MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 5(10) pp. 511-518, October, 2017
Available online http://www.meritresearchjournals.org/mms/index.htm

Original Research Article

Therapeutic options in secondary neovascular glaucoma

D. M. Stanilă[1,2,3], Alina-Adriana Panga[1,3]* and Adriana Stanilă[1,2,3]

[1]Clinical Emergency County Hospital Sibiu,

[2]Faculty of Medicine, "Lucian Blaga" University of Sibiu

[3]Ocular Surface Research Center Sibiu

***Corresponding Author's E-mail: aliapaly@yahoo.com**
Tel. +40740407918

Abstract

Neovascular glaucoma is a severe type of secondary glaucoma caused by a variety of disorders, most common being diabetic retinopathy, central or branch vein occlusion or vascular ischemic syndrome, and is characterized by fine arborizing blood vessels on the surface of the iris, pupil margin, and trabecular meshwork, which are accompanied by a fibrous membrane. The aim of the study is to show different methods of treatment and follow-up in neovascular glaucoma. We studied a number of 40 cases with neovascular glaucoma caused by the following conditions: diabetic retinopathy, central vein occlusion and ocular ischemic syndrome. In all cases, there was performed trabeculectomy with antimetabolites (Mitomycin C, 5-Florouracil), and antifibrotic agent Interferon alfa-2b. Beside this surgical procedure, we associated panretinal photocoagulation and intravitreal injection with Bevacizumab. In most cases we managed to preserve the remaining vision and reduce the pain, and there were no cases in which evisceration were needed. Interferon was useful in preserving the filtering bleb. Neovascular glaucoma is a very difficult pathology and is very hard to manage. To avoid complete irreversible visual loss of side, the treatment should begin very early. The use of panretinal photocoagulation and intravitreal injection can reduce the neovascularization of the iris and normalize the IOP. Surgery with antimetabolites and antifibrotic agents is important to avoid the bleb fibrosis, and in most of the cases the IOP was preserved for a long period of time.

Keywords: Neovascular glaucoma, Iris neovascularization, Trabeculectomy, Interferon alfa-2b

INTRODUCTION

Neovascular glaucoma (NVG) is a severe type of secondary glaucoma caused by a variety of disorders, most common being diabetic retinopathy, central or branch vein occlusion (CRVO) or vascular ischemic syndrome [10], and is characterized by fine arborizing blood vessels on the surface of the iris, pupil margin, and trabecular meshwork, which are accompanied by a fibrous membrane.

Vascular endothelial growth factor (VEGF) is usually released after retinal ischemia, and it can spread through the aqueous humor to the anterior segment of the eye (Borgman, 2014; Olmos and Lee, 2011). This result in the neovascularization of the iris, angle and connective tissue membrane is followed by synechia of the peripheral iris and trabecular meshwork, which can ultimately cause increased intraocular pressure(IOP) or even loss of vision (Haverly, 2010; Sun et al., 2016).

The natural course of neovascular glaucoma follows three distinct stages, with associated changes in IOP: (1) Rubeosis- angiogenic factors released as a response to retinal ischemia diffuse into the anterior segment and lead to angiogensis from existing vasculature of the iris

and neovascularisation of the angle of the anterior chamber. IOP is usually normal at this stage. (2) Secondary open-angle glaucoma- raised IOP results from a fibrovascular membrane arising from increasing angle neovascularisation, which reduces trabecular meshwork drainage. (3) Secondary angle-closure glaucoma- continued anterior chamber neovascularisation and subsequent contraction of the fibrovascular membrane causes progressive closure of the anterior chamber angle. Circumferential pulling of the iris over the trabecular meshwork results in very high IOP (Rodrigues and Sheng, 2016).

The purpose of the present study is to show different methods of treatment and follow-up in neovascular glaucoma.

