ORIGINAL RESEARCH

A Long-term Clinical Study to Evaluate AGV with Concurrent Intravitreal Ranibizumab vs Primary AGV Implantation in Cases of Refractory Neovascular Glaucoma

Jaya Kaushik[1], Jitendra KS Parihar[2], Rakesh Shetty[3], Ankita Singh[4], Piyush Chaturvedi[5]

Abstract

Purpose: This study was aimed to gauge the efficacy of primary AGV implantation with concurrent intraoperative intravitreal ranibizumab vs primary AGV implantation alone in the management of neovascular glaucoma (NVG).

Methods: This retrospective comparative study was carried out based on the data collected in patients of neovascular glaucoma who underwent Ahmed Glaucoma Valve implantation with or without concurrent intravitreal ranibizumab between the period from Feb 2009 to Feb 2015 involving two groups of 40 patients each, having the clinical diagnosis of neovascular glaucoma, having undergone pan-retinal photocoagulation with minimum 03 intravitreal injections of ranibizumab not less than 4 weeks prior to undergoing primary Ahmed glaucoma valve implantation and allotted randomly to either group to receive concurrent administration of intravitreal ranibizumab with Ahmed glaucoma valve (AGV) implant surgery or AGV implant surgery alone. The minimum qualifying follow-up was 3-years. The functional outcome measures included intraoperative and postoperative complications, intraocular pressure (IOP), and the need for antiglaucoma medication, if any, as well as best corrected visual acuity.

Results: Both the groups showed a significant decrease in IOP ($p < 0.05$). Sight and IOP threatening postoperative complications were significantly low in the study group. NVI regression was higher in the study group and re-emergence was significantly lesser in the study group ($p = 0.002$). Mean postop IOP had shown an excellent reduction in IOP up to 14.25 ± 2.05 mm Hg with 1.5 ± 1 antiglaucoma drugs in ranibizumab group and 15.25 ± 2.95 mm Hg with 1.7 ± 0.87 antiglaucoma drugs in the control group at the 3-years follow-up period. Surgical success rates were comparable between the two groups at 1 and 3-year.

Conclusion: Concurrent intravitreal ranibizumab along with primary AGV implantation minimizes postoperative complications, regresses NVI while accelerating stabilization of IOP and visual functions.

Keywords: Ahmed glaucoma valve, Anti-VEGF with AGV implantation in NVG, Decreased postoperative complications with ranibizumab in AGV implantation for NVG, ranibizumab with AGV implantation in NVG, ranibizumab in NVG.

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Introduction

Neovascular glaucoma (NVG) is an aggressive, refractory form of secondary glaucoma caused by the proliferation of abnormal fibro-vascular tissue on the iris and anterior chamber angle structures and associated with the subsequent progressive contraction of this fibro-vascular tissue, resulting in angle closure and intractable elevation of intraocular pressure, as an inevitable sequelae.[1-3] The abnormal, extensive fibrosis and progressive neovascularization, are the most crucial factors leading to debatable outcomes and higher failure rates following conventional glaucoma surgeries such as modulated trabeculectomy with antimetabolites, cyclocryotherapy, cyclophotocoagulation, or laser trabeculoplasty in cases of NVG.[4-6] This has prompted the application of glaucoma drainage devices, as a more efficacious and safer option for the management of NVG.[7-12] Over the years, a better understanding of the release of Vascular Endothelial Growth Factor (VEGF) in the retina and its definite correlation with retinal ischemia leading to ocular neovascularization and fibrosis, has opened the way for effective use of intravitreal anti-VEGF molecules as a strong adjuvant treatment modality in cases of retinal vascular pathologies to regress neovascularization and other changes.[13-16] Subsequently, anti-VEGF like Bevacizumab has been introduced as an off-label adjuvant in the management of retinal pathologies as well as in glaucoma surgeries. However, being an off-label drug, its efficacy remains under question. The advent of ranibizumab (Lucentis, Genetech) as a recombinant humanized antibody antigen-binding fragment molecule, has given new and proven dimension to anti-VEGF actions for various indications in retinal pathologies as well as in cases of NVG requiring surgical management including glaucoma drainage device surgeries like Ahmed Glaucoma Valve (AGV) implantation.[10,17,18]

[1,3,4]Department of Ophthalmology, Armed Forces Medical College Pune, Maharashtra, India

[2]Department of Ophthalmology, Centre for Sight, New Delhi, India

[5]Department of Ophthalmology, Command Hospital, Panchkula, Haryana, India

Corresponding Author: Jaya Kaushik, Department of Ophthalmology, Armed Forces Medical College Pune, Maharashtra, India, Phone: +91 8390010094, e-mail: arnavjaya@gmail.com

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However, presently there is scarce data on the definite timing on use of intravitreal as an adjunctive therapy during AGV implantation so as to enable the best possible outcome for the patient while reducing the incidence of intra operative and postoperative complications and iatrogenic morbidity.[18,19] To the best of our knowledge, this is the first study, wherein the effects of concurrent administration of intravitreal ranibizumab with primary AGV implantation in NVG patients were compared with those who underwent primary AGV implantation alone.

