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Role of intravitreal Anti-VEGF as an adjunct in neovascular glaucoma management Contributors

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Abstract
Aim: *To study the role of intravitreal Anti-VEGF as an adjunct in medical & surgical management of neovascular glaucoma.*
Methods: this hospital based interventional study was conducted on 50 patients, with the clinical presentation suggestive of neovascular glaucoma, after an extensive clinical evaluation. Intravitreal Anti-VEGF was given and the effect was recorded on subsequent follow up. Panretinal photocoagulation was done as soon as media clarity permitted. In refractory cases, trabeculectomy with mitomycin C was done
Results: *The common mechanism of neovascular glaucoma was CRVO (60%) and PDR (40%).Mean age was 58.44 years. There was a significant improvement in visual acuity (p= 0.0015) and intraocular pressure (IOP) (p=0.0000) at the end of 16 week follow up. There was significant regression in neovascularization of Iris/angle. Pupil size was significantly improved (p=0.0000), allowing better visualization of fundus. Out of 50 cases, surgery was required in only 18 cases. Success rate of surgery was 83.3%.*
Conclusion: *There is a significant regression of neovascularization in NVG secondary to PDR and CRVO and this regression is stable when the underlying disease is treated well with effective suppression of ischaemic angiogenic factors. Overall, anti-VEGF agents appear very effective in inducing rapid initial regression of ischemia induced ocular neovascularization, but the effect is temporary and requires either additional definitive treatment (such as laser photocoagulation and surgery).*
Clinical significance: early diagnosis and proper treatment can help to save the useful vision as NVG itself is very devastating condition for eye.

Key words: *neovascular glaucoma, Anti-VEGF, trabeculectomy with mitomycin C*

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I. Introduction

Neovascular glaucoma (NVG) is devastating consequence of ocular ischemic diseases. Ischaemia lead to production of vascular endothelial growth factor (VEGF)& ultimately leads to neovascularization of angle (NVA) and neovascularization of iris (NVI). The mechanism of intraocular pressure (IOP) elevation is considered to be proliferation of neovascular tissue & fibrovascular membrane over trabecular meshwork and later angle closure due to contraction of membrane[1, 2].

Panretinal photocoagulation (PRP) is considered standard treatment of choice. Laser photocoagulation indirectly reduces vascular endothelial growth factor levels in patients with ischemic retinal pathologies. However, media opacity such as cataract or vitreous hemorrhage, is limiting factor to perform PRP[3, 4]. And also, in severe and rapid neovascular progression, PRP alone is ineffective. Therefore, Anti-VEGF pharmacotherapy to target VEGF directly, may be another possible therapeutic strategy to treat ocular neovascularization[5].

II. Material & Method

The ethical committee of the hospital approved the study. This hospital-based interventional study included 50 eyes of 50 patients. For the purpose of this study Neovascular Glaucoma [NVG] is defined as presence of Neovascularisation of iris [NVI] and / or Neovascularisation of Angle[NVA] associated withIOP >

21 mmHg (with maximum tolerated antiglaucoma drugs) secondary to ischemic central retinal vein occlusion (CRVO) and proliferative diabetic retinopathy (PDR). Eyes were excluded from the study if they received intravitreal Anti-VEGF strictly for reasons other than NVG, IOP never exceeded 21 mm Hg, or there was less than 1 month of follow-up after initial Anti-VEGF injection.

After discussion of both the natural course of the disease and the results of the alternative approach for NVG, together with the potential risks and benefits of off-label Anti-VEGF intravitreally administered, all patients gave written consent to receive a pars plana injection of 0.05ml of Anti-VEGF.

Visual acuity, Slit lamp & Fundus examination, Applanation tonometry, gonioscopy and B-scan (if media haze present) was done for extensive evaluation of anterior & posterior segment. Pupil size was measured using slit lamp scale before and after the injection. Intravitreal Anti-VEGF was administered under strict aseptic instructions[6].

Iris neovascularization and NVA were graded at each visit according to the classification system of Weiss and Gold[7]. For the purposes of this study, an open angle was defined as normal angle structures visible for at least 180°, while a closed angle was defined as the presence of peripheral anterior synechiae (PAS) for more than 180°.

