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Role of Prostaglandin Analogue in Glaucoma and its Side Effects

Shrutika Tathod, Shailesh Nagpure*

Department of pharmacology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Science, Sawangi, Wardha

ABSTRACT

Glaucoma is disorder in which degeneration of gangliocytes in retina takes place. Intraocular pressure increases in glaucoma. So, only therapeutic approach for consideration of this disorder is to lower the pressure inside which get increased. Prostaglandin analogue causes reduce in intra ocular pressure. Treatment also includes laser therapy and incisional surgery. Laser surgery to create small openings in the trabecular meshwork of eye from which aqueous humor can drain to reduce intraocular pressure which is called as laser trabeculoplasty and selective laser treatment of same, both, increases outflow of aqueous humor through trabecular meshwork. Surgical procedures include trabeculoctomy, implantation of drainage tube or ciliary body cyclodestruction. Still the treatment has to start with intra ocular pressure reduction. Major drug classes which have therapeutic importance for Glaucoma includes cholinergic, drugs that increases response fron the adrenergic receptors, carbonic anhydrase inhibitors, prostaglandin analogues (PGAs). Prostaglandin analogue can be used in combination with other ant glaucoma drugs. PGAs include mainly latanoprost, Bimatoprost, traboprost.

Sustained release intra ocular drugs also have long term intra ocular pressure lowering in glaucoma. Latanoprost and Traboprost both significantly reduce twenty four hours intra ocular pressure. Traboprost have greater hypotensive efficacy. But side effects are also there. Latanoprost causes mild Conjunctival hyperaemia. Irides get damaged during Latanoprost treatment. But Latanoprost do not cause uveitis or cystoid macular oedema, systemic adverse effects. Also it do not have any effect on routine blood analysis. Travoprost causes little diurnal fluctuations but causes decrease intra ocular pressure. Bimatoprost appears more effective than Travoprost. Patient show better tolerance for Latanoprost. Travoprost is better for exfoliative glaucoma.

Ketorolac increases the effect of prostaglandin analogue that is Latanoprost, Travoprost, and Bimatoprost. First commercially available prostaglandin analogue is isopropyl unoprostone. It does not cause any adverse effects usually. Prostaglandin can cause other side effects like pigment deposition on periocular region , damage to blood aqueous barrier and cystoid macular oedema i.e. disorder which affects the central retina or macula, swap in eywlashes ,iris pigmentation, etc.

Key words: Glaucoma, Intra ocular pressure, Prostaglandin analogue, Periocular pigmentation

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Corresponding author: Shailesh Nagpure

e-mail✉: Shrutikatathod2@gmail.com

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INTRODUCTION

Glaucoma is disorder in which degeneration of gangliocytes in retina takes place. Intraocular pressure increases in glaucoma. So, only therapeutic approach for consideration of this disorder is to lower the pressure inside which get increased. Prostaglandin analogue causes reduce in intra ocular pressure. Still the treatment has to start with intra ocular pressure reduction. Major drug classes which have therapeutic importance for Glaucoma includes cholinergic, drugs that increases response from the adrenergic receptors, carbonic anhydrase inhibitors, prostaglandin analogues (PGAs). Prostaglandin analogue can be used in combination with other antiglaucoma drugs. PGAs include mainly latanoprost, Bimatoprost, traboprost. Glaucoma is a condition in which gangliocytes in retina which is deteriorating creates notable sight problems. Glaucoma is considered as a formation of situations correlated with fluctuating increase in intraocular pressure (IOP) that causes retinal ganglion cells (RGC) loss because of mechanical stress, vascular malformation, and

other action, such as related to immunity. The clinical recognition of glaucoma needs estimation of the ocular anterior segment with a technique in which high intensity light source can be focused to shine a thin sheet of light into the eye which is in conjunction with bio microscope (slit lamp bio microscopy), which permit the clinician to find out or identify the signs of conditions that could lead to increase in intraocular pressure [1]. To reduce the intraocular pressure (IOP) is now the only medicinal perspective to treat the glaucoma. The development of IOP- reducing eye drops which are with good tolerance and are easy to administer are also essential for the healing of glaucoma as well conformance is important for therapy [2]. New treatments must be shielded, with more effectiveness, worthier than already existing treatments, bearable and with effective cost [3].

Prostaglandin analogues

Prostaglandin analogue deducts IOP be valued at development of adverse effects of prostaglandin related periorbitopathy so they can be called as double-edged sword in the administration of increased intraocular pressure [4]. They are divided into PG analogues and prostamides as they have difference in their molecular structure. Prostaglandin analogues include unoprostone, latanoprost and travoprost and prostamides include bimatoprost [5]. To study the hydrodynamic pathways taking place in glaucoma and positive changes occur during treatment, conjunctiva is considered as important marked tissue [6].