METHODS

We conducted a retrospective study on a number of 40 cases with 43 eyes, hospitalized in the Clinical County Hospital of Sibiu, Romania, for a period of 6 years (September 2010- September 2016) with neovascular glaucoma caused by the following conditions: diabetic retinopathy - 24 cases, patients with longstanding diabetes, proliferative diabetic retinopathy (PDR), especially with optic disc neovascularization, central vein, or branch vein occlusion – 12 cases. The incidence of iris neovascularization in neovascular glaucoma to CRVO patients was significantly correlated with the extension of retinal capillary nonperfusion. With central retinal artery obstruction (CRAO), there were 2 cases and for carotid stenosis, there were 2 cases. Carotid artery obstructive disease is the third most common cause of NVG.

The inclusion criteria for the patients in the study were: NVG was caused by retinal vascular diseases, IOP > 24 mmHg, iris and angle neovascularization, angle closed.

Data collected included, age, history of vascular disease, glaucoma treatment, the best-corrected visual acuity (BCVA) pre-operatively and post-operatively, the IOP before and after surgery. The amount of IOP reduction after surgery was described as the percentage of IOP reduction from the pre-operative IOP and the IOP after surgery and three months later. Surgical success were defined as IOP< 21 mmHg at 3 months after surgery, either with glaucoma medications or without glaucoma medications. IOP readings were taken using usually I-Care tonometer and aplanotonometer.

The visual acuity was tested with the Snellen chart using the patients' spectacles if horn, the best vision achieved (BCVA) being recorded. In patients with light perception or no light perception the important criteria was the IOP and pain reduction.

The surgical technique that we approached was trabeculectomy with antimetabolite and antifibrotic agent application on the trabecular meshwork. The antimetabolites that we used were Mitomycin C, 5 Fluorouracil and the antifibrotic agent was Interferon alfa-2b. We made a scleral flap of trapezoidal shape with a length of 8-10 mm and a width of 4-6mm preferably a thickness of about 1/3 of the thickness of the sclera. We consider that a thin flap is helpful in maintaining long-term filtrate. For 3 minutes, we were applying the antimetabolite or the antifibrotic agent soaked on a cotton swab. The trabecular meshwork was sent for histopathological analysis. The histopathological analysis was made in the Department of Pathological Anatomy within the Clinical County Hospital of Sibiu.

RESULTS

Depending on the etiology of GNV, we conducted a treatment plan that was medical, laser and surgical. The first measure that we adopted was to assess the condition of the patient, by carrying out the blood exams and other examinations. Twenty four patients presented long standing diabetes over 10 years with decompensation and hypertension and developed PDR. The general treatment of diabetes and hypertension was initiated after preliminary examination of the patient by a cardiologist and a diabetes specialist. To treat the patients with NVG we elaborated an algorithm of treatment (Figure 1).

Medical therapy

Pharmacological treatment of elevated IOP is usually accomplished with aqueous suppressants. Local ocular hypotensive therapy was made with fixed combinations of carbonic anhydrase inhibitors and beta blockers, alpha-adrenergic agonist, and for putting at rest ciliary body and reduce the pain we administrated atropine, cyclopentolate and anti-inflammatory topical agents (Steroids, Nonsteroids). Systemic therapy with acetazolamide was used to drop the aqueous humor production and osmotic agents to reduce the vitreous volume. Antalgic agents and anti -inflammatory agents were used to reduce the inflammation and pain.

Laser therapy

Panretinal photocoagulation was performed in 17 cases with 20 eyes with PDR and 12 cases with CRVO, where ocular membranes were transparent. In cases with PDR, focal photocoagulation or grille fotocoagulation were made in the interested area. The laser was first applied avoiding the center of the retina, near the macular zone with a spot of 50-100 microns and intensity up to 100 mW. If there was macular edema and the macular zone had thickness over 400 µ, we performed intravitreal injections with bevacizumab, and when the macular thickness was under 400 µ we continued the laser

