

lop spike control after intravitreal anti-vegf



**ASSIGN
BUSTER**

In ophthalmology many ophthalmic procedures are there in which there is a spike of intraocular pressure after the procedures. Cataract surgery, argon laser trabulectomy (ALT), yag laser capsulotomy, yag laser iridotomy, trabulectomy, pars plana vitrectomy are few to be named. The new anti VEGF therapy is an addition to the prior list.

Many IOP lowering drugs have been used in different procedures to stop these spikes. For ALT 1% apraclonidine, an alpha agonist has been found to be the most effective against the IOP spikes, but 0.5% has also been found to be equally effective. Brimonidine an alpha 2 adrenergic agonist has also been shown to be effective and safe choice.

For cataract surgery different drugs have been used to treat the postoperative increase in IOP. These include carbonic anhydrase inhibitors, prostaglandin analogs like latanoprost, alpha agonists like apraclonidine and brimonidine, beta-blockers and miotics (intracameral carbachol and acetylcholine).

Similarly intravitreal injection of triamcinolone has been complicated with a rise of IOP and have been controlled effectively by beta blockers, but some may need aggressive treatment.

Different researchers have worked on the control of acute spikes after the intravitreal injection of anti-VEGF, showing varied results. Some have advocated the use of IOP lowering medicine while others negating the need all together.

Lim Young et al showed that the prophylactic use of fixed dorzolamide/timolol combination eye drops before the intravitreal anti-VEGF

injection was a safe method of preventing IOP spikes occurring immediately after the intravitreal injection of anti-VEGF. He showed that the mean IOP at 5 minutes and 30 minutes postoperative was 14.12 ± 4.18 mm Hg and 10.87 ± 1.58 mm Hg in group 1 using IOP lowering medication while it was 28.21 ± 3.16 mm Hg and 17.48 ± 2.34 mm Hg in control group 2, respectively. 9 He showed that there was a significant lowering of mean IOP at each reading at 5 minutes of interval.

Frenkel et al showed the use of IOP-lowering medication prior to injection of pegaptanib, ranibizumab, or bevacizumab had little effect on the IOP spike. The failure of lowering the IOP spike was implicated to be due to the inability of these medications to counteract the volume-related mechanism of the IOP spikes after anti-VEGF injections. However, it was stated that there might be benefit to lower the IOP before intravitreal injection. In their study 2 cases of sudden loss of vision were reported due to the high IOP spike which prompted them to do anterior chamber paracentesis. 8 It was also stated that the prophylactic use of medication in patients with advanced glaucoma receiving pegaptanib intravitreal injection or patients receiving 0.1 ml of bevacizumab could be considered because their study showed that it lowered IOP at the 3- to 10-minute interval in these patients.

In another study done in 2013 the IOP lowering effect of Dorzolamide/Timolol and Brinzolamide/Timolol were compared with a control group. They measured the IOP after every 5 minutes for the first half hour and the next day and week after that. For all the 3 groups, the changes relative to the baseline at 5 and 30 minutes after intravitreal injection was found to be significant. Also when the groups were broken down as to whether receiving

<https://assignbuster.com/iop-spike-control-after-intravitreal-anti-vegf/>

bevacizumab or ranibizumab, again the mean decrease of IOP compared to the control group was found significant.

El Chehab et al have also found that the prophylactic use of fixed combination of timolol with brimonidine or dorzolamide and of 1% apraclonidine could not only reduce the IOP spikes but also their duration; and both the combination and 1% apraclonidine had equal effect. However the use of oral acetazolamide 20 minutes prior to the intravitreal injection was not proven to be effective.

Evaluating the efficacy of timolol 0.5% and brimonidine 0.2% eye drops as a fixed combination in preventing IOP spikes Theoulakis et al found that twice a day instillation on the day before and before the time of injection in eyes which were scheduled for intravitreal ranibizumab was a safe and also effective in controlling the IOP spikes.