History of glaucoma

From calarbean, the physostigmine was isolated in 1862. From that point, the main history related to glaucoma treatment gets its onset. Epinephrine can also reduce intra ocular pressure so can be used to treat glaucoma; it came with that of physostigmine but some forty years later. Drug discovery and development take up acceleration during 20th century when introduction of beta blockers, PGAs, carbonic anhydrase inhibitors takes place [7].

Causes, types and treatment

Loss of vision all over the world occurs mainly because of glaucoma. Primary open angle glaucoma which is most usual and mostly occurring foam of glaucoma shows elevation in intra ocular pressure(IOP). In glaucoma, specially defect occur in peripheral visual field because of loss of retinal ganglion cell and optic nerve head excavation. Though there is no history of increase in intra ocular pressure, those patients with normal tension glaucoma also shows typical visual field and changes in optic nerve head. Pigment dispersion syndrome is considered as secondary cause for glaucoma. Also the ocular trauma may lead to glaucoma. Intra ocular pressure reduction can be done by using argon laser trabeculoplasty. Selective laser trabeculoplasty is also effective. Outflow of aquoushumor through trabecular meshwork is main outcome happening in both techniques. Glaucoma can be treated by using surgical techniques also. Trabeculoctomy or implantation of glaucoma drainage tube can be done. All those technique are proved to be effective to reduce Intra ocular pressure, still in treatment of glaucoma, first preference is given to medications and drugs. Drugs show their action by one of the two ways. They may increase the outflow of aqueous humor. Five main classes' ofdrugs are introduced to treat glaucoma:

- ✓ Cholinergic (acetylcholine receptor agonists)
- ✓ Adrenoceptor agonists
- ✓ Carbonic anhydrase inhibitors (CAIs)
- ✓ β-adrenoceptor antagonists
- ✓ Prostaglandin analogues (PGAs).

Therapy mainly starts with of intra ocular pressure. Number of clinicians prefers beta adrenoceptor antagonists. But as first line therapy of glaucoma, prostaglandin analogs are considered as important [8]. For avoidable blindness, glaucoma is considered as second leading cause which affects approximately sixty seven million people worldwide. Elevation in intra ocular pressure is main risk factor which is manly required to treat glaucoma [9]. Loss of vision, cupping of optic disk occur because of increase in severity of disease. Latanoprost, Bimatoprost, Travoprost lead to effective lowering in intra ocular pressure. In patients with primary open angle glaucoma, ocular hypertension, prostaglandin analogues seem tube well tolerated so as to reduce intra ocular pressure. Prostaglandin analogues can be used as better option for beta adrenergic antagonists if there are any contraindications or other antiglaucoma drugs.

On the basis of data we have earlier bimatoprost, latanoprost, and travoprost have same efficacy as thatof timolol butunoprostone is slightly less effective. Prostaglandin can be combine with other antiglaucoma drugs. Education must be given to patients regarding adverse events occurring due to prostaglandin analogs, more specifically for variation in pigmentation of irrigant eyelashes [10]. Prostaglandin analogues are latest contribution added to therapeutic treatment of glaucoma. They are new class of ocular drugs which reduce tension. Its main target is uveoscleral outflow of ocular aqueous humor. Latanoprost and unoprostone are commercially available at present [11]. As first line treatment of glaucoma, prostaglandin or prostamides are mainly considered. They have intraocular pressure lowering efficacy that's why they are chosen, also they don't have that much related adverse effect, for only once daily dosing are sufficient for them to act and also they have good tolerability. The latanoprost is an ester prodrug of PGF2α in management of glaucoma. Latanoprost has appreciable efficacy and tolerance so it is given in number of prostaglandin prescriptions. It was first of all presently existing topical PGF2α analogues which are introduced for glaucoma treatment. Whenever any trauma or injury occurs to eye, some prostaglandins are released naturally by iris and ciliary