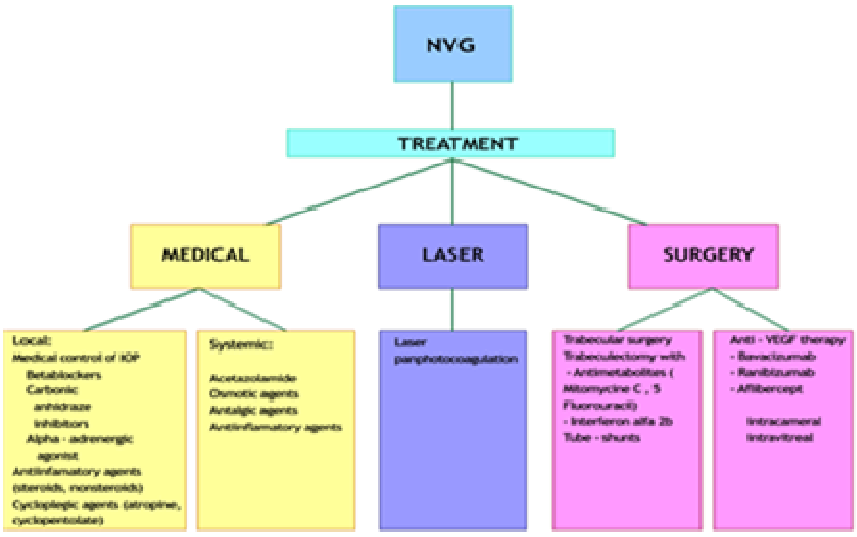

Figure 1. Treatment algorithm

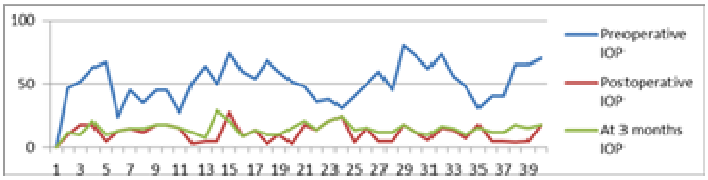

Figure 2. The values of the IOP before the surgery, after surgery and at 3 months

treatment. The photocoagulation was conducted in three sessions and began with the lower retinal area and continued with upper zone, then nasal and temporal zone with a spot of 250 µ and variable intensity up to 100 mW and 100 ms. In the CRVO eyes, panphotocoagulation was performed in the adjacent area of the occluded vein with a spot of 250- 500 µ and a time of 200 ms and variable intensity until we got a blue grey spot. If photocoagulation could not be completed because of hemorrhaging in the retinal surface, anti-VEGF therapy was repeated every month until the blood was absorbed to complete photocoagulation.

Surgical treatment

Beside this surgical procedure, we associated panretinal photocoagulation and intravitreal injection with bevacizumab. We performed intravitreal and intracameral injections with bevacizumab and triamcinolone intravitreal preoperatively within one week before surgery to reduce bleeding complication by causing regression of the neovascular vessels, which tend to be more fragile and leaky. Anti-VEGF has a short half-live up to 20 days. After surgery, for the reactivation of the neovascularization process, we repeated the intraocular injections with bevacizumab between 4 and 8 weeks. The frequency of intravitreal injections was related to the fundus examination and the thickness of macula by macular OCT. After the treatment algorithm that we applied in this study, we observed that the average preoperative IOP was 52.17 mmHg; postoperative IOP was 11.6 mm Hg and at 3 months after surgery, it increased to 15.05 mmHg. We noticed that the average IOP before surgery was very high and decreased by 40.57 mmHg after surgery at 3 days and was maintained 3 months later (Figure 2). The percentage of IOP reduction was the result of pressure difference between the highest IOP measured preoperatively, postoperatively and 3 months after surgery. IOP decrease percentages were divided into 3 groups: <50% decrease from the initial IOP, there were 6 cases, between 50-75% - 20 cases, >75% decrease in IOP there were 14 cases. The results in IOP reductions after the treatment algorithm that we followed were very good, over half of the group that we study recorded an important decrease in IOP with good results after 3 months of follow up. Statistical analysis shows a significant positive relationship regarding the Pearson's correlation coefficient r =0.509840554 low value and p = 0.000777981, which is <0.05 and rejected the null hypothesis, which assumes a statistical significance (Table 1).

