

# Intracameral bevacizumab and mitomycin C Trabeculectomy for eyes with neovascular glaucoma: a case series

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**Abstract** The purpose of this study was to describe the surgical outcomes and safety of intracameral bevacizumab during trabeculectomy in eyes with neovascular glaucoma. Pilot study included four eyes (four patients) with refractory neovascular glaucoma submitted to fornix-based trabeculectomy with adjunctive use of bevacizumab in the anterior chamber during the procedure. Patients were previously treated with panretinal photocoagulation as standard therapy. Variables evaluated were intraocular pressure, bleb appearance, iris neovascularization, intraoperative/postoperative complications, and visual outcomes. No intraoperative complication was observed. The mean follow-up period was 12.75 (range, 12–15 months). All eyes showed significant intraocular pressure control postoperatively. Iris neovascularization reduced significantly within 1 month after surgery. Mild anterior chamber inflammation was observed during follow-up in all eyes. No significant postoperative complication was observed, and no patient presented visual acuity deterioration. Intracameral bevacizumab may be used as an adjunctive therapy during trabeculectomy in eyes with neovascular glaucoma.

**Keywords** Neovascular glaucoma · Intraocular pressure · Bevacizumab · Trabeculectomy

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## Introduction

Neovascular glaucoma (NVG) is an optic disc 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 [1, 2]. Most cases of NVG are caused by ischemic retinal diseases, such as diabetic retinopathy and central or branch vein occlusions [2].

In such cases, standard treatment includes panretinal photocoagulation (PRP) in addition to anti-glaucomatous topical therapy [3–6]. Laser treatment aims to decrease the stimulus of retinal neovascularization, which is attributed to an increased concentration of vascular endothelial growth factor (VEGF) in retinal ischemic tissue [7–9]. Adjunctive therapy with topical medication delays the onset of glaucomatous optic neuropathy, and most of these patients will need glaucoma filtering procedures during follow-up [1, 10–15].

There is currently no prospective, randomized trial comparing success rates between trabeculectomy with antimetabolites and tube implantation in eyes with NVG. Non-comparative recent reports in the literature have shown similar success rates between the two procedures [12–15]. Yalvac et al. reported 63% success rate at 1 year using valved implants in eyes with NVG [15], whereas the success rates of trabeculectomy with antimetabolites ranged from 62% to 67% during the same follow-up time [13, 14]. The Tube Versus Trabeculectomy Study Group excluded cases of iris neovascularization from their enrollment criteria. The investigators based on the consensus that the use of a glaucoma drainage implant (GDI) is the preferred surgical approach with these types of refractory glaucomas [16]. Nevertheless, most authors agree that GDIs are a

better option in cases of NVG in a long-term follow-up [11, 15, 16]. Higher rates of failure following trabeculectomy could be caused by the growth of a neovascular membrane in the internal ostium of trabeculectomy, greater proximity of the iris to corneal endothelium, and increased anterior chamber inflammations in NVG eyes.

Bevacizumab (Avastin<sup>®</sup>, Genentech, Inc., USA) is a monoclonal VEGF inhibitor that was first used in ophthalmology to treat subretinal neovascularization in eyes with age-related macular disease [17–19]. Recently, intravitreal injection of bevacizumab has been demonstrated to be a safe and successful alternative to treat retinal neovascularization in diabetic retinopathy and central or branch vein occlusions [20–25]. Previous studies reported that anterior chamber neovascularization may regress following intravitreal injection of bevacizumab in eyes with NVG [26–30], with [28, 29] or without [26, 30] adjunctive laser treatment. Similar results were observed following intracameral injections [31]. Since anterior chamber inflammation and neovascular membranes may cause increased risk of failure of filtration procedures, bevacizumab may be used as an adjunctive therapy during surgical treatment of NVG.

The aim of this study was to describe the surgical outcomes and safety of intracameral bevacizumab during trabeculectomy in eyes with NVG.

**Methods**

This is a pilot study including four NVG patients who underwent trabeculectomy with adjunctive use of bevacizumab in the anterior chamber during the procedure. Approval from the Institutional Review Board Ethics Committee was obtained for the study. The study followed the principles of the Declaration of Helsinki, and informed consent was obtained from all subjects.

