EFFECT OF SINGLE DOSE OF INTRAVITREAL RANIBIZUMAB INJECTION FOLLOWED BY TRABECULECTOMY WITH MITOMYCIN-C IN CASES OF NEOVASCULAR GLAUCOMA WITH HAZY MEDIA OBSCURING PRP IN A PERIPHERAL MEDICAL COLLEGE IN WEST BENGAL

Kaushik Sadhukhan¹, Tamal Roy², Subhrajyoti Naskar³, Dhritashree Mandal⁴

¹Assistant Professor, Department of Ophthalmology, Malda Medical College, Malda, West Bengal, India.

²Assistant Professor, Department of Ophthalmology, Malda Medical College, Malda, West Bengal, India.

³Assistant Professor, Department of Community Medicine, Malda Medical College, Malda, West Bengal, India.

⁴Clinical Tutor, Department of Plastic Surgery, NRS Medical College, Kolkata, West Bengal, India.

ABSTRACT

BACKGROUND

We wanted to study the effect of single dose of intravitreal Ranibizumab injection under topical anaesthesia followed by trabeculectomy with Mitomycin-C (MMC) under local anaesthesia in neovascular glaucoma (NVG) cases with hazy media which obscures panretinal photocoagulation (PRP).

METHODS

23 patients with neovascular glaucoma with hazy media of various aetiology were included in this study. After proper history taking and clinical examination, patients received single dose of intravitreal Ranibizumab (0.3 mg) injection under topical anaesthesia followed by trabeculectomy with Mitomycin-C under local anaesthesia 1 week later. Then we assessed best corrected visual acuity (BCVA), anterior chamber neovascularisation, intraocular pressure (IOP) measurement on 1st post-operative day, after 1 week, 1 month, 3 months, 6 months postoperatively. Hospital based experimental, clinical research (retrospective interventional) was used to assess the improvement of BCVA and IOP and its design pattern was concurrently studied (uncontrolled clinical trial) with before and after comparison without any control group.

RESULTS

It was clearly evident from statistical data which we derived that open angle glaucoma cases respond more profoundly to above therapy compared to angle closure cases as far as intraocular pressure reduction and improvement in best corrected visual acuity are concerned.

CONCLUSIONS

Neovascular glaucoma (NVG) with mild hazy media can be managed initially by intravitreal Ranibizumab injection followed by trabeculectomy with Mitomycin-C (MMC) although the long-term result remains uncertain.

KEY WORDS

MMC-Mitomycin, NVG-Neovascular Glaucoma, BCVA- Best Corrected Visual Acuity, IOP-Intraocular Pressure, PRP-Panretinal Photocoagulation

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BACKGROUND

Neovascular glaucoma (NVG), an intractable disease of eyeball, mainly characterized by iris and angle neovascularisation¹ can culminate in permanent blindness. The pathogenesis of NVG includes angiogenesis and vascular leakage in which vascular endothelial growth factor- A (VEGF-A) acts as a major mediator.^{2,3,4} And it results from imbalance between proangiogenic factors (VEGF) and angiogenic inhibitors (Pigment epithelial derived growth factor).⁵ VEGF is a dimeric 36-46 kd glycosylated protein usually released from ganglion cells, muller cells, astrocytes.

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Corresponding Author:

Tamal Roy,

#102/2, Sreerampore Road,

North Garia,

Kolkata-700084,

West Bengal, India.

E-mail: tamal_oph@yahoo.com

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Human isoforms are VEGF - 121, 145, 165, 189, 206 of which 165 is the predominant fraction. It has got equal diffusion and heparin binding capacity. The main stimulus for VEGF release is hypoxia. It causes basement membrane degradation of endothelial cells and injury to pericytes thus leading to increased vascular permeability. Glaucoma occurs because of neo-vessels obstructing aqueous outflow secondary to posterior segment ischaemia.⁶ Fibrovascular membrane which develops on anterior surface of iris and anterior chamber angle⁷ initially causes open angle glaucoma and later contracts to produce secondary synechiae leading to angle closure glaucoma and IOP rise.⁶

The most common causes of NVG include central retinal vein occlusion, proliferative diabetic retinopathy, ocular ischaemic syndrome and central retinal artery occlusion.