Patients were required to return to the clinic for follow up visits at 1, 3, 7 days. They underwent a thorough ophthalmological examination weekly up to 8 weeks.Visual acuity, IOP, Slit lamp examination,Gonioscopy & fundus examination was performed in every follow up visits. Further follow up visits were done biweekly upto 16 weeks.

Anatomical regression of number of vessels in neovascularisation of iris [NVI], neovascularisation of angle [NVA] & peripheral anterior synechiae [PAS] detected on slit lamp biomicroscopy as well as functional improvement in terms of mean change in IOP, visual improvement was noted.

PRP was done as soon as media clarity permitted. Second injection of Anti-VEGFgiven after 4 week if NVI/NVA persists or reoccurs.

Patients whose still had inadequately controlled IOP, underwent trabeculectomy with mitomycin C (MMC)(0.2 mg/ml for 2 minutes). They were followed up for 12 months after surgery. Follow up schedule was every day for one week, then weekly for 2 months, then monthly till 6th month and then 3 monthly in last 6 months. Surgical failure was defined as inadequate IOP reduction (IOP > 21 mmHg, < 20% IOP reduction, or further glaucoma surgeries), devastating complications (loss of light perception, phthisis bulbi, and endophthalmitis), or significant hypotony (hypotony with IOP ≤ 5 mmHg continuing ≥ 6 months and until the last follow-up visit).

III. Results

Out of the 50 patients, 12 (24%) were females and 38 (76%) were males. Mean age was found to be 58.44 years. Majority of patients [84%] belonged to the urban and suburban background. 42 eyes was phakic, rest 8 eyes had already undergone cataract surgery with PCIOL. In 24 cases right eye was treated and in 26 cases left eye was treated. The fundus examination revealed that 60% patients had Central retinal vein occlusion [CRVO], 40 % had proliferative diabetic retinopathy [PDR].

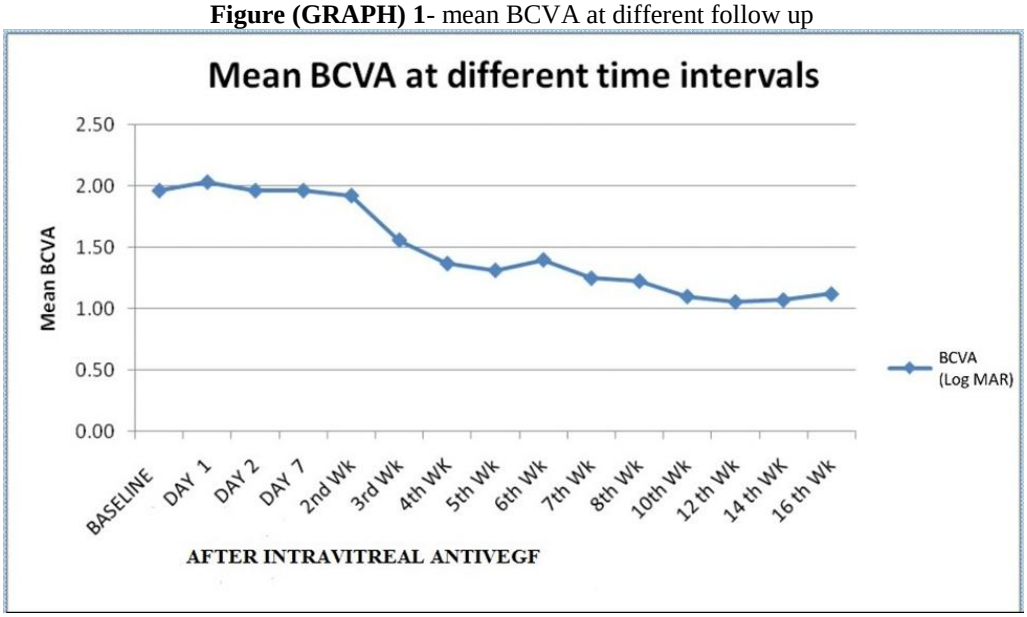
Table 1

PATIENT DEMOGRAPHICS	
SEX	MALE- 38 FEMALE- 12
BACKGROUND	URBAN – 42 RURAL- 08
EYE	RIGHT- 24 LEFT-26
DIAGNOSIS	CRVO- 30 PDR-20
MEAN AGE (years)	58.44±14.68

Symptomatically, pain and discomfort was present in 24 [48%] patients at the time of presentation which was decreased upto 18 [36%] at the end of follow up. Maximum effect was seen in 70-80 age group upto 28% & min effect upto 4% seen in 30-39 age group. 12% patients had past history of use of Anti- glaucoma medications.

