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Evaluation of the Effect of Intracameral Injection of Bevacizumab in the Treatment of Neovascular Glaucoma

Salim Mohamed Osemy*, **Mahmoud Abd El-Badie Mohamed**. **Emad Abd eI-Aal Saleem**
Ophthalmology department, Faculty of Medicine, Al-Azhar University (Assuit), Egypt
***Corresponding author:** Salim M. Osemy, **E-mail:** drsalim2017@gmail.com

ABSTRACT

Background: neovascular glaucoma (NVG) is a severe condition resulting from ischemia caused by conditions such as central retinal vein occlusion (CRVO), diabetic retinopathy (DR) and chronic uveitis. In NVG, there is neovascularization of the iris (NVI) and anterior chamber angle (NVA) mediated by vascular endothelial growth factor (VEGF) leads to elevation in the intraocular pressure (IOP). Intracameral injection of Bevacizumab show good result in regression of iris neovascularization.

Objective: it was to determine the effect of intracameral injection of bevacizumab on the neo-vessels over the iris, and on the IOP in patients with NVG.

Patients and Methods: this research is a comparative, prospective, non-randomized study. Fifteen patients of neovascular glaucoma (NVG) (≥21mmHg) (with rubeosis iridis) were divided into four groups. Group 1 had peripupillary vessel dilatations, group 2 had early neovascularization mainly in the chamber angle plus to peripupillary vessel dilatations, group 3 had prominent rubeosis with/without neovascular glaucoma, group 4 had most advanced rubeosis and injected with a single intracamerlar bevacizumab (0.05 ml at the limbus in the upper temporal quadrant*)* at Al-Azhar University hospital between March 2017-March 2018.

Results: after six months of following up the 15 patients, only group 1 showed complete regression of iris neovascularization; group 2, group 3 showed partial regression at first but finally there was recurrence of iris neovascularization; and group 4 didnot show response at all to the treatment.

Conclusion: regression of iris neovascularization was inversely proportional to the pre-injection grade. Lower grades were associated with a better response.

Keywords: Neovascular glaucoma, Central retinal vein occlusion**,** Diabetic retinopathy**,** Bevacizumab.

INTRODUCTION

Neovascular glaucoma (NVG) is a devastating ocular disease, often caused as an end stage complication of retinal ischemia. It is caused by a fibro-vascular membrane that develops over the surface of iris and angle. It is rarely, occurs as a primary condition but always associated with other abnormalities, most commonly some forms of ocular ischemia such as Central retinal vein occlusion and Diabetic retinopathy [(1)]. The most accepted theory on the pathogenesis of NVG is that ischemia of retina liberates an angiogenic factor that diffuses forward and causes new vessel formation on iris and angle which include vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), transforming growth factor-alpha (TGF-a), trans-forming growth factor-beta (TGF-b), tumor necrosis factor-alpha (TNF-a), insulin like growth factor (IGF), inter-leukin-6 (IL-6) and platelet derived growth factor (PDGF)[(2)]**.** This process stimulates a cascade leading to activation, proliferation and migration of endothelial cells with the formation of new, leaky, fragile blood vessels [(3).]

The clinical and histological events that lead from a predisposing factor through rubeosis iridis to advanced neovascular glaucoma may be thought in three stages[(4)]:

1. Rubeotic stage.
2. Secondary open angle glaucoma stage.
3. Secondary angle closure glaucoma stage.

Clinically, new vessels are first detected as small tufts at pupillary margin. The new vessels have an irregular size and irregular course and they branch frequently and also lie on the iris surface rather than the stroma as normal vessels do [(5)].

Various anti-VEGF agents have been tried in neovascular glaucoma. Intravitreal and intracameral injection of Bevacizumab have shown a dramatic regression of neovascular glaucoma and neovascularization of the iris [(6,7)].

Also, bevacizumab had excellent efficacy against the permeability and the proliferative effects of VEGF isoforms. It is found to be effective in slowing tumor growth through its effect on angiogenesis[(8)].

PATIENTS AND METHODS

This study included 15 patients of neovascular glaucoma (NVG) with neo-vessels extending on the iris border *(*rubeosis iridis) will be divided into four groups according to iris neovascularization's. Group 1 has four eyes, group 2 has also 4 eyes, group 3 has 3 eyes, and finally group 4 has 4 eyes. All groups were injected with

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a single intracamerllary injection of bevacizumab (0.05 ml bevacizumab solution using a 27-gauge needle at the

Figure (1): Eye has grade 1 iris neovascularization.

limbus in the upper temporal quadrant) and followed up for six months at Al-Azhar University hospital (Assuit) between March 2017 to March 2018.