body. Impactful decrease in intraocular pressure occurs due to PGF2α.This tension lowering capacities mainly because of increase in uveoscleral outflow. According to studies done in animals, trabecular outflow and aqueous flow also contribute majorly. Regulation of matrix metalloproteinase is one of the mechanisms for this increase in outflow. Remodeling of extracellular matrix also contribute to it. It causes changes in permeability of tissues associated with outflow pathways which resulting fluctuation in outflow resistance or outflow rates. Esterification of carboxylic acid of PGF2α is the first step to increase corneal penetration and deduction of side effects. PGF2α has excellent pharmacological effect but it leads to foreign body sensation which is unacceptable and Conjuctival hyperemia. By doing moderation of omega chain of PGF, selectively for PGF receptor can be improved along with great improvement in tolerability. And this molecule is Latanoprost. According to study did on mice, for lowering intra ocular pressure intact PGF and PGE2 receptors are required. Latanoprost is more lipophilic as compared to its parent molecule. Its absorption is better through cornea. It occurs hydrolysis to Latanoprostacid there. Latanoprost attain highest of its concentration in aqueous humor after one to two hours of topical dosing. This conc.is found to be 15-30 ng/ml. Latanoprost undergo beta oxidation in liver. Its metabolism leads to 1, 2-dinor and 1,2,3,4-tetranor latanoprost. The excretion of dose mainly occurs via urine i.e.88% while remaining gets excreted via feces [12].

Bimatoprost is associated with Conjuctival hyperaemia while latanoprost is associated with headache. According to a study at every notable point through the entire duration of study, latanoprost was not able to provide that much lower mean pressure as that of bimatoprost. More patients reached low pressures with bimatoprost were effective in lowering intra ocular pressure in more patients therefore it was considered as more effective [13]. Use of Bimatoprost and Latanoprost shows little increase in central corneal thickness. There is no effect of travoprost on central cornel thickness. But there may be interference in intraocular pressure measurement because of central corneal thickness changes. Intra ocular pressure decreasing action of Latanoprost, Travoprost and Bimatoprost get increase significantly because of ketorolac. Bimatoprost is considered as having better efficacy to reduce ocular tension. If direct comparison taken into consideration, Bimatoprost is better impactful than (PG) FP receptor agonist prodrug and beta adrenoceptor antagonist. (PG)FP receptor agonist prodrug is latanoprost and travoprost. Beta adrenoceptor antagonist is timolol. These drugs in alone or in combination with carbonic anhydrase inhibitors i.e. Dorzolamide. Bimatoprost also can be given to patients who are inflexible for Latanoprost [14].

Sustained release intraocular drug delivery systems are also available. They reduce intraocular pressure for longer duration. There is no need of topical administration. In elderly patient having glaucoma ,who are unable to take medication by their own, who are with declining strength, don't have stability ,may have tremors, unable to open the bottle of medications; sustained released drug delivery system are effective. This sustained release implant is effective for slow release of drug with time. Bimatoprost when applied topically is more effective. The patient who are not able to use glaucoma drugs by their own, sustained release implant are effective. It also helps in reducing intraocular pressure. The implant is placed in eye [15].

Outflow of aqueous humor takes place when free acid form of travoprost interact with endogenous FP prostanoid receptor which results in lowering of intraocular pressure. Travoprost is completely agonist at prostaglandin receptor; it makes it different from other prostaglandin analogues which remarketed. It has very less or otherwise no affinity for other prostanoid or non prostanoid receptor present in eye. It is highly selective. In large number of patients, Travoprost causes very less diurnal variation but the effective lowering of intraocular pressure [16]. 0.03% bimatoprost shows more efficacy with long time use i.e. for 3 and 6 month after treatment for intraocular pressure lowering as compared to 0.005% latanoprost, and is more effective compared to 0.004% travoprost after being used for a certain period of time i.e. for 3 months after treatment. 0.005% latanoprost is better tolerated by patients having primary open angle glaucoma [17]. Both Latanoprost and Travoprost markedly decrease intraocular pressure still Travoprost shows more effective intra ocular pressure action especially in late afternoon [18].

Use of Bimatoprost and Latanoprost shows little increase in central corneal thickness. There is no effect of travoprost on central cornel thickness. But there may be interference in intraocular pressure measurement because of central corneal thickness changes [19]. Intra ocular pressure decreasing action of Latanoprost, Travoprost and Bimatoprost get increase significantly because of ketorolac [20].

Latanoprost and unoprostone i.e. isopropyl unoprostone is the first commercially available prostaglandin analogues to be used for treating the glaucoma. Both of them increases uveoscleral outflow there by decrease intra ocular pressure. Latanoprost lead to significant decrease in intra ocular pressure as that of timolol when given one time in a day that too in evening. But it produces little Conjunctival hyperaemia while timolol not. Excessive growth and hyperpigmentation of eyelashes also observed. It does not interfere with blood analysis or don't cause adverse effect like cystoid macular oedema. Unoprostone shows similar adverse effect. Unoprostone have additional corneal and epithelial problems. Otherwise Unoprostone does not show adverse effect generally [21].