Materials and Methods

This retrospective comparative study was carried out based on the data collected in patients of neovascular glaucoma who underwent Ahmed Glaucoma Valve (AGV) implantation with or without concurrent intravitreal ranibizumab between the period from Feb 2009 to Feb 2015 at a tertiary level research institute. The study was approved by the Institutional Review Committee, Army Hospital (R & R), Delhi Cantt, and ethical clearance were obtained. Written informed consent was obtained from the patients to use the data omit obtained from the surgical outcome for research purpose. The data of 87 patients between age group from 40–70 years diagnosed with neovascular glaucoma with a history of prior pan-retinal photocoagulation and 03 dosages of anti-VEGF for the preexisting retinal disease were included to participate in the study. The patients were diagnosed as NVG on the basis of gonioscopic findings of neovascularization of iris and/or anterior chamber of the eye and/or iridocorneal angle, with elevated IOP (>21 mm Hg) refractory to maximum antiglaucoma drugs. Patients having a vision of no light perception, NVG due to causes like uveitis and intraocular tumor, ocular trauma, previous filtration surgery, or cyclodestructive procedures, scleral buckling were excluded.

The data obtained from the patients were divided into two groups: out of 87 patients, 45 patients were assigned to the study group and 42 patients were allotted to the control group. Out of these, seven patients were excluded from the study as five patients from the study group and two patients from the control group had a follow-up of less than 2-years. Hence, the study design was confined to a total of 80 eyes comprising of 40 eyes in each group. Patients from the study group (group A) received intraoperative Intravitreal ranibizumab injection with Primary AGV Implantation as a concurrent procedure. The remaining 40 patients who underwent Primary AGV Implantation only were marked as control (group B). A detailed history was taken from all the patients regarding the duration of glaucoma, associated systemic diseases like diabetes or hypertension, history of previous retinal disease, and treatment received such as panretinal photocoagulation (PRP) or intravitreal anti-VEGF along with etiology of NVG. Visual acuity was assessed using Snellen's visual acuity chart and a detailed slit lamp examination was carried out to evaluate the cornea, lens status, neovascularization at iris, or angle by gonioscopy. Intraocular pressure was measured by Goldman applanation tonometry. Record of preoperative and postoperative antiglaucoma medications and associated intra- and postoperative complications were also analyzed.

The management protocol comprised of PRP as well as pars plana administration of intravitreal ranibizumab 0.05 mL at least for three occasions prior to glaucoma surgery while ensuring a minimum time interval of 4 weeks between last injection and Primary AGV surgery. Measurements of IOP and BCVA, fundus evaluation was done preoperatively and post post AGV implantation at 1st day, 1st, 4th, 12th week and thereafter 6 monthly up to 3-year.

Surgical Procedure

All surgeries were performed by a single surgeon (J.K.S.P.) under peribulbar anesthesia. After peritomy, fornicial based conjunctival flap was raised supero-temporally. A sub-Tenon's pocket was created extending up to the equator and a 4 × 4 mm scleral tunnel was prepared by a 2.5 mm tunnel blade (Fig. 1A). After priming of valve with a balanced salt solution by 30 gauze cannula (Fig. 1B), the valve plate was anchored to sclera by 7–0 nylon sutures 7–8 mm from the limbus (Fig. 1C). The edge of the tube was trimmed obliquely with the bevel facing upwards to ensure intraocular intrusion of about 2 mm (Fig. 1D). The entry into the anterior chamber was made with a 23–G needle and the tunnel was secured by 8–0 vicryl sutures. The author has applied a further modification to the surgical technique by applying three compression sutures over the silicon tube at three different places with 8–0 vicryl sutures to minimize the possibility of extensive hypotony and choroidal effusion in the early postoperative period. To manage postoperative hypotony, the anterior chamber was reformed with the help of intracameral injection of sodium hyaluronate. After conjunctival repositioning, subconjunctival antibiotics and corticosteroids were injected well away from the surgical site. In group A patients, intravitreal ranibizumab (0.5 mg in 0.05 mL) was concurrently administered intraoperatively through pars plana (3.5 mm away from the limbus) with a 1 mL tuberculin syringe attached to a 30–gauge needle at the end of AGV implantation whereas in group B only AGV implantation was done. As per postoperative protocol all patients were given topical antibiotics and steroids (0.1% Dexamethasone) for 6 weeks in tapering dosages. Eye drop Atropine Sulphate 1% was prescribed in all cases for the period of 1 week. Antiglaucoma drugs were given, if required, during the phase of hypertony or during subsequent follow-up.