Table 1. Statistical analysis

Regression	*Statistics*
Pearson r	0,509840554
R Square	0,25993739
Adjusted R Square	0,240462058
Standard Error	5,833960054
Observations	40

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	454,2665833	454,2666	13,347007	0,000777981
Residual	38	1293,333417	34,03509		
Total	39	1747,6			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95,0%*	*Upper 95,0%*
Intercept	0,258407301	3,238575787	0,07979	0,936822682	-6,297746565	6,814561	-6,29775	6,814561
X Variable 1	0,753594199	0,206274528	3,653356	0,000777981	0,336013252	1,171175	0,336013	1,171175

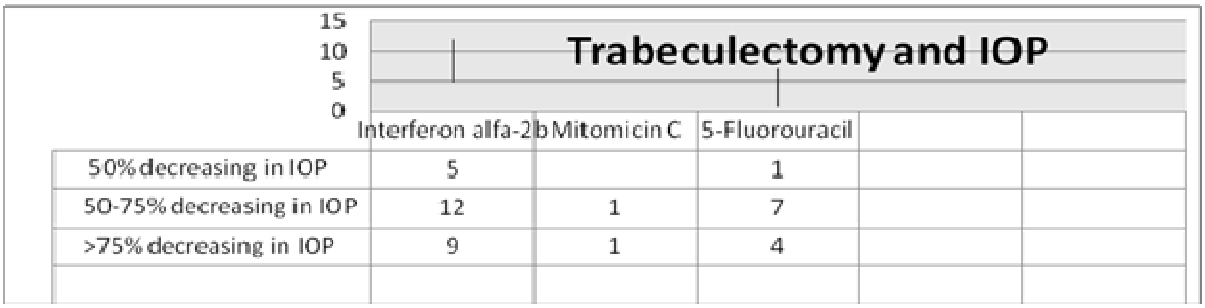

Figure 3. Percentage of decrease in IOP reported in the type of substance used in trabeculectomy

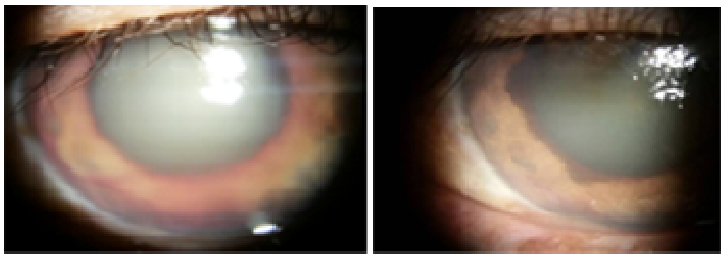

Figure 4. Slit lamp examination A- right eye, B-left eye

Regarding visual acuity, improvements were registered only in 11 cases; patients have won one or two rows in the
Snellen chart. In the study group, 12 patients presented no light perception at the moment that the treatment was initiated, so we did not have positive results in 29 cases regarding improvement in visual acuity.

We have not found significant changes related to lowering IOP in accordance with the substance applied to the scleral meshwork while performing trabeculectomy indicating that interferon alfa 2b through its antifibrotic properties is an option filtering surgery in GNV (Figure 3).

Case 1

R.M.F, age 55 –year old, type 2 Diabetes mellitus with Insulin three times a day and oral anti-diabetic drugs, Hypertension, BCVA RE- 0.14 with correction , LE- nlp, IOP RE- 49 mmHg, IOP LE-65 mmHg, both eyes with iris neovascularization and Diabetic proliferative retinopathy (Figure 4,5).

At first, the treatment was medical locally and generally to drop the high IOP, then we performed intravitreal injections, and in the anterior chamber injections with bevacizumab one week before surgery.