All patients presented with anterior chamber neovascular membranes, closed angles during gonioscopy, and high IOP (>21 mmHg). If the angle could not be

seen due to corneal edema, we based our judgment on the depth of the peripheral anterior chamber (van Herick’s test) and presence of iris neovascularization. PRP was performed at the time of the initial presentation. In order to avoid complications associated with excessive laser treatment in a single session, all eyes were treated within a minimum of three (range, three to five) consecutive visits, with a maximum of 300 shots each visit using a spot size of 250 μm with delivery energy of 200–500 J. The aim was to allow a 360° scatter PRP with a range of 900–1500 shots by the last visit. All eyes were on antiglaucoma medication by the time of the procedure.

Trabeculectomy was performed by two glaucoma specialists (ACFJ and JHC). Briefly, trabeculectomy was performed as follows: A fornix-based flap of conjunctiva and Tenon’s capsule was created. After haemostasis of the episcleral blood vessels with wet-field cautery, a one-half thickness rectangular (4.0×2.0 mm) scleral flap (1.5 mm from the limbus) was outlined and dissected anteriorly without entry into the anterior chamber. Three surgical sponges measuring 2.0×2.0 mm were soaked in a solution of 0.5 mg/ml mitomycin C (MMC). The sponges were placed over the dissected bed; a superficial scleral flap and the conjunctiva-tenon layer were then draped over the MMC-soaked sponges so that only those ocular tissues in contact with the sponges were directly exposed to MMC. After 3 min, the sponges were removed, and MMC was irrigated thoroughly with 20 ml balanced salt solution. A deep trabecular block was removed, and a peripheral iridectomy was performed.

The scleral flap was closed with three interrupted 10-0 nylon sutures. The conjunctivo-tenon flap was closed in the limbus using two interrupted 10-0 nylon sutures (one in each side of the flap, involving the corneal limbus—tenon—conjunctiva). After the closure, the conjunctiva was shown to be watertight.

Then, 1.25 mg of bevacizumab [32] (0.05 ml of 25 mg/ml solution) was injected in the anterior chamber through the

**Table 1** Overview of surgical outcomes

Patient	Diagnosis	Preoperative number of medications	Postoperative number of medications	Preoperative IOP (mmHg)	Last visit IOP (mmHg)	Follow-up time (months)	Complications
1	PDR	4	0	54	14	12	–
2	PDR +BVO	4	0	70	10	15	Flat anterior chamber, serous choroidal detachment
3	PDR	3	0	58	12	12	–
4	PDR	4	0	44	10	12	Transient IOP elevation, hyphema

PDR proliferative diabetic retinopathy, BVO branch vein occlusion

access paracentesis. A drop of antibiotic–corticosteroid preparation and atropine 1% was instilled in the conjunctival sac, and a patch and shield were applied on the eye.

The postoperative medical regimen initially included 1.0% prednisolone eye drops administered every 2 h and then tapered over a period of 6 weeks, depending on the degree of inflammation. Atropine 1% was dropped three times a day for the first 4 weeks after surgery. Topical antibiotic (moxifloxacin, 0.5%) was also administered four times daily during 2 weeks after surgery.

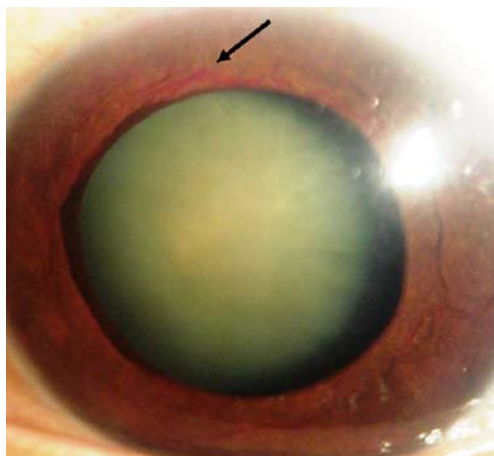
All patients were seen on the first postoperative day and then on the third, fifth, seventh, tenth, and 15th day and then on the first, third, sixth, ninth, and 12th months thereafter. At each visit, complete ophthalmic evaluation included best corrected visual acuity (BCVA), corneal appearance, anterior chamber depth, IOP measurements using Goldman tonometry, bleb appearance, and fundus examination.

## Results

All patients presented with proliferative diabetic retinopathy, and one patient had a superimposed branch vein occlusion. None of the surgeries presented any intraoperative complication. The summary of each case is presented below (overview in Table 1).