The patients were divided into four groups according to **Laatikainen[9] Grading system:**

Grade 1: (Pre-glaucoma stage) Peripupillary vessel dilatations.

Grade 2: (Pre-glaucoma stage) early neovascularization mainly in the chamber angle. In addition to peripupillary vessel dilatations, small irregular arborising superficial newly formed vessels appear in the chamber angle and less commonly elsewhere on the iris. At this stage most of the angle remained open and the intraocular pressure was normal.

Grade 3: (Open angle glaucoma) prominent rubeosis with or without neovascular glaucoma. Superficial arborizing newly formed vessels, usually starting in the chamber angle. Arborizing new vessels are more prominent and had grown out of the angle covering more of the iris surface.

Grade 4: (Closed angle glaucoma) florid rubeosis is the most advanced Grade of rubeosis; extensive arborizing neovascularization coming from the angle covering the whole iris, the result is complete angle closure, neovascular glaucoma and further eversion of the pigmented border of the pupil.

Exclusion criteria:

Current corneal and ocular surface infection whatever the origin, ocular surgery in the studied eyes (including cataract surgery, keratoplasty, ocular surface reconstruction within 3 months prior to study), patients with dense media opacity prevent proper examination of iris and fundus, and patients with corneal complications as corneal ulcers or perforations, which prevent proper measurement of intraocular pressure (IOP).

Ethical consideration:

The study was approved by the Scientific Committee of the Faculty of Medicine, Al-Azhar University - Assuit. Written informed consents had taken from all the participants before the enrollment in the study.

Study procedure:

Preoperative evaluation:

1. **History**: was taken from the patients about medical especially chronic diseases or neurological diseases, past history of ocular trauma or pervious ocular operations.
2. **Systemic examination**: including (medical, dental, and ENT).
3. Laboratory investigation including (random blood glucose, urine analysis, bleeding time, and liver and kidney functions).
4. **Detailed ocular examination:**

a) Anterior segment with the help of standard slit lamp for (lid, lacrimal system, conjunctiva, cornea, iris and lens) with special emphasis on: Corneal condition, grading of iris neovascularization and lens condition

b) Posterior segment for (retina and optic nerve) by volk 78 Diopter lens.

c) Eyes with neovascular glaucoma had been evaluated by measuring IOP and visual acuity (VA).

d) Eyes with neovascular glaucoma caused by conditions such as diabetic retinopathy or central vein occlusion had been confirmed by Fluorescein angiography (FFA) preoperative.

5. **Visual Acuity and IOP:**

a) Measurement of VA was done by Snellen's visual acuity chart and recording the best corrected visual acuity.

b) Measurement of IOP was done by Schiotz tonometer.

c) Gonioscopy: To evaluate anterior chamber angle prior to pupillary dilatation and to determine the stage of neovascular glaucoma.

Operative procedures:

1. Informed consent was obtained from each patient prior to the operation**.**
2. All patients were informed about the use of bevacizumab and the experimental approach.
3. Aseptic preparation (10% povidone-iodine solution) will be used.
4. Topical anesthetic eye drops was used.
5. 0.05 ml bevacizumab solution has been injected using a 27-gauge needle at the limbus in the upper temporal quadrant. The procedure was done under strict sterilization in the operating room.
6. Postoperative treatment with topical antibiotic eye drops for 4 days.

Statistical analysis

The statistical analysis was done by SPSS software version 20.00. The quantitative data was presented as mean± standard deviation (SD). The qualitative data was presented as number and percent.

RESULTS

In this study fifteen eyes of fifteen patients fulfilled inclusion criteria and assigned to one of the four study groups. Mean age of patients in this study were 56.07±4.95 (Table **1**).

Table (1): Age of the participants

	Range	Mean ± SD
Age	45-64	56.07±4.95

The participants were 5 males and 10 females (Table **2** and Figure **2**).

Table (2): The sex of the participants

Sex	No.	%
Male	5	33.3
Female	10	66.7

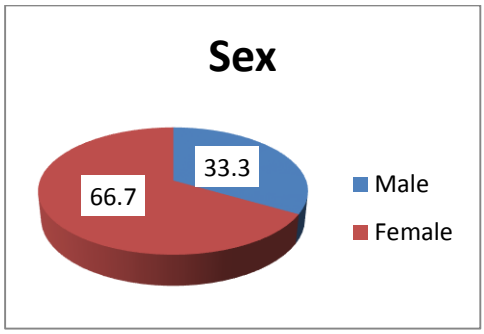

Figure (2): Male to female ratio of the participants

Preoperative visual acuity and IOP:

The visual acuity of the participants before the procedure between [hand motion (HM) and perception of light (PL)] (Table **3** and Figure **3**) and the mean changes in the IOP are shown in (Table **4** and Figure **4)**.

