma patients in India alone, of whom 6.7 million will become blind in both eyes (Rathore et al., 2010). When calculated with the above figures, almost 10 in 100 people will be suffering from glaucoma, and 1 in 1000 will be blinded due to lack of proper treatment of glaucoma. And if such is the scenario, then India will be the most affected than any other countries in the world. There are no means to prevent blindness related to glaucoma as risks are higher, particularly in developing countries like India and countries from the African continent (Thylefors, 1995). So by any means, blindness related to glaucoma is going to increase in times to come. It has been reported that patients suffering from partial or complete blindness due to glaucoma show lesser mobility, and are at higher risk of falling...
and are at higher risk of vehicle collision (McGwin et al., 2005). Glaucoma being a silent progressive disease, patients usually have detection when deterioration of vision has reached to a very last point.

**CLASSIFICATION OF GLAUCOMA MEDICATIONS**

Pharmacologically both topical and oral treatment used in glaucoma act by depleting aqueous humor secretion and/or by enhancing its drainage that causes a drop in Intra-ocular pressure (IOP). The broad classification of glaucoma medication is based on a decline in aqueous humor secretion and enhanced aqueous humor drainage. Medications that cause decline aqueous humor secretion are beta-blockers like timolol maleate, a2 agonists brimonidine tartarte, and CAIs (Carbonic Anhydrase Inhibitors) like dorzolamide and brinzolamide. While medications that enhances aqueous drainage include Cholinergic agonists like pilocarpine, prostaglandins like bimatoprost and travoprost and adrenergic agonists like epinephrine. In depth description of these medications is mentioned below.

**Beta-blockers**

Beta-blockers are of the highest prescribed drugs for glaucoma. Amongst all widely used beta-blockers for glaucoma, Timolol, Levobunolol, Betaxolol, and Carteolol dominate the commercial market. All beta-blockers act by decreasing aqueous humor secretion irrespective of their pharmacological pathways to achieve that. Almost all the drugs of this category are well-tolerated by the patients. Major systemic side effects of these category of drugs include heart failure, bradycardia, and asthma. While local side effects include stinging, burning, redness of the eye, excess tearing and loss of sensitivity in the corneal region.

**Timolol**

Timolol is one of the most widely used topical drugs for glaucoma. Commercially timolol maleate is widely available in a concentration of 0.25% w/v ophthalmic solution and 0.5% w/v ophthalmic solution, while other formulations like a gel-forming solution of timolol maleate in different concentrations are not very common. And its wide spread side effects associated with the drug are keratitis, ocular discomfort, corneal anaesthesia, and visual disturbances.

**Carteolol**

Carteolol hydrochloride ophthalmic solution is available commercially in a concentration of 1 percent. Common side systemic sides effects of carteolol are reduced pulse and blood pressure. And carteolol produces a reduction of IOP in the range of 22 -25 percent. Ocular irritation in carteolol is less in comparison to that of timolol maleate.

**Levobunolol**

Levobunolol, which is commercially available in 0.5% concentration, acts similarly to that of timolol maleate by reducing aqueous humor formation but additionally, it enhances drainage of aqueous humor to a certain level. Levobunolol commences its action within one hour of instillation, and the highest reduction in intraocular pressure can be achieved within six hours of instillation. Additionally, di-hydrolevobunolol, an active Levobunolol metabolite, offers a supplementary reduction in intra-ocular pressure.

**Betaxolol**

Betaxolol is approved for commercial use as an ophthalmic suspension of 0.25 %w/v. Pharmacologically Betaxolol is a competitive antagonist of beta receptors that is responsible for aqueous humor formation. Its IOP lowering effects are similar to that of timolol maleate, and other studies have reported that betaxolol provides additive IOP lowering effects in the presence of dipiverfin (FRACO, 1989). Betaxolol has a faster onset of action in comparison to that of Levobunolol.