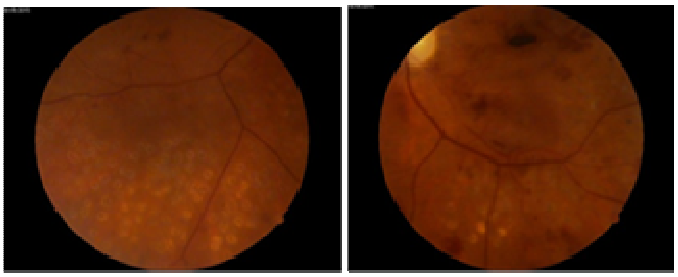

Figure 5. Fundus examination A- right eye, B-left eye

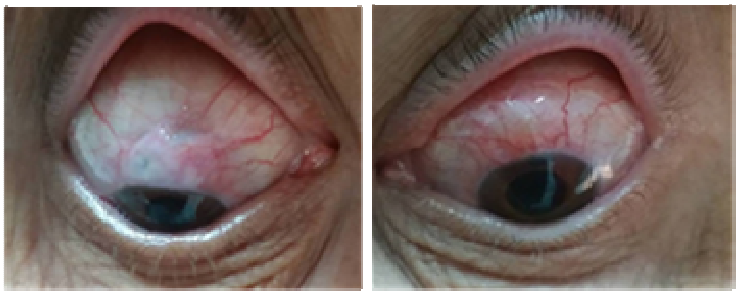

Figure 6. The aspect of filtration bleb to 1 year and a half after trabeculectomy with Interferon alfa-2b A- right eye, B-left eye

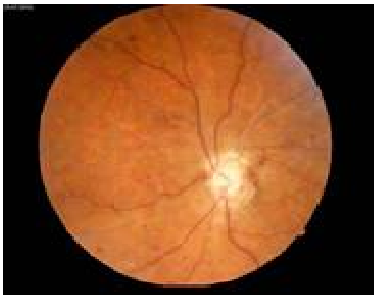

Figure 7. Fundus examination left eye

The IOP was still high so we conducted surgery in the left eye (LE) trabeculectomy with antifibrotic agent Intereferon alfa-2b.

After surgery, the IOP was of 11 mmHg in the right eye and 6 mmHg in the left eye. One month later, the patient presented the decompensation of RE. BCVARE-cf, LE-nlp, IOP RE- 38 mmHg, IOP LE- 16 mmHg, pain and we also performed surgery in the RE with antifibrotic agent Interferon alfa-2b (Figure 6).

Case 2

G.V., M, age 63, hypertension, Carotid artery disease, Ischemic ocular syndrome, (Figure 7,8) RE- nlp, BCVA LE-0.04 nc, IOP RE- 46 mmHg, IOP LE- 53 mmHg, Intravitreal Bevacizumab one week before surgery, Trabeculectomy with antimetabolite Mitomycin C. After surgery, the BVCA LE- 0.1 cc, IOP LE- 9 mmHg, clear cornea (Figure 9).

Case 3

J.S., male, 63-year old, with history of CRVO in RE and one intravitreal injection with Bevacizumab three months before, Hypertension, type 2 Diabetes mellitus, BCVA RE-cf nc, BCVA LE- 1 with correction, IOP RE- 40 mmHg, IOP LE- 18 mmHg (Figure 10).

Treatment plan was medical with a view to lower IOP. After the medical treatment, we performed one intravitreal injection with Bevacizumab, then trabeculectomy with Interferon alfa-2b.

After surgery, the BCVA RE – 0.02 nc, and the IOP-5 mmHg, cornea was clear, 0.5 mm hypema (Figure 11).