Table (3): Visual acuity of the patients before the procedure

Visual acuity pre	No.	%
Hand motion (HM)	6	40.0
Perception of light (PL)	9	60.0

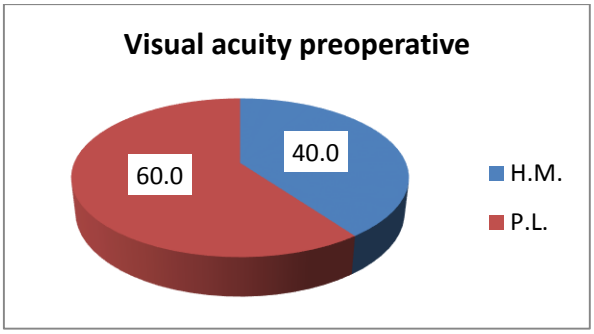

Figure (3): The visual acuity of all patients before the procedure.

Table (4): IOP pre- and post- the procedure

	Range	Mean ± SD
IOP Pre	22-40	29.53±5.82
IOP Post	20-35	24.8±5

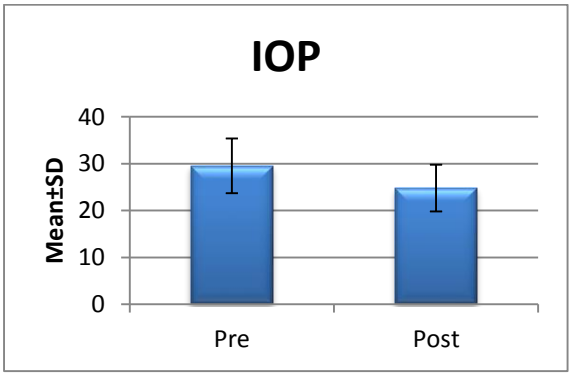

Figure (4): Mean IOP changes before and after the procedure in graphic form. Now, we divide the patients into four groups according to grading system of iris neovascularization: shown in (Table **5** and Figure **5)**.

Table (5): Number of patients according to iris neo-vascularization

INV class	No.	%
Grade 1	4	26.7
Grade 2	4	26.7
Grade 3	3	20.0
Grade 4	4	26.7

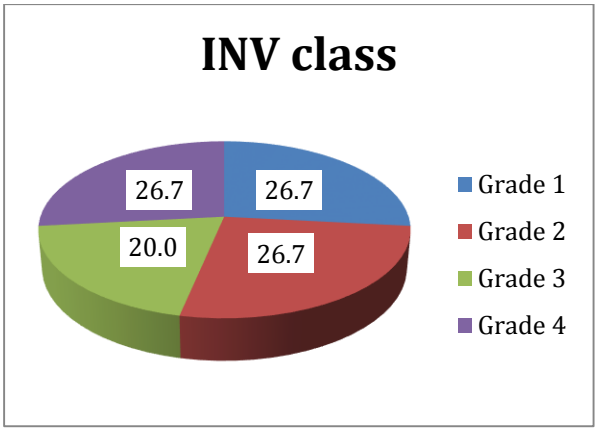

Figure (5): Number of patients according to grades of iris neo-vascularization.

Then we inject bevacizumab intracamerally (Figure **6**).

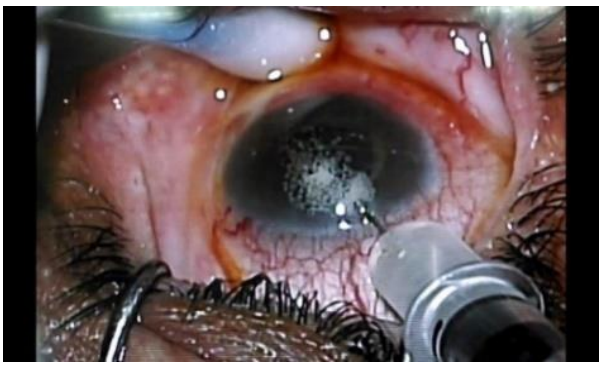

Figure (6): bevacizumab being injected Intracamerally.

Then we followed up all the 15 patients after, one, three and six months and the results are showed in table **7** and figure **7**.