**SYSTEMIC CARBONIC ANHYDRASE INHIBITORS / ACETAZOLAMIDE**

Carbonic anhydrase inhibitors are sulphonamide containing drugs. These drugs act by catalysing carbonic anhydrase isoenzyme II, the enzyme responsible for conversion of CO2 and H2O to form HCO3 and hydrogen ion, a key process in the production of aqueous humor as bicarbonate formation influences fluid transport by affecting active sodium channels by regulating pH. Thus, by suppressing the formation of bicarbonate secretion/production of aqueous humor in the anterior region of the eye can be decreased. Acetazolamide is one of the only successful systemic Carbonic anhydrase inhibitors and is available commercially in two strengths of 125 mg and 250 mg. Major side effects of any systemic carbonic anhydrase inhibitor may include loss of enthusiasm, kidney stones, mental depression, and aplastic anemia.

**Topical carbonic anhydrase inhibitors (CAIs)**

Similar to systemic CAIs, topical CAIs blocks the action of carbonic anhydrase in local tissues of the anterior segment of the eye, reducing suppressing formation of bicarbonate secretion leading to reduced production of aqueous humor. Dorzo-
lamine and Brinzolamide are the only two commercially available topical CAIs. Ocular irritation, unpleasant after-taste, vascular anomalies, and keratoconjunctivitis are some of the major side effects observed in these categories of drugs.

**Dorzolamide**

Dorzolamide was the first commercially approved topical CAIs. The Daily recommended dose of dorzolamide 2% eye drops is three times a day. Unlike timolol maleate it is effective in reducing IOP at night time. Dorzolamide in the first choice of drug in patients with beta-blockers contraindications. And when additive effects are required from dorzolamide, it can be used along with beta-blockers or cholinergic agonists like pilocarpine (Talluto et al., 1997). Dorzolamide observes lesser side effects in comparison to that of acetazolamide due to its local application. However, certain side effects like corneal oedema, erosion of endothelial layer, ocular irritation and frequent allergic reaction are very common.

**Brinzolamide**

Brinzolamide was one of the first ophthalmic suspensions approved in the category of topical CAIs for the treatment of glaucoma. Brinzolamide 1%w/v ophthalmic suspension offered at 7.5 pH is almost a neutral pH drug as compared to dorzolamide, which has a slightly acidic pH of 5.5. Due to its neutral pH, it observes less ocular irritation than dorzolamide.

**PROSTAGLANDIN ANALOGUES**

Prostaglandins, when used in lower concentrations, increases the uveoscleral outflow of aqueous humor, which leads to a decrease in IOP. But on the contrary, when used in higher concentration causes increase in IOP. Travoprost, latanoprost and bimatoprost are the most commonly available prostaglandin analogues used for the treatment of glaucoma. Other uncommon drugs include tafluprost and unoprostone.

**Latanoprost**

Latanoprost has been available commercially since 1996. It is one of the most popular prostaglandins used for glaucoma. Latanoprost is an prodrug which acts as an prostanooid receptor agonist. Latanoprost is commercially available in only one strength of 0.005% w/v eye drops. Along with lower concentration, its daily recombed dose of once-daily is highly recommended for patient compliance. Like all other prostaglandins, it reduces IOP by enhancing drainage of aqueous humor from the uveoscleral region. Due to which is provides an additive effect with other categories of drugs, namely beta-blockers and CAIs. Storing temperature of 2-8 degrees Celsius stands as a major shortcoming for latanoprost (Morgan et al., 2001). Acute conjunctival hyperemia and iris pigmentation are major side effects of latanoprost, and enhancement of eye lashes in long term use of latanoprost is very common. Reduced systemic side effects are observed in latanoprost owing to its rapid elimination half-life.

**Unoprostone**

Unoprostone Isopropylate is a docosanoid, and it is structurally different from other prostaglandins as unoprostone has two extra carbon chains. It commercially available as 0.15% eye drops. But unlike lantanoprost, it is required to be instilled into the eye twice daily. Like all other prostaglandin analogues, unoprostone also reduces IOP by enhancing drainage of aqueous humor from the uveoscleral region without interfering with aqueous humor production (Gazzarro et al., 2012). Side effects like eye lash enhancement and hyper pigmentation of iris are comparatively less common in unoprostone to that of lantanoprost.