### Patient 1

A 65-year-old white woman with history of diabetic retinopathy presented with proliferative disease in the left eye. Preoperative IOP was 54 mmHg using beta-blocker, alpha-agonist, and dorzolamide eye drops and oral acetazolamide 250 mg four times daily. Peripheral anterior



**Fig. 1** Preoperative biomicroscopic examination. Note the extensive iris neovascularization, corneal edema, and mydriasis (*black arrow*)

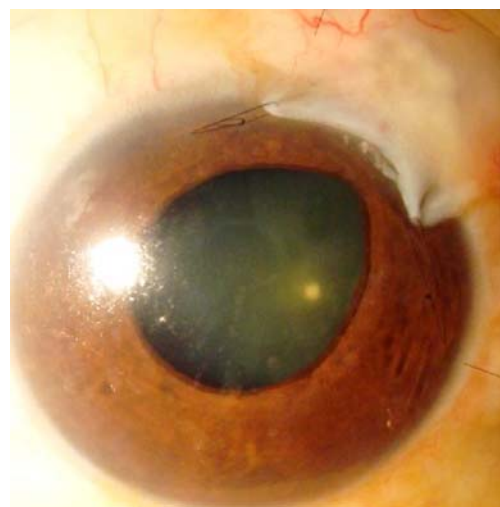


**Fig. 2** First day post-surgery. Note the significant reduction of iris neovascularization

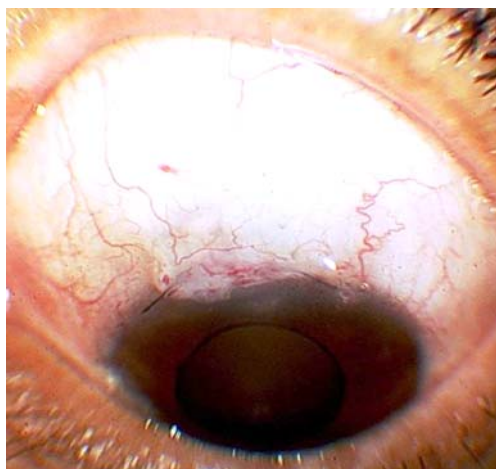
synechiae (PAS) were present in 180° extension of the angle. BCVA was count fingers at 2 m (Fig. 1).

On the first postoperative day, the IOP was 12 mmHg (initial reduction, 77%), with a diffuse elevated bleb, mild corneal edema, and little anterior chamber reaction (Fig. 2). No change in fundus appearance was observed during indirect ophthalmoscopy.

By the end of the first week, the IOP was 10 mmHg. Suture lysis (one suture) was performed using argon laser on the 15th day visit due to transient mild IOP elevation. At the last follow-up visit (12 months), she presented with a visual acuity of 20/200, likely due to decreased corneal edema, and the IOP was 14 mmHg (final IOP reduction, 74%). There was no sign of iris neovascularization by the last visit. The bleb conjunctiva looked more avascular than preoperatively and also less hyperemic than the surrounding non-operated conjunctiva.



**Fig. 3** One week after surgery. The bleb is diffuse, conjunctival vessels have small caliber, and anterior chamber inflammation is mild



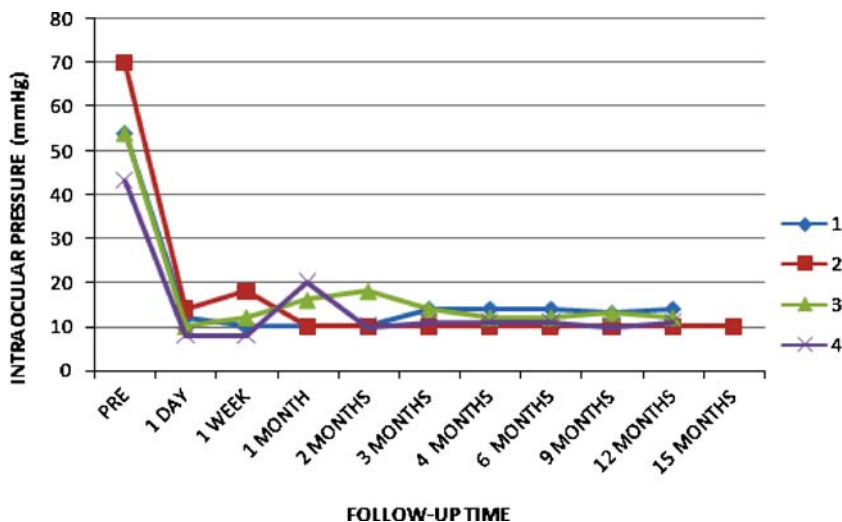
**Fig. 4** One month after surgery. Note that the bleb is diffuse and avascular

**Patient 2**

A 37-year-old black man with previous diagnosis of diabetic retinopathy presented with branch vein occlusion in the right eye. Preoperative IOP was 70 mmHg on maximal tolerated therapy. BCVA was hand-motion. The angle was closed in all four sectors during gonioscopy.