To deal with the ocular neovascular disorders, various VEGF-A inhibitors are clinically developed^{8,9,10} of which Ranibizumab is a high affinity recombinant Fab that neutralizes all isoforms of VEGF-A.¹¹ The human antibody fragment is produced by an E.coli expression system. It has got half-life of 2-4 days resulting in very rapid systemic clearance and high systemic safety. Transient subconjunctival

haemorrhage and vitreous floaters and transient intraocular pressure rise are some rare side effects noticed after it. Although pars plana vitrectomy (PPV) with endolaser with foot bleb is the treatment of choice in neovascular glaucoma with hazy media (Obscuring PRP) because of mild vitreous haemorrhage, in a peripheral set up it is difficult to have a vitrectomy machine in our disposal. That is why we tried a relatively easier approach that is intravitreal Ranibizumab followed by trabeculectomy with MMC. Trabeculectomy produces a fistula in between anterior chamber of eyeball and sub tenon space and enhances aqueous outflow thus lowering intraocular pressure. After trabeculectomy there might be over filtration or filtration failure. The success rate of trabeculectomy in patients with NVG is limited owing to associated severe inflammation. Here comes the role of antimetabolites like 5-Fluorouracil and Mitomycin-C. The first one inhibits DNA synthesis by blocking S phase while latter being an alkylating agent inhibits DNA replication. Both of them hinder fibroblast proliferation. Corneal epithelial defects and thin walled bleb are two main complications following antimetabolites use.

Trabeculectomy with adjunct 5- fluorouracil showed high success rate initially which decreased with long term follow up.¹² Risk factors for progressive failure of MMC treated trabeculectomies include younger age and prior vitrectomy.¹³ Hence in recent times different drainage implants including anti glaucoma valves most notably Ahmed glaucoma valves are being used to increase the success rate as far as intraocular pressure reduction is concerned.

METHODS

This is a hospital based experimental clinical research (Uncontrolled clinical trial which is retrospective interventional) where we included 23 cases of NVG (23 eyes) of various aetiology in a time frame of 2 years from July 2015 to June 2017. The age of patients were 54 to 67 years. When patients did turn up first time in our outpatient department, we had taken detailed history including onset of diminished vision, any associated pain, photophobia, nausea, vomiting, any systemic association of diabetes mellitus, hypertension, dyslipidaemia, nephropathy etc. Then we had performed detailed ophthalmological examination including best corrected visual acuity (BCVA) with Snellen's chart, pupillary reaction with torch light, IOP measurement with Goldman applanation tonometer, slit lamp examination to evaluate cornea, anterior chamber depth, iris and gonioscopy to evaluate the anterior chamber angle and funduscopy to evaluate the fundus. Then we advised the patients to do routine blood examination including fasting and post prandial blood sugar, glycosylated haemoglobin and lipid profile, ECG, ocular USG- B scan to assess the extent of vitreous haemorrhage properly. After pre-operative medical fitness and prior informed consents from the patients, we planned to give intravitreal Ranibizumab (0.3 mg) injection under topical anaesthesia. First of all, each patient was advised to use topical broad-spectrum antibiotic moxifloxacin and tobramycin 1 drop 4 times a day each 3 days prior to intended date of injection. On the scheduled date each patient was taken to operation theatre with utmost sterilisation where particular eye was cleaned with 5% povidone iodine as aseptic measure. Then eye drape was applied, and a mark was made at 4 mm from limbus at supero-temporal quadrant by caliper in case of phakic patient and at 3.5 mm in case of

pseudophakic patient. There after topical proparacaine 0.5% was instilled 4 -5 times as topical anaesthesia. Then 0.5 mg Ranibizumab was loaded in 30 gauge fitted syringe and it was injected with tip of the needle was directed towards mid vitreous. Broad spectrum topical antibiotics was prescribed as before along with topical antiglaucoma drugs. There after trabeculectomy with MMC under local anaesthesia was performed 1 week later under same strict aseptic measures. Here with having miosed pupil fornix or limbal based conjunctival flap was made and then superficial scleral flap was made, and it was dissected forwards until clear cornea had been reached and next a paracentesis was made, and then deep scleral block was excised followed by peripheral iridectomy. After that 0.5 mg/ml Mitomycin-C soaked cotton was placed underlying superficial scleral flap for 5 minutes. Then superficial scleral flap was sutured at its posterior corner and followed by suturing of conjunctival flap. Balanced salt solution was injected into anterior chamber to maintain its depth. Then we assessed the BCVA, anterior chamber neovascularisation and IOP on 1st post-operative day, after 1 week, 1 month, 3 months and 6 months respectively with suitable statistical test (paired t test)

Inclusion Criteria

1. IOP greater than 24 mm of Hg.
2. Iris and or anterior chamber neovascularisation.
3. Presence of media haziness which obscures PRP.
4. Patients with BCVA above no PL.
5. Noncompliant patient.