Table (7): The visual acuity of the patients after the procedure

Visual acuity post procedure	No.	%
Stable	12	80.0
Decreased	3	20.0

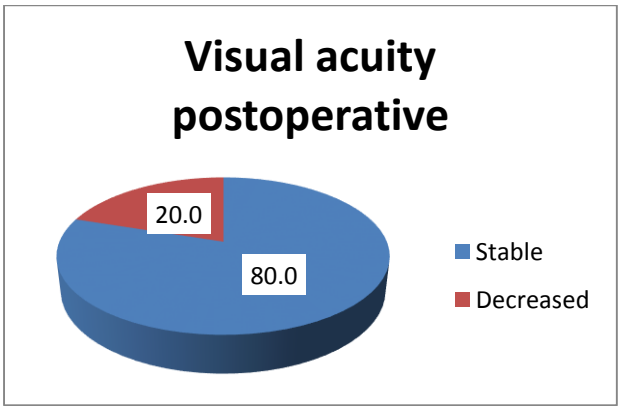

Figure (7): The visual acuity of all patients after the procedure.

Table (8): The mean changes in all grades of iris neo-vascularizations

	INV class							
	Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
INV 1 month								
No response	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**4**	**100.0**
Partial regression	**0**	**0.0**	**0**	**0.0**	**3**	**100.0**	**0**	**0.0**
Regression	**4**	**100.0**	**4**	**100.0**	**0**	**0.0**	**0**	**0.0**
INV 3 months								
No response	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**4**	**100.0**
Regression	**4**	**100.0**	**2**	**50.0**	**0**	**0.0**	**0**	**0.0**
Recurrence	**0**	**0.0**	**2**	**50.0**	**3**	**100.0**	**0**	**0.0**
INV 6 months								
No response	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**4**	**100.0**
Regression	**4**	**100.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**
Recurrence	**0**	**0.0**	**4**	**100.0**	**3**	**100.0**	**0**	**0.0**

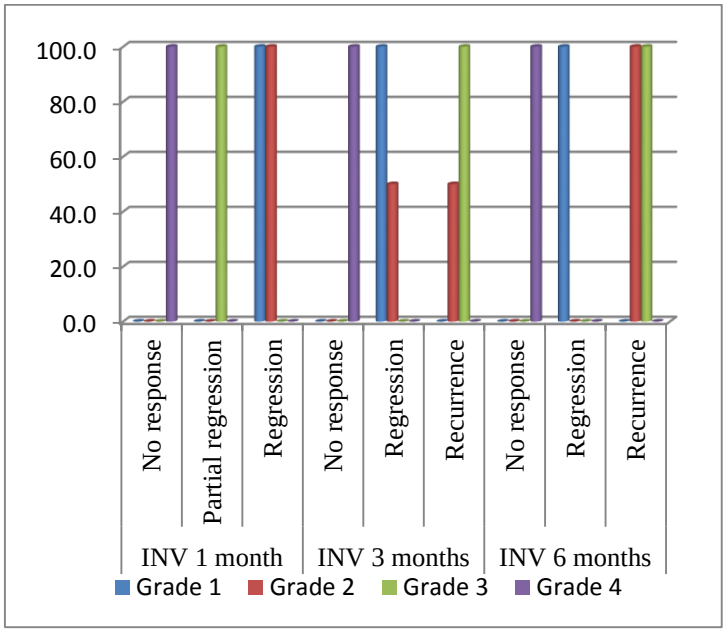

Fig (8): The mean changes in all grades of iris neo-vascularizations

DISCUSSION

The aim of our study is comparing the results of Intracameral injection of bevacizumab in patients of neovascular glaucoma as regard visual acuity and intraocular pressure.

There are other studies reporting the effect of bevacizumab on iris neovascularization including, **Grisanti *et al.*[10]** (Germany) and **Chalam *et al.*[11]** (USA) used the Intracameral route to inject bevacizumab (ICB). While **Oshima *et al.*[12]** (Japan) and **Avery *et al.*[13]** (USA) used the Intravitreal route to inject bevacizumab (IVB).

In the studies that used the intracameral route to inject bevacizumab, **Chalam *et al.*[11]** studied 16 eyes of 15 patients; nine eyes (56%) of the 16 eyes had neovascular NVG. While, **Oshima *et al.*[12]** studied 7 eyes of 5 patients; 6 eyes (85.7%) of them had NVG.

When we compared the results of the bevacizumab injection in eyes with iris neovascularization in the different studies, there was general agreement that there was regression of new vessels occurs in the majority of patients, as early as 24 hours to 1 week following the injection[11]. In **Chalam *et al.*[11]** study, the early results of iris neovascularization after one day of injection were regression of iris neovessels in 15 eyes (94%) and in 8 eyes (89%) with NVG. (Only one eye with neovascular glaucoma didn't show regression).