Outcome Measures

Surgical success was defined as IOP <21 and >8 mm Hg without additional surgical maneuver with or without antiglaucoma medication at 3-years follow-up. Failure was defined as IOP <8 or >21 mm Hg with antiglaucoma medicines during three consecutive follow-ups or need of additional glaucoma surgery or light perception negative after surgery. The patients were also assessed for intraoperative and postoperative complications.

Statistical Analysis

Statistical analysis was done by using STATA 15.0 and SPSS (Statistical Package for social science version) 22:0 Statistical Software. Qualitative data variables are expressed by using frequency and Percentage (%). Quantitative data variables are expressed by using Mean and Standard deviation (SD). Chi-square test/Fisher's exact test was used to compare the qualitative data variables like complication, NVI regression, and recurrence in both the groups. Unpaired *t*-test was used to compare the quantitative variables (Age, mean IOP, mean number of AGM) for intragroup comparison (between postoperative and preoperative within the group) and intergroup comparison (between group A and B), respectively during follow-up at 1-year and 3-year. *p*-value <0.05 were considered as statistically significant.

Results

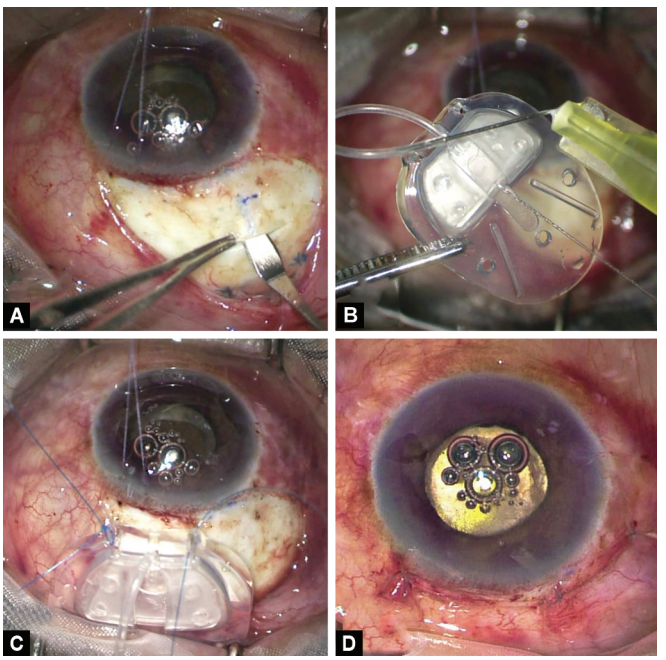
In total, 87 patients (87 eyes) with NVG were enrolled in the study. Out of these seven patients were excluded due to inadequate follow-up. The study comprised of 40 patients (40 eyes) each in both study (group A) and the control group (group B).

The demographic and baseline characteristics of the patients are as shown in Table 1. The mean age of patients was 60.28 ± 6.37 years in group A and 59.20 ± 6.44 years in group B. The most common etiology was proliferative diabetic retinopathy (PDR) in group A (16 patients, 40%) as well as in group B (19 patients, 47.5%) followed by, central retinal vein occlusion (CRVO) in group A (13 patients, 32.5%) and in group B (12 patients, 30%) followed by branch retinal vein occlusion (BRVO) and ocular ischemic syndrome (OIS). Preoperatively 20 eyes (50%) were pseudophakic in group A and 19 eyes (47.5%) in group B. The mean follow-up period was 3.12 ± 0.7 years in all the patients.