Exclusion Criteria

1. Any intraocular infection.
2. Use of systemic steroids, immunosuppressives,
3. Thromboembolic disorders.
4. Known hypersensitivity to Ranibizumab.
5. Female of child bearing age not using oral contraceptives.
6. Use of intravitreal anti -VEGF over the last 30 days.
7. Known HIV infected patient.
8. Any pre-existing dense central corneal opacity.
9. Any pre-existing dense cataract.

Outcome Measures

1. IOP (Time frame 6 months).
2. BCVA (Time frame 6 months).
3. Anterior segment neovascularization (Time frame 6 months).

RESULTS

Out of the 23 patients, 17 were male and 6 were female. 22 patients had associated diabetes mellitus, 5 patients had hypertension, 6 were having dyslipidaemia. Then we made two groups among the patients: (A) Anterior chamber neovascularisation with open angle. (B) Fibrovascular membrane with angle closure. In this study, hospital based experimental, clinical research (retrospective interventional) was used to assess the improvement of BCVA and IOP in patients with NVG after single dose of intravitreal Ranibizumab under topical anaesthesia followed by trabeculectomy with MMC and its design pattern is concurrent study design (Uncontrolled clinical trial) with before and after comparison without any control group. We have used paired T test to have the data.

	Group	N	Mean	Std. Deviation	Std. Error Mean	df	Sig (Tailed) ²
TNPRE	OAG	15	27.07	2.764	.714	.21	.000
	ACG	8	33.63	2.446	.865	16.057	.000
TNID	OAG	15	19.13	17.67	.456	21	.000
	ACG	8	25.63	2.774	.981	10.121	.000
TN1W	OAG	15	18.73	1.668	.431	21	.000
	ACG	8	25.50	2.390	.845	10.743	.000
TN1M	OAG	15	18.87	1.992	.496	21	.000
	ACG	8	25.63	1.847	.653	14.934	.000
TN3M	OAG	15	19.33	1.952	.504	21	.000
	ACG	8	25.63	1.847	.653	15.138	.000
TN6M	OAG	15	20.87	2.264	.584	21	.000
	ACG	8	25.88	1.727	.611	18.105	.000
Tabulation of Final Results as Per Paired T-Test (Concurrent Study without Control), Total Patients 23 (In Relation to IOP)							
TNPRE= IOP preoperative, TNID= IOP on 1 st postoperative day, TN1W=IOP after 1 week, TN1M=IOP after 1 month, TN3M= IOP after 3 months, TN6M= IOP after 6 months, OAG= Open angle glaucoma, ACG= Angle closure glaucoma							

It was clearly evident from the above uncontrolled clinical trial, that single dose of intravitreal Ranimizumab followed by trabeculectomy with MMC in NVG has got decent positive outcomes particularly in open angle cases compared to angle closure cases in terms of reduction of IOP and although improvement in best corrected visual acuity also occurred but that was not statistically proven. But it is also to be accepted that the long-term effects gradually wane over the course of time and the situation might be alarming to the ophthalmologists on later date and becomes difficult to be handled.

Patient No. 1 Pre-Operative

Patient No. 1 Post-Operative

Patient No. 2 Pre-Operative

Patient No. 2 Post-Operative

DISCUSSION

Neovascular glaucoma (NVG) is a potentially devastating sequela of serious underlying ocular and/or systemic diseases. The ocular diseases responsible for neovascularization of the iris (NVI) or neovascularization of the angle (NVA) that ultimately lead to NVG are almost always ischemic in nature. Under hypoxic conditions, diffusible angiogenic factors, including vascular endothelial growth factor, have been detected in the human and animal retina and vitreous, promoting new vessel growth. Vasoinhibitory factors which are released from vitreous and lens usually inhibit the angiogenic factors this probably explains why vitrectomy and lensectomy increase the risk of formation of rubeosis iridis in cases of proliferative diabetic retinopathy. It has been also postulated that hypoxia causes vascular dilatation which in turn acts as a stimulus for neovessels to grow extensively. Clinically, the three most common conditions responsible for NVG are diabetic retinopathy, central retinal vein occlusion and carotid artery obstructive disease. Apart from that rhegmatogenous retinal detachment, sickle cell retinopathy, severe uveitis, carotid artery obstructive disease, carotid-cavernous fistula are other notable causes of neovascular glaucoma.