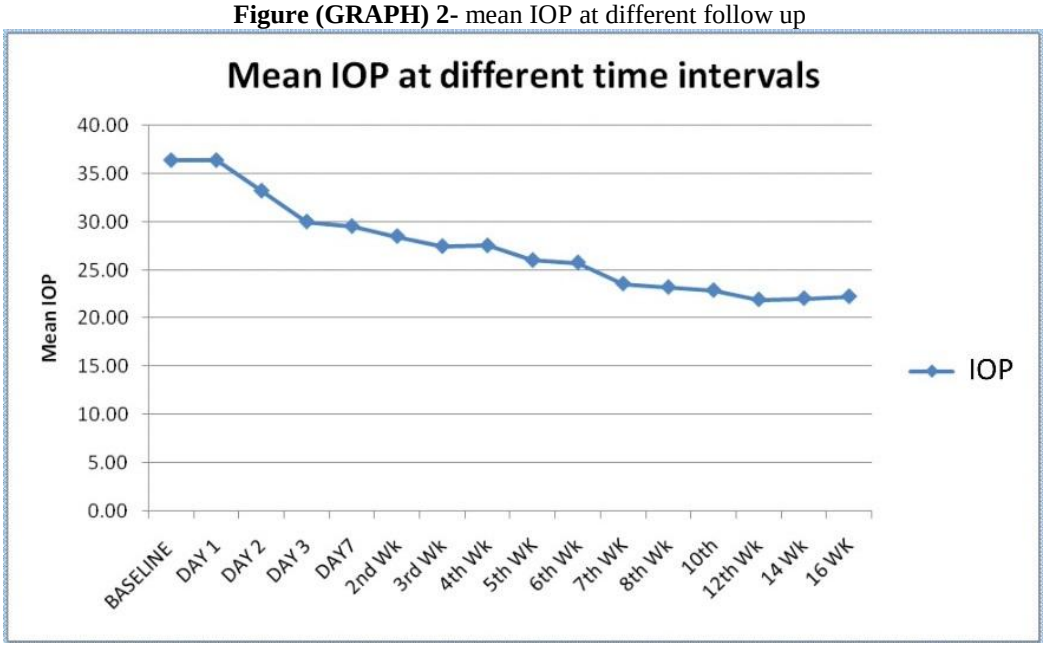
Baseline Mean BCVA was 1.96±1.01, whilemean BCVA at day 1 was 2.03±0.97 (p=0.8071). Subsequent results at the end of 16 week showed a mean of 1.12±0.71 (p= 0.0015) suggestive of statistically significant visual improvement.

Figure (GRAPH) 1- mean BCVA at different follow up



Baseline IOP was 36.66±8.49 mm Hg. But mean IOP results at the end of follow up (16 weeks) was 22.24±4.04 mm Hg (p=0.0000) showing that the change in IOP was statistically highly significant.

Figure (GRAPH) 2- mean IOP at different follow up



In all eyes, the NVI (baseline mean NVI=2.64±1.11) rapidly regressed or disappeared without an IOP elevation within 1 week after 1 injection. But there was recurrence of NVI in second week (mean=1.12±0.93, p=0.0000) which was regressed completely after second injection. At the end of 16 week, mean NVI was 0.52±0.59 (p=0.0000), suggestive of statistically significant effect of intravitreal Anti-VEGF on anatomical regression of NVI.At the end of 16 weeks, there was complete regression of NVA in all the cases in which gonioscopy was possible.

Regression if NVI was accompanied with the pupil dilatation. Mean pupil size before and after injection was 4.00±0.71 and 5.56±0.77 respectively, (p=0.0000), suggestive of highly significant response of therapy. This allowed better visualization of fundus and hence, earlier and aggressive PRP was made possible.

Table 2- Baseline gonioscopic findings

BASELINE GONIOSCOPIC CHARACTERISTICS	
ANGLE FINDING	NUMBER (%)
No view (media hazy)	3
No PAS or open angle in minimum 3 quadrants	22

Upto 180° PAS	9
180°-360° PAS	10
360° PAS	6

Table 2 detailed the baseline gonioscopic findings of this study cohort. Most of the cases had open angle (PAS < 180°). These cases responded well to anti-VEGF therapy and IOP was well maintained with antiglaucoma drugs. Surgery was required in only 4 cases while among the closed angle, 14 cases required surgery.