Latanoprost may be associated with anterior uveitis. Prostaglandin analogue are generally not given to patients who had uveitis or any ocular surgery earlier [22]. In patients having glaucoma and ocular hypertension, Bimatoprost, Latanoprost and Unoprostone are

successfully used to decrease the into ocular pressure. But side effects because of them are frequent. They include both reversible and irreversible side effects. Few local side effects are also there. But only because of side effects, stoppage of therapy occur very rarely [23].

According to one of the study 272 patients were there in study; it was found that discontinuation of the treatment occurred because of some non-medical reason, systemic medical problems, increase pigmentation of iris, inappropriate intraocular pressure control. Latanoprost is proved to be effective in treatment of chronic glaucoma too [24]. Therapeutic use of latanoprost in pediatric glaucoma, Latanoprost showed observable, marked positive effect in patients with juvenile onset open angle glaucoma. It was also effective in children with bit older age but was disappointing results in most children patients. It showed very little and milder adverse effects in pediatric age group [25]. Prostaglandin F2α analogue shows complications like deepening of upper eyelid sulcus. But the patients having this side effects which is occurred because of Bimatoprost or Travoprost, can show good tolerance to Latanoprost treatment as such side effects are negligibly shown by Latanoprost [26].

Preservative free PGAs Therapy and its effectiveness

Prostaglandin F2α analogue shows complications like deepening of upper eyelid sulcus. But the patients having this side effects which is occurred because of Bimatoprost or Travoprost, can show good tolerance to Latanoprost treatment as such side effects are negligibly shown by Latanoprost. Bimatoprost is considered as having better efficacy to reduce ocular tension. If direct comparison taken into consideration ,Bimatoprost is better impactful than (PG)FP receptor agonist prodrug and beta adrenoceptor antagonist. (PG)FP receptor agonist prodrug are latanoprost and travoprost. Beta adrenoceptor antagonist are timolol. These drugs in alone or in combination with carbonic anhydrase inhibitors i.e. Dorzolamide. Bimatoprost also can be given to patients which are inflexible for Latanoprost. Preservatives free prostaglandin analogue were also effective for treatment of glaucoma. Shifting of preservative added prostaglandin analogue therapy to preservative free Prostaglandin analogue therapy shows same degree of effectiveness [27]. One of the study showed repeated occurrence of herpetic keratitis because of travoprost. More studies show that this disease is bcoz of two variable prostaglandin analogues. This is associated with addition of preservatives [28]. Tafluprost is first preservative free prostaglandin. It is effective as like other agents. It effectively treats raised intra ocular pressure inturn treats glaucoma [29]. Switching if preserved PGAs therapy to monotherapy by using preservative free tafluprost; effective control of Intra ocular pressure and other related side effects and signs were observed [30]. BAK i.e. Benzalkonium chloride, is a preservative used commonly. It causes disruption of tear film and may also lead to inflammation of conjunctiva. Use of non BAK preserved PGA cause marked up gradation of Tear Break up Time [31].

These preservatives are required for inhibition of microorganisms growing especially in eye drop bottles. It's cationic surfactant. It get attached to microorganisms more specifically to cell membrane, which increases its permeability resulting in lysis of cell. Benzalkonium chloride affects surface tension because it has detergent like properties on tear film so it is somewhat toxic. It causes programmed cell death of goblet cells [32].

Aggregation of ocular surface disease (OSD) causes because of Benzalkonium chloride. It is difficult to manage such patients as they have glaucoma too. To eliminate such negative effect of such preservatives, preservative free prostaglandin and timolol or prostaglandin in fixed combination is better options [33-42].

BAK, sodium perbonate, stabilized oxychloro complex, chlorobutanol are the preservatives which are most commonly used for preparations used in ophthalmology. Stabilized oxychloro complex found to be least damaging among all preservative. So, the preservative like stabilized oxychloro complex having low risk should preferred [34]. Cytotoxicity induced by BAC depends on dose but the preservative free PGAs found to be more effective than BAC added medications [35]. Use of preservative free prostaglandin analogue showed very less side effects. It increases tolerability and compliance of patients thereby reducing aggravation of glaucoma [36]. On the basis of data we have earlier bimatoprost, latanoprost, and Travoprost have same efficacy as that of timolol butunoprostone is slightly less effective. Prostaglandin can be combine with other antiglaucoma drugs. Education must be given to patients regarding adverse events occurring due to prostaglandin analogs, more specifically for variation in pigmentation of iris and eye lashes. Monotherapy can be given for longer duration if Benzalkonium chloride free prostaglandin analogue are used. All the data studied earlier or the clinical trials performed showed that preservative free prostaglandin analogue is effective over all drugs which includes preservative in them. Glaucoma has to major cause of blindness all over the world which is affecting adults as well as paediatric age group too. Prostaglandin analogue provide satisfying therapeutic approach towards glaucoma [37].

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