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ORIGINAL RESEARCH

Intravitreal bevacizumab with or without mitomycin C trabeculectomy in the treatment of neovascular glaucoma

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Hatem M Marey
Amin F Ellakwa

Department of Ophthalmology, Faculty of Medicine, Menoufiya University, Shibin el Kom, Egypt

Purpose: To demonstrate the role of intravitreal bevacizumab in regression of iris neovascularization, and intraocular pressure (IOP) control in neovascular glaucoma.

Methods: A retrospective random case series study was performed. Twenty eyes of 20 patients who presented with neovascular glaucoma were treated with intravitreal bevacizumab 2.5 mg in 0.1 mL. Retinal photocoagulation was performed for all cases as soon as possible after intravitreal injection and subscleral trabeculectomy with mitomycin C 0.4 mg/mL for 3 minutes for cases having peripheral anterior synechiae. Cases were followed up for 12 months when regression of iris neovessels, IOP control, improvement in visual acuity, and success of filtering surgery were recorded.

Results: All cases showed complete regression of iris neovessels at 2 months after injection; recurrence of iris neovessels was observed in 4 cases (20%) at 4 months and in 14 cases (70%) at 8 months follow-up. The mean IOP dropped from 41.45 ± 5.89 mmHg preoperatively, to 19.3 ± 5.5 mmHg and 17.75 ± 3.74 mmHg at 6 months and 12 months postoperatively, respectively. The success rate of subscleral trabeculectomy with mitomycin C after intravitreal bevacizumab was 77.8%. Visual acuity was improved in 17 cases (85%) from preoperative 0.12 ± 0.11 to 0.26 ± 0.2 postoperative.

Conclusion: Intravitreal bevacizumab has a role in regression of iris neovessels and IOP control in neovascular glaucoma cases and also in increasing the success rate of subscleral trabeculectomy with mitomycin C; however this role has a limited time and reinjection is needed to maintain this effect.

Keywords: bevacizumab, intravitreal injection, mitomycin C, neovascular glaucoma, subscleral trabeculectomy

Introduction

Ischemic retinopathies can cause new vessel growth on the iris surface and in the anterior chamber angle, which can lead to neovascular glaucoma (NVG). Dysregulation of vascular endothelial growth factor (VEGF), a mitogen specific for vascular endothelial cells, has been implicated in several ocular diseases, including diabetic retinopathy and exudative age-related macular degeneration (AMD).[1,2]

NVG is an optic neuropathy caused by increased intraocular pressure (IOP), which results from secondary angle closure due to the growth of a neovascular membrane in the anterior chamber and trabecular meshwork.[3,4]

Most cases of NVG are caused by ischemic retinal diseases, such as diabetic retinopathy and central or branch retinal vein occlusions.[4]

The management of NVG includes lowering IOP (often surgically) and pan retinal photocoagulation (PRP), which reduces the production of vasoproliferative factors by

Corrrespondence: Amin F Ellakwa
Department of Ophthalmology, Faculty of Medicine, Menoufiya University, Shibin el Kom, Egypt
Email ellakwah@hotmail.com

ischemic retina and can induce regression of anterior segment neovascularization.[5]

Bevacizumab is a neutralizing anti-VEGF recombinant humanized monoclonal antibody that is approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer and nonsmall cell lung cancer.[6]

Intravitreal bevacizumab (IVB) is used in an off-label fashion to treat VEGF-mediated ocular conditions such as choroidal revascularization secondary to AMD, diabetic macular edema, and central retinal vein occlusion-associated macular edema.[7–9]

Intravitreal bevacizumab was used in this study to evaluate its role in NVG.

Patients and methods

A retrospective random case series study was performed to demonstrate the role of IVB in regression of iris neovascularization, control of IOP, and its effect on the result of subscleral trabeculectomy with mitomycin C. The studied group consisted of 20 eyes of 20 patients presented with iris neovascularization and increased IOP as a complication of proliferative diabetic retinopathy or central retinal vein occlusion. Ocular examination included visual acuity (VA) assessment, slit lamp examination, gonioscopy, applanation tonometry, and indirect ophthalmoscopy.

All patients received IVB 2.5 mg in 0.1 mL after diagnosis of NVG. Intravitreal injection was performed as follows: eye speculum was applied, and conjunctival disinfection with 5% bovidine iodine, routine eye draping, and then intravitreal injection were done in the lower outer quadrant 3.5–4 mm posterior to the limbus.

Retinal photocoagulation was performed for all cases as soon as possible after intravitreal injection; laser was applied in 3–5 sessions with 250 μm spot sizes, at 200–450 mw power with the aim of completing 360° scatter PRP with a range of 1000–1500 total shots.

All cases were followed up for 2 weeks for regression of iris neovascularization (NVI), then the 9 cases with preinjection peripheral anterior synechiae (PAS) were treated by subscleral trabeculectomy (SST) as follows: fornix based conjunctival flap, one half thickness scleral flap 4 × 3 mm were performed, 2 sponges 2 × 2 mm soaked with 0.4 mg/mL mitomycin C were applied over the dissected bed, the scleral flap and the conjunctiva were draped over the sponges for 3 minutes, then sponges were removed and the bed was irrigated thoroughly with 50 mL balanced salt solution.