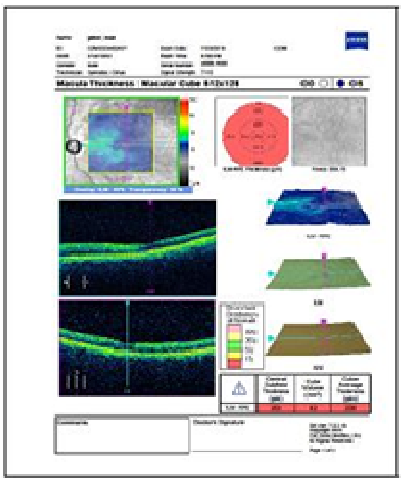

Figure 8. OCT appearance shows a low thickness of the retina in the macular zone

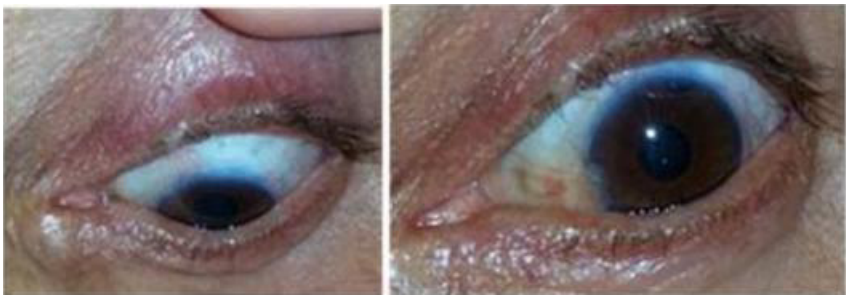

Figure 9. Filtration bleeb to 3 months after trabeculectomy with Mitomicin C left eye A- white flat filtration bleb, B- peripheral iridectomy at one o'clock

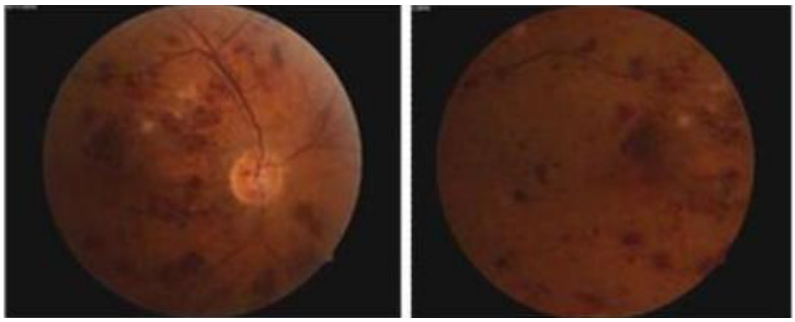

Figure 10. Fundus examination in right eye reveals multiples hemorrhages disseminated across the entire surface of the retina A - optic disc nerve B - the periphery of the retina

Three months later, the BCVA - RE was 0.2.

DISCUSSIONS

Conjunctival and subconjunctival fibrogenesis and inflammation are side effects that can occur in glaucoma filtration surgery (Yamana et al., 2015). In this study, based on the antifibrotic proprieties of interferon alfa-2b mentioned in the literature in some studies on laboratories animals (Gillies et al., 1993) and also on topic medication for the treatment for intraepithelial neoplasia (Karp et al., 2001) and in order to prevent the fibrosis of Tenon's capsule (Falavarjani and Nguyen, 2013) and to prevent the pterygium recurrence (Esquenazi, 2005) and also in subconjunctival injection to

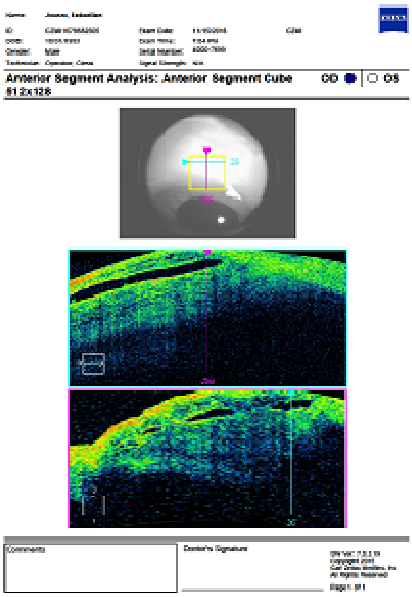

Figure 11. The OCT appearance of anterior segment of the right eye at 3 months after surgery - filtration bleb