IOP LOWERING MEDICATIONS

Most of the IOP lowering medicines are administered topically. They are absorbed through the cornea and conjunctiva; mainly acting locally on the eye. Many anti glaucoma medicines have been used. The main groups of drugs are as following:

BETA- ADRENERGICANTAGONISTS

They are the most prescribed drugs of IOP control. There are a total of five topical beta-adrenergic antagonists which are currently FDA approved for managing high intra ocular pressure. They are timolol betaxolol, carteolol,

metipranolol, levobunolol. Betaxolol is selective beta1 selective antagonist, and is safe to use this drug in patients with pulmonary and cardiac problems.

The mechanism of action is to reduce IOP by decreasing the production of aqueous by inhibiting the production of cyclic adenosine monophosphate (cAMP) in ciliary epithelium. The IOP reduction is upto 20 to 35%. The effects of beta blockers occur within an hour after its instillation. Timolol is available in the market in concentrations of 0.1%, 0.25% and 0.5%. The recommended dosage is 1 drop two times a day. Burning, allergy and corneal epithelial erosions are the main ocular side effects. It can be absorbed systemically and can cause systemic side effects like bronchospasm, bradycardia, hypotension, respiratory failure.

Timolol maleate has a molecular weight of 432.50. It is an odorless, white, crystalline powder that is soluble in methanol, water and alcohol.

It is compounded as an isotonic, sterile, buffered solution available in two strengths: 0.25% Timolol maleate eye drops contains 2.5 mg of timolol (about 3.4 mg of timolol maleate). It has a pH of approximately 7.0, and an osmolarity of 274-328 milliosmole. And each ml of 0.5% Timolol Maleate eye drops contains 5 mg of timolol (about 6.8 mg of timolol maleate). The inactive ingredients are usually monobasic and dibasic sodium phosphate and sodium hydroxide to adjust pH. Preservative used is Benzalkonium chloride 0.01%.

PARA SYMPATHOMIMETIC AGENTS

They act by stimulating sphincter pupillae and ciliary body by acting on the muscarinic receptors. They cause the contraction of the ciliary muscles which thus increases the aqueous outflow through the trabecular meshwork. Pilocarpine is the commercially available drug in this group and is compounded in concentration of 1%, 2%, 3%, and 4% and the recommended dosage is 1 drop 4 times per day.

Ocular side effects are miosis, induced myopia with brow ache, retinal detachment, and cataract. Systemic side effects after its absorption can be of diarrhea, vomiting, abdominal cramps and bronchial spasm.

CARBONIC ANHYDRASE INHIBITORS (CAIs)

The enzyme required for aqueous formation is carbonic anhydrase. The CAIs cause inhibition of this enzyme and thus cause a decrease in the aqueous humor secretion by the ciliary epithelium. Carbonic anhydrase is required for catalyzing the reaction of CO_2 to H_2CO_3 which further splits into HCO_3^- and H^+ . The bicarbonate ions are pumped along with sodium ions into the posterior chamber along with diffusion of water for the formation of aqueous humor.

Carbonic anhydrase is present in ciliary body in excess. 99.9% of the enzyme must be inhibited before a significant decrease in IOP can occur. Dorzolamide and brinzolamide are the commercially available eye drops in market. They have a good corneal penetration, and are also water soluble. These agents are able to reduce IOP upto 14-17%. Adverse effects of topical CAIs are burning and stinging of eyes on instillation, conjunctivitis, blephritis, corneal allergy, corneal punctate keratitis and can also cause bitter taste.

<https://assignbuster.com/iop-spike-control-after-intravitreal-anti-vegf/>

The systemic used CAIs are methazolamide and acetazolamide. They also cause inhibition of carbonic anhydrase in ciliary epithelium thus reducing the production of aqueous humor. As it is taken orally systemic side effects of CAIs include metabolic acidosis, leading to alkaline diuresis which result in hypokalemia. So potassium levels should be regularly checked in patients using CAIs on long term basis and oral potassium supplement should be recommended to all these patients. Other side effects include renal stones formation and central nervous system side effects like numbness and tingling of hands and feet, depression, anorexia, and nausea.

Dorzolamide hydrochloride has a molecular weight of 360.91. It is a white to off-white in colour, in a crystalline powder form, which is also soluble in water, methanol and ethanol.