Table 2 represents various postoperative outcome measures and their comparison between the two groups. The mean IOP at first clinical presentation was 45 ± 4.87 mm Hg in group A and 45 ± 4.53 mm Hg in group B whereas mean IOP on maximum antiglaucoma medication was 38.73 ± 6.44 mm Hg in the study group and 38.95 ± 6.11 mm Hg in the control group. The mean IOPs after AGV implantation were significantly reduced ($p < 0.05$) to 8.65, 15.38, and 14.25 mm Hg for 1st day, 3rd month, and 3rd year follow-up period in group A and 7.38, 16.55, 15.25 mm Hg for 1st day, 3rd month and 3rd year respectively in the group B. Compared with preoperative IOP, the two groups showed a statistically significant IOP decrease at postoperative day 1, 3rd month and at 3rd year of follow up. In all examinations during the postoperative period, the mean IOP values in the study group were slightly lower than those in the control group, but the differences were not statistically significant apart from the values for the 1st day and 1st week after surgery.

The mean number of antiglaucoma drugs used also decreased significantly in group A (from 3.96 ± 0.26–1.5 ± 1) and in group B (from 4.01 ± 0.11–1.7 ± 0.87) at 3-year follow-up ($p < 0.01$). However, a comparison of the number of antiglaucoma medications used at 1st and 3rd year were not statistically significant between both groups. At 3rd year 7 patients in group A and 9 patients in group B were on single AGM and three patients each in both groups was on two drugs. Postoperative visual acuity improvement of two lines on Snellen's chart from preoperative visual acuity was observed in 19 patients (47.5%) in group A and 18 patients (46%) in group B. According to outcome criteria, the cumulative probability of success rate of group A was 85% whereas in group B was 80% (Fig. 2).

Postoperatively, three eyes (7.5%) in group A had hyphema as compared to eight eyes (20%) in group B. Four eyes (10%) in group A and seven eyes (17.5%) in group B experienced hypotony (IOP < 5 mm Hg). A shallow anterior chamber was seen in four eyes (10%) and eight eyes (20%) respectively groups A and B, in initial postoperative periods, for which AC reformation was performed by injecting sodium hyaluronate into the anterior chamber. Hyphema resolved spontaneously, lasting 3 days up to 2 weeks depending upon the amount of hyphema. Three eyes (7.5%) in group A and six eyes (15%) in group B had choroidal effusion with shallow AC, which was treated conservatively with systemic steroids and eye drop Atropine 1%. Corneal decompensation was seen in one patient (2.5%) in group A and three patients (7.5%) in group B. Five eyes in group A and six eyes in group B, who had lenticular opacities before the surgery, developed visually significant cataracts during follow-up. In group A, six eyes (15.5%) were labeled as failed, reasons being corneal decompensation with high IOP uncontrolled on



Figs 1A to D: Surgical technique

Table 1: Demographic characteristics of patients undergoing primary AGV with concurrent ranibizumab or primary AGV alone

Characteristics		*Group A (AGV with concurrent ranibizumab)*	*Group B (AGV)*	*p-value*
No. of eyes		40 (50%)	40 (50%)	
Mean age (± SD)	Years	60.28 ± 6.37	59.20 ± 6.44	
Sex	Male	29	31	
	Female	11	9	
Etiology of NVG	BRVO	6 (15%)	7 (17.5)	
	CRVO	13 (32.5%)	12 (30%)	
	OIS	5 (12.5%)	3 (7.5%)	
	PDR	16 (40%)	19 (47.5%)	
Lens status	Phakic	20(50%)	19 (47.5%)	
	Pseudophakia	20 (50%)	21 (52.5%)	
Mean IOP ± SD baseline		38.73 ± 6.44	38.95 ± 6.11	0.873
Visual acuity baseline		0.9 ± 1.2	0.9 ± 1.2	0.837

Table 2: Postoperative data of patients undergoing primary AGV with concurrent ranibizumab vs primary AGV only

Variables	*Group A (AGV with concurrent ranibizumab)*	*Group B (AGV)*	*p-value*
IOP (mm Hg) Mean ± SD at 3 months	15.38 ± 2.13	16.55 ± 6.11	0.058
IOP (mm Hg) Mean ± SD at 3 years	14.25 ± 2.05	15.25 ± 2.95	0.083
No of antiglaucoma medications (Mean ± SD) at 3 years	1.5 ± 1	1.7 ± 0.87	0.063
Visual acuity at 3 years	0.4 ± 0.8	0.5 ± 0.8	0.099