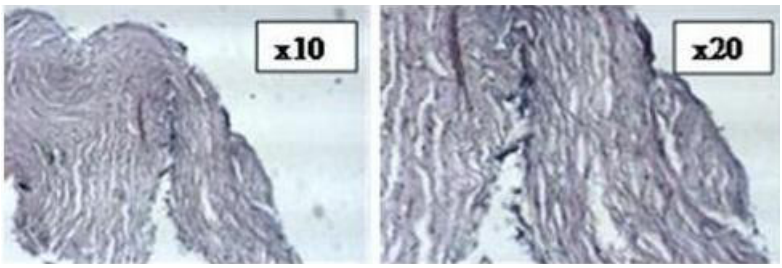

Figure 12. Microscopic observation of NV trabecular meshwork- with mild inflammatory infiltration after surgery with no application of any antimetabolite or antifibrotic agent. A- x 10 magnification, B- x20 magnification

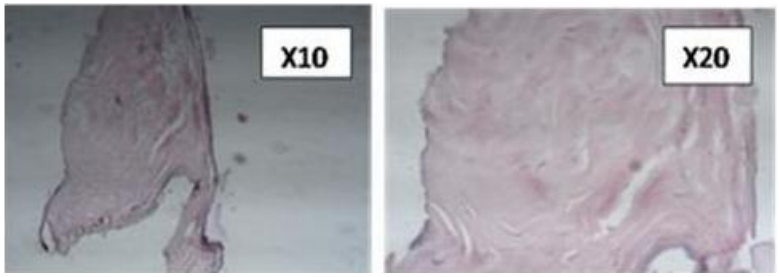

Figure 13. Microscopic observation of NV trabecular meshwork after application of Interferon alfa-2b with the histological result of small piece of tissue made up of an acellular hyaline material spaces, A- x10 magnification, B- x20 magnification

reduce the risk of failure in glaucoma filtering surgery (Gillies et al., 1999) we used the interferon alfa- 2b on the scleral bed under the flap to prevent the risk of failure of filtration bleb.

Histopathological analysis of trabecular meshwork

The histopathological analysis of trabecular mesh-work with no application of antifibrotic agents and with

application of Interferon alfa-2b showed that the application of Interferon alfa-2b reduces the local inflammation that can lead to the possible fibrosis of the filtration bleb (Figure 12, 13).

Interferons inhibit chemotaxis and proliferation of fibroblasts and collagen production as well. The role of interferon alfa -2b in the treatment of ocular fibrosis was demonstrated in animal studies. Also, we had good results in this study (Gillies et al., 1993)

In these two cases, we performed a second trabeculectomy because the IOP was high (Nakano et al., 2016) and the patients presented pain and decompensation of ocular surface with corneal edema at 6 months after the first trabeculectomy (Rossi, 2014).

Bleeding in the anterior chamber occurred in some cases (Nakatake et al., 2014). Massive bleeding did not occur as a result of pre- and postoperative anti-VEGF treatment (Falavarjani and Nguyen, 2013). Six eyes had mild anterior chamber bleeding that regressed within 1 week after the surgery.

In 28 cases, we managed to preserve the remaining vision and reduce the pain in 11 cases we had an improvement and in 12 cases with no light perception we reduced the pain and maintained the anatomical integrity of eye ball so that the quality of the patients life was improved (Liao et al., 2016).

CONCLUSIONS

Neovascular glaucoma is a very difficult pathology and is very hard to manage.To avoid completed irreversible visual loss of side, the treatment should begin very early. The use of panretinal photocoagulation and intravitreal injection, beside the surgery, can reduce the neovascularization of the iris and normalize the IOP. We suggest managing the neovascular glaucoma according to a good algorithm of treatment.

Surgery with antimetabolites and antifibrotic agent is important to avoid the bleep fibrosis, and in most of the cases the IOP was preserved for a long period of time. Interferon alfa-2b applied under the scleral flap during trabeculectomy may be a good solution in filtration surgery in NVG.