The trabecular block was then removed and a peripheral iridectomy was performed, the scleral flap was closed with 2 × 10/0 nylon stitches 1 at each side of the flap, the conjunctiva was closed with 2 × 8/0 vicryl sutures, and combined antibiotic-steroid drops (tobramycin 0.3% with dexamethazone 0.1%) and atropine drops were applied.

Postoperatively, combined antibiotic–steroid drops (tobramycin 0.3% with dexamethazone 0.1%) were applied 6 times a day for 4 weeks and atropine drops were applied 3 times a day for 2 weeks.

All patients were followed up for 1 week, 1 month, 3 months, 6 months, and 12 months after injection; cases of recurrence of NVI were reinjected with the same dose of IVB at the fourth month and then at the eighth month and follow-up was completed as regular. Medical treatment was applied to control the IOP for nonoperative cases and operative cases not controlled after surgery using topical beta blockers then combined topical beta blockers and carbonic anhydrase inhibitors (CAIs). Results were collected, tabulated, and statistically analyzed by statistical package SPSS version 19.

Results

The study included 20 eyes of 20 different patients, 8 males and 12 females, with a mean age of 58.4 ± 0.99 (range 50 to 65 years). Mean preoperative VA was 0.1 ± 0.1 and the mean IOP was 41.45 ± 5.89 mmHg, and NVI was present in all cases. The descriptive statistics of the preinjection and follow-up data are shown in Table 1.

Peripheral anterior synechiae were present in 9 cases (45%). The causes of retinal ischemia and NVI were proliferative diabetic retinopathy in 13 cases (65%), and central retinal vein occlusion in 7 cases (35%).

Two weeks postinjection, all cases showed regression of neovessels, 14 cases (70%) showed complete regression, 6 cases (30%) showed partial regression, and there was no change in the angle PAS present in the 9 cases for which SST with mitomycin C was performed with a success rate of 77.8%. (Criteria for success were IOP ≤ 21 mmHg with or without medications, and a functioning bleb.)

Table 1 Descriptive statistics of the preinjection and follow-up data

Variable	Minimum	Maximum	Mean	Standard deviation
Age	50.00	65.00	58.4000	4.4414
VA preinjection	0.05	0.40	0.1135	9.928E-02
IOP preinjection	30.00	50.00	41.4500	5.8891
VA at 12 months	0.05	0.70	0.2310	0.1933
IOP at 6 months	14.00	30.00	19.3000	5.4974
IOP at 12 months	14.00	28.00	17.7000	3.7290

Abbreviations: IOP, intraocular pressure; VA, visual acuity.

Two months postinjection, all cases showed regression of NVI, but at 4 months, 5 cases (25%) showed recurrence that needed a second injection of IVB (2 cases had previously been treated by SST, and 3 cases had not). These 5 cases showed clearance of neovessels at 6 months follow-up, and at 8 months 14 cases (70%) showed recurrence of NVI (6 cases had previously been treated by SST, and 8 cases had not), of which 9 new cases (45%) needed a second injection and the 5 previously injected cases (25%) needed a third injection; at 12 months all cases showed complete clearance of NVI. The recurrence of NVI over the follow-up period is shown in Table 2.

Mean IOP at 6 months was 19.3 ± 5.5 mmHg; 15 cases (75%) were controlled at IOP ≤ 21 mmHg (6 cases had previously been treated by SST, and 9 cases had not), 2 were controlled with topical beta blockers and 1 with combined topical beta blockers and CAIs, and 5 cases (25%) were not controlled with combined topical beta blockers and CAIs.

At 12 months follow-up, the IOP was controlled in all cases with a mean of 17.75 ± 3.74 mmHg (9 cases were previously treated by SST, and 11 cases were not); 2 cases (10%) were controlled with beta blockers and 2 cases (10%) were controlled with combined topical beta blockers and CAIs. Three cases had controlled IOP after the third injection without medication where the combined topical beta blocker and CAIs were discontinued. Table 3 shows the IOP control and antiglaucoma medications used over the follow-up period.

At 12 months follow-up; the mean VA was 0.23 ± 0.19, where it improved in 17 cases (85%) from preoperative VA of 0.12 ± 0.11 to a postoperative VA of 0.26 ± 0.2. The difference in the VA and IOP over the follow-up period is shown in Table 4.

Discussion

The treatment of NVG includes PRP, ocular antihypertensive medications, glaucoma drainage surgeries, and cyclodestructive procedures. However, it can be refractory and may not be controlled by any of these means.[10] Pharmacological treatment with IVB may have a good additive effect on IOP control and regression of NVI as proved by many studies.[11–13]

Table 2 Recurrence of neovascularization over the follow-up period

Recurrence	4 months	8 months	12 months
Yes	5	14	0
No	15	6	20

Table 3 Intraocular pressure (IOP) control and antiglaucoma medications used over the follow-up period

Variable	Preinjection	6 months	12 months
IOP	41.45	19.3	17.7
Controlled cases	None	15	18
Cases received beta blockers		2	2
Cases received combined beta blockers and CAIs		1	2

Abbreviations: CAI, carbonic anhydrase inhibitors; IOP, intraocular pressure.