There was need of single injection of Anti-VEGF in 2 cases (4%), two injections in 12 cases (24%) & three injections in 36 cases (72%).After Anti-VEGF, PRP was done in 80% of patients, and there was media haze in rest 20%. 2 cases underwent cyclodestructive procedure due to painful blind eye. In the end, Trabeculectomy with mitomycin –C (0.2mg/ml) was done in 18 (36%) cases & Pars plana vitrectomy (PPV) in 4% cases in proliferative diabetic retinopathy (PDR). Rest all were on anti-glaucoma medications only.

All the trabeculectomies were performed by single surgeon. The cumulative surgical success rate was 83.3% (15 eyes) at the end of 12 months. The mean IOP before surgery was 44.7±8.2 mm Hg, whereas the mean postoperative IOP was significantly lower, being 17.1±3.5 mm Hg at 12 months ($p<0.01$). While, no significant change was found in postoperative visual acuity as compared with the preoperative visual acuity at the end of follow-up. Intraoperative and postoperative complications listed in table no 3. No bleb infections developed. An additional intraocular ANTIVEGF injection was needed in 2 eyes to treat the recurrence of rubeosis. Bleb revision was performed in one eyes.

Table no 3

SURGICAL COMPLICATIONS		
	Eyes (number)	Remark
INTRAOPERATIVE Marked Hyphema	0	
EARLY POSTOPERATIVE		
Hyphema	3	Medical management
Shallow anterior chamber	2	Treated by suture adjustment
Bleb leak	1	Treated by conjunctival sutures
Choroidal detachment	1	
LATE POSTOPERATIVE		
Vitreous hemorrhage	3	Treated by pars plana vitrectomy
Hypotony maculopathy	1	Treated by scleral flap suture adjustment
Bullous keratopathy	1	Occurred at 11 month

IV. Discussion

Aqueous humour study of patients with rubeosis and NVG have shown increased levels of VEGF-A[8]. These angiogenic vessels are highly permeable, and VEGF has also been shown to increase the permeability of established microvasculature[9]. This results in an increased presence of inflammatory mediators within the ocular tissues. Reduction of intraocular VEGF concentrationcauses regression of these new vessels and hence reduce this inflammatory effect. Panretinal photocoagulation is currently the established modality to reduce the production of vasoproliferative factors by ischaemic retina and hence, control the elevated IOP in NVG. In recent advances, several case reports and case series have demonstrated intravitreal Anti-VEGF-induced regression of iris and angle neovascularisation associated with NVG with promising results[10, 11]. Our study represents a larger study group with NVG treated with intravitreal Anti-VEGF with long-term follow-up.

Our data showed a significant and rapid reduction in NVI and NVA by 1 week after intravitreal injection. In literature it has been shown that Anti-VEGF therapy is very effective to reduce NVI[11, 12]. There was also a significant effect on mean pupil size.This effect was due to regression of neovascularisation of iris (NVI) allowing pupil dilatation with topical medications so that further PRP was possible.

Structural lesions of the trabecular meshwork and the extension of the fibrovascular membrane and goniosynechiae on the iridocorneal angle plays an important role in determining the efficacy of Anti-VEGF to improve the IOP control in patients with NVG. Wakabayashi et al. in 2008 reported that the intravitreal Anti-VEGF were not capable of extinguishing the synechia. They had effect on only new vessels[12]. In our study,IOP was well controlled with topical eye drops alone in patients who had iris and angle neovascularization without peripheral anterior synechiae (PAS). However, subsequent glaucoma surgery was needed in the patients with PAS at the time of presentation.This IOP-reducing effect of Anti-VEGF in NVG has been demonstrated in some case reports (Vatavuk et al. 2007[13]; Yalvac et al. 2007[14]; Batioglu et al[15]. 2008;Martınez- Carpio et al. 2008[16]; Moraczewski et al. 2009[17]; Yazdani et al. 2009[18]). Wakabayashi et al. 2008, confirmed that the

patients with NVG and an open angle, responded well with intravitreal Anti-VEGF in more than 70% of the cases, avoiding many cases of surgery. But, more than 90% of the caseswith closed angles needed surgery[12]. Ehlers et al. (2008) compared the advantages of PRP associated with Intravitreal Anti-VEGF and PRP alone in NVG[19]. After a 4-month follow-up, the group treated with both methods, showed earlier and greater neovascular regression, as in our study.