ACKNOWLEDGEMENT

We have no conflict of interest to declare.

REFERENCES

Borgman CJ (2014). Neovascular Glaucoma: A Serious Secondary Condition, OD, Review of Optometry. https://www.reviewofoptometry.com /ce/neovascular-glaucoma-a-serious-secondary. Accessed 13 Jan 2017

Esquenazi S (2005). Treatment of early pterygium recurrence with topical administration of interferon alpha-2b, CJO 40:185-187 http://www.canadianjournalofophthalmology.ca/article/S0008-4182(05)80031-6/pdf Accessed Sep 2010.

Falavarjani KG, Nguyen QD (2013). Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature, Eye (Lond) 27(7):787-94. doi: 10.1038/eye.2013.107. Epub 2013 May 31

Gillies M, Su T, Sarossy M, Hollows F (1993). Interferon-alpha 2b inhibits proliferation of human Tenon's capsule fibroblasts, Department of Ophthalmology Pince of Wales Hospital Ranwick, Auastralia.

Gillies MC, Goldberg I, Young SH, Su T (1993) Glaucoma filtering surgery with interferon alfa 2b. JGlaucoma 2:229-235

Gillies MC, Morlet N, Sarossy MG (1999). Treating ophthalmic fibrosis using interferon-.alpha, Sydney, Australia

Haverly RF (2010). Surgical Management of Neovascular Glaucoma, FACS, Tech Ophthalmology, September 8:87-93

Karp CL, Moore JK, Rosa RH Jr (2001). Treatment of conjunctival and corneal intraepithelial neoplasia with topical interferon alpha-2b. Ophthalmology 108:1093-8 https://www.ncbi.nlm.nih.gov/pubmed/113 82635 Accessed Sep 2011

Liao N, Li C, Jiang H, Fang A,Zhou S, Wang Q (2016) Neovascular glaucoma: a retrospective review from a tertiary center in China, BMC Ophthalmol 16:14. doi: 10.1186/s12886-016-0190-8

Malhotra R, Gregory-Evans K (2000) Management of ocular ischaemic syndrome. Br J Ophthalmol 84:1428-1431

Nakano S, Nakamuro T, Yokoyama K, Kiyosaki K, KubotaT (2016) Prognostic Factor Analysis of Intraocular Pressure with Neovascular Glaucoma, J. Ophtalmol. https://www.hindawi.com/journals/joph/2016/1205895/ Accessed 20 Dec 2016

Nakatake S, Yoshida S, Nakao S, Arita R, Yasuda M, Kita T, Enaida H, Ohshima Y, Ishibashi T (2014). Hyphema is a risk factor for failure of trabeculectomy in neovascular glaucoma: a retrospective analysis, BMC Ophthalmol 26:14:55. doi: 10.1186/1471-2415-14-55

Rodrigues AI, Sheng L (2016) Reversing the rubeotic rampage – Current approaches in the management of neovascular glaucoma, European Ophthalmic Review, 10(1):19–21. doi: http://doi.org/10.17925/EOR.2016.10.01.19

Rossi GCM (2014) Diagnosis and Treatment Methods for Ocular Surface Disease in Glaucoma, European Ophthalmic Review 8(1):40. doi: http://doi.org/10.17925/EOR.2014.08.01.40

Sun Y, Liang Y, Zhou P, Wu H, Hou X, Ren Z, Li X, Zhao M (2016) Anti-VEGF treatment is the key strategy for neovascular glaucoma management in the short term, Sun et al. BMC Ophthalmology 16:150

Yamana O, Kitano-Izutani A, Tomoyose K, Reinach PS (2015) Pathobiology of wound healing after glaucoma filtration surgery, BMC Ophthalmology 15(Suppl 1):157. doi: 10.1186/s12886-015-0134-8 http://bmcophthalmol.biomedcentral.com/articles/10.1186/s12886-015-0134-8. Accessed 20 Dec 2016