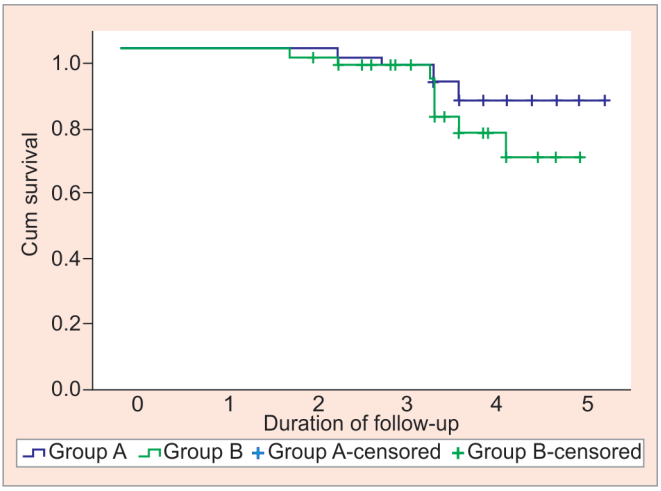


Fig. 2: Cumulative probability of success rate of group A vs group B

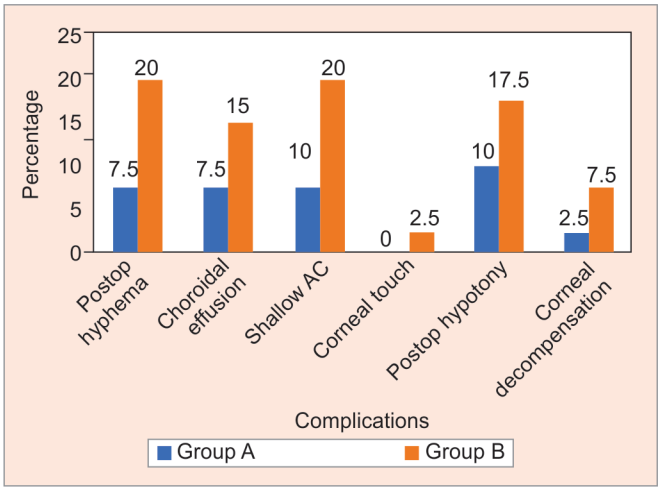


Fig. 3: Graph showing the comparison of postoperative complications occurring in both the groups

maximal medications and loss of light perception (one eye) and uncontrolled IOP (>21 mm Hg) on maximal antiglaucoma therapy needing another glaucoma intervention (five eyes). Eight eyes (20%) were designated as failed due to corneal decompensation with uncontrolled high IOP (three eyes), high IOP needing another glaucoma intervention (five eyes) out of which two eyes lost perception of light in group B. A comparison of the proportion of various postoperative complications between the two groups is depicted as a graph in Figure 3.

Discussion

Neovascular glaucoma, an aggressive, refractory form of secondary glaucoma, was first described by Coats in 1906, as new blood vessel growth over the surface of the iris in the eyes with central retinal vein occlusion.[20] The most common etiologies leading to neovascular glaucoma include central retinal vein occlusion, diabetic retinopathy, ocular ischemic syndrome and, central retinal artery occlusion.[1,2,21] Over the years it has been established that neovascular glaucoma is due to the elaboration of cytokines and proteins, especially Vascular Endothelial Growth Factor (VEGF), in response to severe, diffuse, and chronic retinal ischemia.[1-3,15] This leads to the creation of a pro-angiogenic milieu, that foments the formation of a new fragile network of leaky vessels with associated connective tissue scaffolding over the iris and anterior chamber angles. This abnormal fibrovascular tissue initially impairs aqueous outflow in the presence of an open angle with subsequent progression to typically severe and unrelenting secondary synechial angle closure glaucoma which is refractory to treatment. Raised VEGF levels in aqueous humor can trigger fibrosis in tissues around the plate, the most important factor in surgical failure.[2,15,22] The fragile new vessels in the iris and anterior chamber angle tend to bleed leading to inflammation, hyphema, and fibrinous reaction in the postoperative period and adversely affecting the success rate.