In this case series, 20 eyes of 20 different patients who had presented with NVG were injected with IVB 2.5 mg in 0.1 mL, Peripheral anterior synechiae were present in 9 cases (45%) and remained unchanged after injection; subscleral trabeculectomy with 0.4 mg/mL mitomycin C for 3 minutes was done for these cases.

All cases showed complete regression of NVI within 2 months after injection, which is consistent with Ileiv et al[10] who noticed complete regression of NVI at the end of follow-up period (range 4 to 16 weeks) in 100% of cases. On the contrary, Ghanem et al[14] observed complete regression of NVI in 37.5% of cases within only 2 months and Oshima et al[15] recorded complete regression in 29% only of their cases.

Recurrence of NVI was observed in 4 cases (20%) at 4 months where reinjection was done, a second recurrence of NVI was observed in 14 cases (70%) at 8 months follow-up, including the 4 cases that were injected previously, which is consistent with the results of Oshima et al[15] who reported recurrence of NVI in 29% of cases at 2 months after a single injection, and those of Ghanem et al[14] who reported recurrence in 4 cases (25%) at 6 weeks after IVB (although the time of recurrence differs between studies), and those of Gheith et al[16] who reported recurrence in 1 case (17%) after 3 months and in a second case (17%) after 5 months.

The cause of recurrence seemed to be the persistence of retinal ischemia due to inadequate PRP. The recurrence of NVI was discovered in the 4 cases that showed the first recurrence at 4 months and the second recurrence at 8 months, so that PRP was adequately completed in these cases after the second recurrence. The recurrence of NVI seemed to be

Table 4 The difference in the VA and IOP over the follow-up period

Variable	t	df	Sig.
VA preinjection and at 12 months	–4.252	19	.000
IOP preinjection and at 6 months	13.650	19	.000
IOP preinjection and 12 months	16.495	19	.000

Abbreviations: IOP, intraocular pressure; VA, visual acuity.

caused not only by incomplete PRP but also by the limited effective period of IVB, so that after a second injection NVI regressed again.

Trabeculectomy alone or Ahmed valve operations for NVG have a low success rate, probably due to excessive intra- and postoperative inflammation and bleeding from NVI.[17,18]

A well functioning bleb was observed after a glaucoma filtering procedure combined with IVB.[19] IVB was also demonstrated to be a valuable addition in the treatment of neovascular glaucoma by hastening the resolution of anterior segment neovessels, improving the results of glaucoma surgeries, and appearing to give long-term control when used in combination with PRP in the case series of Gheith et al.[16]

In our case series, IOP was controlled in 15 cases (75%) at 6 months and in 18 cases (90%) at 12 months follow-up. After the third injection, the mean IOP dropped from 41.45 ± 5.89 mmHg preoperatively to 19.3 ± 5.5 mmHg at 6 months and 17.75 ± 3.74 mmHg at 12 months postoperatively, consecutively; the change at 6 and 12 months is highly significant with a *P* value of 0.001 for both. This is consistent with the reports of Ileiv et al,[10] where mean IOP dropped markedly from 36 ± 0.1 mmHg before IVB to 16.8 ± 3.4 mmHg at the end of the follow-up period (range 4 to 16 weeks).

There were 5 cases (25%) not controlled at 6 months, of which 3 cases were controlled at 12 months after the second injection, which proved the role of the third injection in IOP control. The success rate of SST with mitomycin C after IVB was 77.8%, which is higher than the rate of de Moraes et al[20] who used SST with mitomycin C with a success rate of approximately 58% in 2 years, and consistent with the results of Chen et al[21] who concluded that IVB might be useful adjunctive therapy in addition to trabeculectomy in the treatment of NVG. In our case series, however, we lacked a control group to compare the effects of SST with mitomycin C, with or without IVB. We could have faced ethical issues with a control group, because of the well known high risk of failure in NVG.

VA was improved in 17 cases (85%) from a preoperative VA of 0.12 ± 0.11 to a postoperative VA of 0.26 ± 0.2, due to clearance of corneal edema, hyphema, and/or vitreous hemorrhage and improvement in macular edema, which was not studied in this case series. This improvement in visual acuity is highly significant with a *P* value of 0.001, and was higher than that reported by Ghanem et al[14] who observed improvement in 9 cases (56.25%).

Conclusion

This study showed clearly that IVB had a good additive effect in regression of NVI and IOP control in neovascular glaucoma cases and also in increasing the success rate of SST with mitomycin C. However, IVB has only a limited time to work, and repeated injections are needed to maintain this effect. More research is needed to clarify the numbers of injections needed for different cases of neovascular glaucoma and the duration between each injection.

Disclosure

The authors report no conflicts of interest.

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