In this current study, IOP outcomes were found more encouraging than the visual acuity outcomes. Cyclodestructive procedures were performed in only 2 eyes to lower IOP, which is a viable option in eyes with poor visual potential[20]. Anti-VEGF-induced regression of neovascularisation is often temporary, and so, recurrence is inevitable[21] while PRP have a more permanent effect on the ischaemic angiogenic stimulus.That is why a regular and close follow up is required after the initial injection. This is in the support of our view that all eyes with NVG should receive PRP either in a clinical setting or via endolaser at the time of PPV.

Our study also showed the favorable effect of ANTI-VEGF on pupil size. Better visualization of fundus helps in better understanding and assessment of underlying pathology and hence better planning of treatment modality whether it is extensive PRP (anterior to equator) or vitrectomy and thus halting the disease progression.Traditional treatment regimens for neovascular glaucoma are often ineffective in halting vision loss and reversing IOP control. Adjunctive intravitreous Anti-VEGF helped to maintain or improve visual acuity upto a significant level in our patients. This is rare in NVG. Oshima Y. et al in 2006 reported that the Anti-VEGF stabilized or improved the visual acuity at the end of 2 month follow up in cases with NVG after PDR[22].

Another clinically vitaladvantage of treating NVG with intravitreal Anti-VEGF is that eyes requiring subsequent incisional glaucoma surgery can be performed in a quieter eye with less operative time, decreased risk of hemorrhage and quicker recovery[10, 23].

When useful vision exists, filtering surgery has been an increasingly common means of achieving IOP control in NVG. Surgical success rate of trabeculectomy at 1 year was about 65 to 85% with preoperative bevacizumab treatment and 30 to 75% without treatment[24, 25]. Our decision to use MMC in glaucoma filtering surgery for patients with NVG was based on several prospective randomised studies in adults with high-risk glaucoma filtering surgery. These studies have shown that intraoperative MMC may be a superior alternative to postoperative 5-FU. Effects of adjunctive use of intraocular anti-VEGF agents on glaucoma filtration surgeries for NVG have been evaluated in a number of studies. Less postoperative hemorrhagic complications and better surgical outcomes were anticipated because of the remarkable rapid and steady suppression of rubeosis after an intraocular injection of ANTI-VEGF[26, 27]. Furthermore, short-term surgical success rate was significantly better in eyes with preoperative Anti-VEGF injections in trabeculectomy.

In conclusion, we feel that once NVI is regressed with retinal ablation and ANTI-VEGF in patients with refractory NVG, the intraoperative use of MMC with trabeculectomy is an excellent option. Although a study with longer follow up and larger sample size is required to assess the long term result of filtering surgery after ANTI-VEGF & PRP.

Neither systemic nor ocular adverse effect was noted with the intravitreal Anti-VEGF in this study. Our average follow-up was of 16 weeks, which is a sufficient time to evaluate efficacy and safety of intravitreal Anti-VEGF.

V. Conclusions

Our impression both clinically and from a review of the literature is that early diagnosis and treatment of NVG with Anti-VEGF may lead to improved outcomes. The current study reflects our practice pattern with the rapid acceptance of intravitreal Anti-VEGF as an adjunct to NVG treatment. There is a significant regression of neovascularizationin NVG secondary to PDR and CRVO and this regression is stable when the underlying disease is treated well with effective suppression of ischaemic angiogenic factors. Overall, anti-VEGF agents appear very effective in inducing rapid initial regression of ischemia induced ocular neovascularization, but the effect is temporary and requires either additional definitive treatment (such as laser photocoagulation and surgery).

In literature, effect of intravitreal Anti-VEGF on pupil size has never been mentioned. We documented its favorable effect on pupil size, which is further helpful for diagnostic and therapeutic purpose and ultimately halting the disease process.

In the current study, we could not elucidate the strong predictive factors necessitating subsequent surgery. Considering the overall promising results with Anti-VEGF as an adjunctive, further study should be done to determine the appropriate frequency of Anti-VEGF and optimal timing of surgery for IOP stabilization in patients in this subgroup.

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