Neovascular glaucoma has got three stages which are pre-glaucoma stage that is nothing but rubeosis iridis characterised by neovessel formation at either peri pupillary iris or anterior chamber angle specially in diabetic retinopathy cases, open angle glaucoma stage and lastly angle closure glaucoma stage. Anterior segment neovascularization

involving the iris, the angle or both is accompanied by the formation of a fibrovascular membrane that is seen histologically. This membrane initially obstructs the aqueous outflow through the trabecular meshwork and results in open-angle glaucoma, which may be amenable to pharmacological management of the elevated IOP and to panretinal photocoagulation (PRP) of the underlying ischemic disease. However, as the disease progresses, the proliferating myofibroblasts of the fibrovascular membrane contract, leading to ectropion uveae, peripheral anterior synechiae and, ultimately, total synechial angle closure. This stage is not reversible by PRP. The resultant secondary glaucoma is often refractory to pharmacological management and requires surgical intervention.

Traditionally, NVG has been treated with extensive panretinal photocoagulation (PRP), which causes NVI and NVA to regress over the course of at least several weeks. PRP destroys ischemic retinal cells, thereby decreasing the stimulus for NV. PRP may be useful in decreasing elevated IOP in open angle glaucoma stage but can be effective in early phases of angle closure glaucoma too. When there is cloudy media making PRP very difficult to perform, trans-scleral panretinal cryotherapy along with cyclocryotherapy can be considered to keep IOP under control. Gonio photocoagulation which is direct application of neovessels of anterior chamber angle is useful in early stage of glaucoma that basically retard the disease progression and intractable glaucoma cannot occur. Initially the open angle stage can be treated with topical antiglaucoma medications such as beta blockers, alpha agonists, carbonic anhydrase inhibitors etc. Vascular endothelial growth factor (VEGF) has been identified as one of the main ocular angiogenic signals (although others have been found), and it is the target of most clinical interventions. When treating hypoxic retinal vascular diseases, it is useful to separate patients into two categories, NVG and NV without glaucoma. Several studies have demonstrated that, in patients with NV but not glaucoma, intravitreal bevacizumab (IVB) injections with or without PRP can sufficiently treat NV and cause regression of NVI and NVA (within days to weeks) without damaging the inherent drainage structures of the eye. Glaucoma surgery is required when NVG cannot be controlled with antiglaucoma medications.

Glaucoma drainage implants, trabeculectomy with mitomycin C, cyclocryotherapy, or diode laser coagulation of the ciliary body is another treatment option available for the treatment of recalcitrant and end-stage NVG. Pars plana vitrectomy (PPV) combined with glaucoma drainage implantation can produce good control of intraocular pressure (IOP) in NVG patients with PDR. The optimal approaches to treating NVG with VH are to provide patients with an individualized management plan according to etiology, stage of disease, and visual potential among other factors. Future treatment options might include neutralisation of anti- VEGF antibodies and systemic alpha interferon that inhibits proliferation and migration of endothelial cells and Troxerutin being semisynthetic flavonoid derivative which inhibits platelet and red cell aggregation thereby enhancing microvascular perfusion.

CONCLUSIONS

NVG is usually a challenge to every ophthalmologist and menace to every patient. Most of the patients usually turn up to the hospital at the end stage with irreversible blindness having very grave visual prognosis however it can be tackled if adequate measures are taken at appropriate time.

We can cope up with NVG with mild vitreous haemorrhage, by administration of intravitreal Ranibizumab under topical anaesthesia followed by trabeculectomy with MMC under local anaesthesia when PPV with endolaser is not possible due to unavailability of vitrectomy machine with endolaser facility particularly in peripheral set up. Intravitreal anti-VEGF drugs are known to have a half-life of 7-10 days in the eye and their clinical efficacy is as short as 4 weeks. As anti-VEGF agents block new vessel formation, and also induce regression of existing vessels, they can theoretically prevent new haemorrhages from pre-existing or new loci in VH patients. Thus, injection of anti-VEGF drugs facilitates clearing of the media and should allow the application of PRP in more patients in the early phase. This is consistent with the results.

Scarring at the surgical site is the most common cause of failure of glaucoma filtering surgery.^{1,2} Fibroblasts play a critical role in the healing process and agents which inhibit their proliferation have been introduced to modulate tissue reaction after fistulising surgery.³⁻⁶ Mitomycin C (MMC) is one such agent which has been shown to successfully prolong the surgical results after trabeculectomy in both high risk and uncomplicated glaucoma.⁷⁻¹

Our current study has shown promising result in this regard particularly in terms of reduction of intraocular pressure and improvement of best corrected visual acuity which was more evident in open angle cases compared to angle closure cases. This is possibly because of already formed fibrovascular membrane in angle closure cases which makes them refractory to treatment.

So, in spite of putting best possible efforts, these cases will still remain and secondary optic atrophy will occur following elevated intraocular pressure of prolonged duration thus causing end stage glaucoma with irreversible blindness.

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