The leakage in iris fluorescein angiography had noted to diminish as early as 24 hours after injection in all cases (100%) in **Oshima *et al.*[12]** and **Avery *et al.*[13]** studies.

Grisanti *et al.*[10] study showed decrease in leakage detected in all eyes as early as one day after injection, no inflammation was observed and no relapses were seen within the follow-up of four weeks. It might be due to the PRP that was given to all patients, decreases the recurrence of iris neo-vessels by permanent burning to the ischemic areas of VEGF production. So, it cuts the cycle of continuous VEGF production.

The neovascularization in **Chalam *et al.*[11]** study resolved within one week in 9 eyes (56%) and within 2 weeks in 14 eyes (87.5%). No complications or adverse events were associated with the treatment. Two eyes (12.5%) in the series received a repeated injection after one month for recurrent iris neovascularization. Iris angiography (IFA) was performed in 12 eyes (75%) and showed complete resolution of the iris neovascularization in 6 eyes. Four eyes benefited with a 2-grade improvement, and a 1-grade change occurred in two eyes. Better results gained with low grades of rubeosis iridis.

CONCLUSIONS

Regression of iris neovascularization was inversely proportional to the pre-injection grade. It was found that lower grades were associated with a better response. Intracameral bevacizumab prevents the progression of lower grades of iris neovascularization to higher grades of neovascular glaucoma. There is Stabilization of intraocular pressure in early grades of iris neovascularization. Finally advanced grades of neovascular glaucoma showed a very poor response to Intracameral bevacizumab as regards the effect on stabilization of the intraocular pressure and on the upgrading of iris neovascularization.

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REFERENCES

1. **Tsai JC and Shields MB (2000):** Neovascular glaucoma. In: Tombran Tink J, Barnstable CJ (Eds). Ophthalmology: Ocular Angiogenesis: Diseases, Mechanisms, and Therapeutics. Totowa, NJ: Humana Press Inc., 105:232-236.
2. **Tripathi RC, Li J, Tripathi BJ *et al*. (1998):** Increased level of vascular endothelial growth factor in aqueous humor of patients with neovascular glaucoma, Ophthalmology, 105:232-237.
3. **Tombran-Tink J and Barnstable CJ (2003):** Therapeutic prospects for PEDF: more than a promising angiogenesis inhibitor. Trends Mol Med., 9:244-50.
4. **Madsen PH (1999):** Ocular findings in 123 patients with diabetic retinopathy. Doc Ophthalmol., 29:331-345.
5. **Philteos J, Bedi H, Ing E (2019):** Morning Rounds. The Eyelid Lump that wouldn't go away. EyeNet, 23(6): 35-37.
6. **Hahn R, Sacu S and Michels S *et al*. (2007):** Intravitreal bevacizumab versus verteporfin and intravitreal triamcinolone acetonide in patients with neovascular age-related macula degeneration (in German). Ophthalmologe, 104:588–593.
7. **Costa RA, Jorge R and Calucci D *et al.* (2006):** Intravitreal bevacizumab for choroidal neovascularization caused by AMD (IBeNA Study): results of a phase 1 dose escalation study. Invest Ophthalmol Vis Sci., 47:4569–4578.
8. **Artunay O, Yuzbasioglu E and Rasier R *et al.* (2009):** Incidence and management of acute endophthalmitis after intravitreal bevacizumab (Avastin) injection. Eye (Lond), 23:2187–2193.
9. **Laatikainen L (1979):** Development and classification of rubeosis iridis in diabetic eye disease.Br J Ophthalmol., 63:150-6.
10. **Grisanti S, Biester S, Peters S, Tatar O, Ziemssen F, Bartz-Schmidt KU and Tuebingen Bevacizumab Study Group (2006):** Intracameral bevacizumab for iris neovascularization Am j ophthalmol., 142(1): 158-60.
11. **Chalam KV (2004):** Intracameral bevacizumab (Avastin) in treatment of proliferative diabetic retinopathy ophthalmo., 100(10):1675.e1-20.
12. **Oshima Y, Sakaguchi H, Gomi F, Tano Y (2006):** Regression of iris neovascularitzaions after Intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy. Am J Ophthalmol., 18:155-158.
13. **Avery RL, Pearlman J, Pieramici DJ *et al.* (2006):** Intravitreal bevacizumab (Avastin) in treatment of proliferative diabetic retinopathy. Ophthalmology, 113(10): 1695.e1-15.