**Bimatoprost**

Bimatoprost is a prostamide analogue consisting of amide ester at the carboxy-terminal end of a carbon chain. Being prostamide analogue, it interacts with prostamide receptors in the trabecular meshwork to improve drainage of aqueous humor (Wan et al., 2007). Bimatoprost is approved for glaucoma use at a concentration of 0.03% and 0.01%. Like latanoprost its recommended dosage is one drop daily. But unlike lantanoprost, bimatoprost is stable at room temperature. Its side effects are almost similar to that of latanoprost.

**Travoprost**

Travoprost is also a prostaglandin F 2a analogue which, like latanoprost, binds at prostanooid receptor too but unlike other prostaglandins like lantanoprost, travoprost is a full agonist of the PGF2a receptor (Hellberg et al., 2001). Travoprost is approved at a concentration of 0.004% in case of glaucoma. Unlike lantanoprost and like bimatoprost, it is stable at room temperature. And its daily recommended dose is one drop once a day. Side effects related to eye lashes comparatively less than other prostaglandins, but cystoid macular oedema is one of the most severe side effects of Travoprost.

**COMBINATION THERAPY**

Prescribers opt for a combination of more than one drug when reduction is IOP cannot be achieved by individual remedy. Usually, combinations are available of drugs with a different mechanism of action.
like a beta-blocker added with topical CAIs can provide an additional reduction in IOP. While a combination of standard dosage of latanoprost and timolol maleate can impart additive effect in IOP reduction in range of 13-37%, depending upon variables of frequency and concentration. Timolol maleate is the most common choice for combination therapy. Timolol maleate is usually available in combination along with CAIs and Prostaglandins alongside alpha agonists.

Table 1 indicates the pharmacotherapy of the most common drugs used in the treatment of glaucoma.

**SURGERY AND LASER PROCEDURES**

Laser therapy is a second-line option for the treatment of glaucoma in patients not responding to drug therapy. Amongst other Argon laser trabeculoplasty (ALT) is the preferred procedure in which holes are created in blocked trabecular meshwork cells leading to increased outflow of aqueous humor from these cells. (*Schwartz and Budenz, 2004*). Neodymium-doped yttrium aluminium garnet laser can also be used in closed-angle glaucoma to make a small peripheral hole in the iris, to allow the aqueous fluid to flow easily. Selective laser trabeculoplasty (SLT) delivers energy to pigmented trabecular meshwork cells in a process called photothermolysis. The advantage of SLT is that non-pigmented trabecular meshwork (TM) cells may sustain less damage compared with ALT (*Kramer and Noecker, 2001*). Similar to that of laser trabecu- loplasty, a surgical procedure called trabeculectomy should be carried out when patients do not respond to drug therapy. After, both the type of surgery patient can completely discontinue drug therapy. But major side effects of these surgical procedures include the development of cataracts in almost 30 percent of a patient within the first five years of surgery. Other uncommon surgical procedures for glaucoma include molteno tubes, cyclocryotherapy, and cyclophotocoagulation.

**COMPLEMENTARY AND ALTERNATIVE SYSTEM OF MEDICINE**

Modern era has gained more awareness in the use of complementary medicine. But due to lack of clinical studies of herbal drugs to be used in glaucoma, its use for the disease has remained insignificant. Although initial studies on several herbal medicines has recorded promising results, but large scale study are further required to acknowledge the claims of these formulations. Herbal drugs like...
gingko biloba has various advantageous actions like enhanced ocular blood flow, antioxidant property, neuroprotective effect, inhibition of platelet activation factors strongly suggest its role in the treatment of glaucoma. Also, a randomized trial recorded an better visual fields in glaucoma volunteers after usage of Ginkgo biloba for four weeks (Quaranta et al., 2003). Another study recommended the used of Alpha-lipoic acid in glaucoma patients due to its strong antioxidant properties, which limits cell damage because of oxidative stress (Rathore et al., 2010; Filina et al., 1995). Vitamin C is expected to work on glaucoma patients due to its property of modify viscosity hyaluronic acid present in the trabecular meshwork. While Cannabinoids are believed to decrease IOP by enhancing uveoscleral outflow. While few of Chinese herbal medicine derived from Pueraria flavonoids, areca seed extract, and alkaloids from ericibe recorded results in a reduction of IOP similar to that of pilocarpine (Zhang, 1981).