Panretinal photocoagulation, though an important tool, cannot prevent the re-emergence of neovascularization, until the etiological factor responsible for retinal ischemia is remedied. Filtering surgery has a poor outcome in terms of IOP control in these patients, and varying rates of success have been reported with trabeculectomy as well as with antimetabolites.[3,5,6] Cyclodestructive procedures have a limited effect on these patients because of their high rate of postoperative complications and low predictability.[4] Aqueous shunting tube surgeries, like AGV, have been shown to be more successful both with respect to IOP control as well as postoperative complications.[3,7-12,23] The addition of anti-VEGF agents with AGV, with their antifibrotic and antiangiogenic properties, have shown to be beneficial, especially to reduce surgery related complications like postoperative hyphema and also to improve success rates of the IOP lowering procedures by decreasing the fibrovascular response around these devices and therefore tube-blockage rate.[18,21-30]

There have been several studies about the efficacy and safety of preoperative intravitreal Bevacizumab in NVG.[22-24,30-34] However, very limited literature is available on the use of intravitreal ranibizumab in NVG patients undergoing AGV implantation.[18,19] Over and above, we could not find any prospective study evaluating the efficacy of intraoperative ranibizumab intravitreally concurrent with AGV implantation as a primary surgical intervention in Indian eyes with a long-term follow-up of 3 years.

In our study, the efficacy of administration of ranibizumab (Lucentis, Genetech) concurrent with primary AGV implantation on IOP was reviewed over a period of 3 years follow-up. We observed a significant reduction of IOP in both the groups, AGV with adjuvant ranibizumab and AGV alone at 3-years (p = 0.083) follow-up. However, both groups were comparable in terms of IOP control

Table 3: Proportion of patients with NVI regression (at 6 months)

	Group			
NVI regression	*Group A*	*Group B*	*Total*	*p-value*
Present	25 (62.5%)	11 (27.5%)	36	0.002
Absent	15 (37.5%)	29 (72.5%)	44	
Total	40	40	80	

at 1st year ($p = 0.953$) and ($p = 0.326$) at 2-years of IOP readings at respective follow-up points. At the time of final follow-up, the mean IOP was 14.25 ± 2.05 mm Hg and 15.25 ± 2.95 mm Hg in the study and control group. Thus, the study group had lower mean IOP values although not statistically significant ($p = 0.083$), as compared to the control group respectively at 3-years follow-up.

The rate of NVI regression was significantly different between the two groups at 6-month follow-up. NVI regression was seen in 62.5% of patients in the study group as compared to only 27.5% of patients in the control group ($p = 0.002$) (Table 3). The re-emergence of neovascularization when observed at 1-year follow-up period was significant ($p < 0.001$) in the control group (77.5%) as compared to the study group (40%). In the study group, both postoperative hyphema and fibrin reaction in the anterior chamber were less frequently observed.

The favorable overall outcome was further enabled by the modified surgical technique, an innovation by the surgeon (J.K.S.P.), that included construction of partial thickness small scleral pocket tunnel for the insertion of Glaucoma valve tube into anterior chamber as well as application of multiple, absorbable compression sutures over the tube which facilitated gradual opening of the tube lumen over a course of 2–3 weeks, allowing maintenance of adequate depth of AC, reducing impact and incidence of hypotony related dreaded complications which contributed to improved overall structural and functional integrity of aqueous outflow and success rate of the entire regimen.

Systematic literature review of many studies[35] reports better but statistically nonsignificant surgical success rates with statistically significant lesser rates of postoperative complications with adjuvant administration of Bevacizumab whether administered preoperatively or concurrently with AGV implantation in patients of NVG as compared to AGV implantation alone in NVG. Our study too demonstrates that there was no significant difference in surgical success rates, IOP control levels, reduction in requirement of antiglaucoma medications or gain of vision between the two groups, with concurrent administration of ranibizumab along with AGV implantation for NVG although there was significantly lesser postoperative complications, faster NVI regression and delayed NVI re-emergence in the study group as compared to the control group. Thus, when compared to the available literature, the results of our study suggest that the efficacy of ranibizumab, as an adjuvant administered concurrently in treatment of NVG with AGV implantation, may be similar to Bevacizumab although there is a need for more research to be done with concurrent administration of ranibizumab with AGV implantation for NVG patients, to confirm this and also to determine clinical indicators and timing of anti-VEGF injection for delivering best outcomes for the patient.

Conclusion

Concurrent intravitreal ranibizumab along with primary AGV implantation in patients of refractory NVG reduced operative and postoperative as well as restricted NVI, progression of retinal changes by delayed re-emergence of neovascularization. Concurrent intravitreal administration of ranibizumab had facilitates controlled fibrovascular proliferation around the AGV plate thereby resulting in accelerated as well as sustained stabilization of IOP and visual functions.

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Orcid

Jaya Kaushik https://orcid.org/0000-0002-6058-4875
Jitendra KS Parihar https://orcid.org/0000-0003-2428-1364
Rakesh Shetty https://orcid.org/0000-0003-3338-5771
Ankita Singh https://orcid.org/0000-0002-8136-6375

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