ADRENERGIC AGONISTS

Adrenergic agonists act by increasing the uveoscleral and trabecular meshwork outflow thus causing decrease in IOP. Epinephrine has a mixed action of being an alpha and a beta agonist. Its effect usually begins at 1 hour and reaches a maximum at 2-6 hours. Topical epinephrine drops usage has been stopped due to frequent systemic side effects of headache, palpitation and cardiac arrhythmias. The main ocular side effect is cystoid macular edema and black pigmentation of conjunctiva.

Commercially available topical form is dipivefrin hydrochloride 0.1% eye drops, which is a prodrug of epinephrine. It is converted by the enzyme esterase into epinephrine in the cornea. Because of its high lipid solubility

and corneal penetration a low dose is required as compared to epinephrine and thus has less side effects.

The selective alpha 2 agonist apraclonidine and brimonidine are indirect acting adrenergic agonist which act by decreasing aqueous production and also the episcleral venous pressure and thus improving the trabecular outflow. Apraclonidine is associated with tachyphylaxis while brimonidine has less of this problem. Brimonidine tartrate is available commercially in 0.25 and 0.15% eye drops. Its reduces IOP by 26% at 2 hour of interval.

PROSTAGLANDIN ANALOGUES

Prostaglandin analogues are relatively a new class of IOP lowering drugs. Four prostaglandin analogues have been approved by the FDA for clinical use. Latanoprost was the pioneer drug to be developed and used in this group. Others are travoprost, bimatoprost, and unoprostone.

Latanoprost is a pro drug which penetrates the cornea and then is turned into active form. It enhances the uveoscleral outflow and thus lowers the IOP upto 25-35%. The dosage is one drop per day which makes the compliance of the patient better.

The main ocular side effect is darkening of the iris and the periocular skin, by increase in the number of melanosomes in the melanocytes. Other side effects include conjunctival hyperemia, hypertrichosis, uveitis and cystoid macular edema. Systemic side effects are flu like symptoms, skin rash and uterine bleeding.

OSMOTIC AGENTS

<https://assignbuster.com/iop-spike-control-after-intravitreal-anti-vegf/>

Osmotic agents act by decreasing the vitreous volume by removing the liquid out of the eye into the circulation. The osmotic agents can be given orally or intravenously. Oral agent is glycerin while urea and mannitol are given intravenously.

The osmotic activity is dependent upon the number of particles in the solution which cannot cross over and maintains the osmotic gradient between the compartments.

Mannitol is given intravenously because it cannot be absorbed from the gastro-intestinal tract. A rebound increase in IOP and local tissue necrosis limit the use of urea.

Glycerin is most commonly used oral osmotic agent which is given along with cracked ice to dilute its nauseating feeling. In patients with diabetes a non-metabolized sugar isosorbide can be used instead.

Several fixed combinations have been developed which are available in markets used for IOP-lowering. Most of these fixed combinations contain timolol (dosed once or twice daily) combined with either adrenergic agonists, prostaglandin analogs, and CAIs.

COMBINATION

Fixed combination timolol maleate 0.5% with dorzolamide hydrochloride 2% was first introduced in market in 1998. Each milliliter of drug consisting of 6.83 mg timolol maleate and 22.26 mg dorzolamide hydrochloride.

Timolol inhibits aqueous humor production by down-regulating adenylate cyclase by inhibiting β 2-adrenergic receptor sites on the ciliary process .

While dorzolamide acts as a selective inhibitor of Carbonic anhydrase II enzyme, present on the ciliary process. The local bicarbonate production is slowed down, which as a result decreases sodium and fluid transport and, finally, decreases the aqueous humor production thus lowering the IOP.

Because the mechanisms of action of both the drugs differ, they provide an additive effect when used together.

Fixed combinations of drugs have been found to improve the compliance of the patient by reducing the number of eye drops used daily. Moreover the IOP-lowering effect of fixed combination timolol and dorzolamide was found to be greater than that of either drug instilled as monotherapy. In addition the load of preservative is also reduced along with any wash out of drug when the drugs in monotherapy are instilled one after the other.