DISCUSSION

Since the introduction of timolol maleate in 1979, beta-blockers have remained to be the highest prescribed and first-choice drugs for the treatment of glaucoma. With its daily recommended dose based on its concentration, timolol maleate causes up to 23% reduction in IOP (Hoyng and van Beek, 2000). But after six months of therapy, an average reduction in IOP of three-time daily use of Timolol maleate was observed to 4.9 mmHg, significantly less compared to that of 6.7 mmHg of once-daily Latanoprost (Camras, 1996). The main reason behind higher reduction in IOP could be the effectiveness of latanoprost of reduction of IOP at night time, unlike timolol maleate. While other reason could be the loss of efficacy of timolol maleate on prolonged use. Not only latanoprost but Bimatoprost too has better IOP reduction capacity than timolol maleate (Sherwood and Brandt, 2001).

Travoprost once daily recorded even better reduction IOP in between 7-8 mmHg after a similar span of treatment (Netland et al., 2001). Additionally, travoprost in combination with timolol observed further reduction of average 6mmHg to glaucoma patients (Dubiner et al., 2004). Not only timolol but latanoprost is more effective in reducing IOP than brimonidine tartrate and dorzolamide hydrochloride when compared in terms of dosage and frequency (Leelachaikul and Euswas, 2005). When compared within prostaglandins, a study reported that although the extent of IOP reduction of all the molecules are similar in terms of ocular tolerability, but latanoprost stand out to be better than the others (Parrish et al., 2003).

While a combination of latanoprost with timolol, pilocarpine, dorzolamide and dipivefrin observed an average reduction in IOP of 25, 10.5, 19.55 and 21.5, respectively (Higginbotham et al., 2002), when comparing reduction of IOP based on the daily recommended dose of formulation, it was observed that Betaxolol administered twice daily produces a reduction in IOP similar to that of dorzolamide three times daily as per their recommended daily doses. While Unoprsotone twice daily had a reduction of IOP similar to that of betaxolol twice daily but less than that of twice-daily of timolol and once-daily latanoprost (Nordmann et al., 2002).

Comparing single-drug therapy to combination therapy, it was observed that travoprost (0.004%) in its standard dose and frequency of once-daily records improved IOP reduction than standards combination of Dorzolamide (2%) and timolol (0.5%) (Suzuki et al., 2006). But combination drugs like Dorzolamide (2%) and timolol (0.5%) finds its place when a patient is not responsive to beta-blockers monotherapy (Frampton and Perry, 2006). The difference in efficacy has been observed when different molecules from the same categories are used as combination therapy, like timolol in combination with unoprostone has a lesser reduction in IOP in comparison to Betaxolol with unoprostone (Ohtake et al., 2004), in both combinations of unoprostone with beta-blockers systemic side effects are not observed.

CONCLUSION

A comprehensive study on commonly used glaucoma therapy determined that all types of treatments of the alternative therapy are still at an initial stage, and there are various scopes of development, so further clinical studies to extend its usage as a primary choice of therapy such as Gingko biloba, Alpha lipolic acid, Vitamin C, Cannabinoids and other alkaloid seems to be promising sources that may produce effective results. Surgical procedures like argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT) provides effective results for the patients, but it is not very suitable for all the patients due to few post-operative complications. Acetazolamide is the only successful systemic medication. While Timolol Maleate and its combinations are the most widely used topical medications. Latanoprost and its combination provides the highest reduction in intra-ocular pressure, but due to its thermal instability, bimatoprost and Travoprost are being studied as alternatives to latanoprost. Hence, clinical study on alternative therapies, modern sur-
gical procedures with reduced post-operative complication and novel drugs with thermal stability and efficacy shall help the mankind from this serious vision-threatening disease of glaucoma.

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IOP - Intra-ocular pressure, CAIs – Carbonic anhydrase inhibitors, ALT- Argon laser trabeculoplasty, SLT- selective laser trabeculoplasty.

Conflict of Interest

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