In the first postoperative day, the IOP was 14 mmHg (initial reduction, 80%). On the fifth day, he presented with flat anterior chamber (iridocorneal contact), with spontaneous resolution on the seventh day. An elevated non-vascular bleb was observed during all further follow-up visits. Fifteen months later, the IOP was 10 mmHg, and the BCVA was count fingers at 1 m (final IOP reduction, 86%). There was significant decrease in iris neovascularization, and the bleb showed little hyperemia.

**Fig. 5** Intraocular pressure profile following trabeculectomy with bevacizumab



**Patient 3**

A 56-year-old white woman was diagnosed with proliferative diabetic retinopathy in the right eye. Preoperative IOP was 58 mmHg on three antiglaucoma medications (beta blocker, alpha-agonist, and oral acetazolamide 250 mg four times daily). BCVA was 20/80 preoperatively. The four sectors of the angle were closed during gonioscopy.

The intraocular pressure (IOP) was 10 mmHg on the first postoperative day (initial reduction, 83%). By the end of the first week, the IOP was 12 mmHg, and no sign of iris neovascularization was present (Fig. 3). By the last follow-up visit (12 months), the IOP was 12 mmHg (final IOP reduction, 80%) and visual acuity remained 20/80. The iris and bleb remained avascular until the final visit.

**Patient 4**

A 45-year-old white woman presented with proliferative diabetic retinopathy, and the IOP was 44 mmHg on maximal tolerated medication. BCVA was count-fingers at 2 m, and anterior segment biomicroscopy showed intense iris neovascularization with flat anterior chamber. On the first postoperative day, the IOP was 8 mmHg (initial reduction, 82%) and showed continuous elevation until the 30th day visit when it reached 20 mmHg. Suture lysis was performed associated with subconjunctival injection of 0.5 mg of 5-fluorouracil. One month later, the IOP was 10 mmHg and remained the same until the last visit (12 months; final IOP reduction, 77%). BCVA improved to 20/100. Iris neovascularization was not evident during biomicroscopic evaluation, and the bleb was avascular and less hyperemic than the surrounding conjunctiva (Fig. 4).



## Considerations/complications

Biomicroscopic examination revealed complete regression of iris rubeosis by the last follow-up visit in all patients. Subjective evaluation of conjunctival vessels showed an improvement of ocular surface hyperemia following the procedure. Anterior chamber inflammation was considered mild (aqueous humor flare during slit-lamp examination) in all eyes within 1 week follow-up. By the second week after surgery, none of the operated eyes showed any subjective signs of anterior segment inflammation as determined by biomicroscopic evaluation. Patient 4 presented with hyphema (2 mm) during the first week, with further spontaneous resolution by the end of the second week. Mild serous choroidal detachment was seen in patient 3 with no further clinical consequences and resolved spontaneously (Fig. 5).

## Discussion

In this study, a selected group of patients presented significant IOP reduction following trabeculectomy with adjunctive use of intracameral bevacizumab after an average follow-up period of 12.75 months. No significant intraoperative or late onset complication was reported.

Secondary glaucomas and eyes with previous intraocular surgery are at increased risk of failure following glaucomatous filtering procedures [33–35]. NVG may affect the properties of the conjunctiva and anterior chamber, resulting in increased risk of failure in eyes submitted to trabeculectomy. Glaucoma drainage implants are thus indicated as a further procedure in patients who did not present satisfactory IOP control with topical medication. Yet, GDIs are more expensive than standard trabeculectomy and may result in increased risk of short- and long-term complications (e.g., extrusion, diplopia, and endophthalmitis) [11]. Eyes with NVG were excluded from the Tube Versus Trabeculectomy Study, which may not allow us to make any definite assumptions whether GDIs represent an increased risk of future complications in NVG eyes [16]. Alternatively, adjunctive use of bevacizumab during trabeculectomy could be a safe and efficient procedure in NVG, as suggested in our study.

Intravitreal injection of bevacizumab has already been studied in NVG [28–30]. Geith and colleagues described a case series of six NVG patients who underwent PRP followed by intravitreal injection of bevacizumab [28]. The authors reported that eyes without synechiae showed satisfactory IOP control with topical eye drops alone, while those with PAS at the time of presentation needed subsequent glaucoma surgery. They suggested that intravitreal bevacizumab may be a valuable addition in the

treatment of NVG by hastening the resolution of anterior segment neovascularization, improving the results of glaucoma surgeries, and appearing to give long-term control when used in combination with PRP. The procedure did not result in any relevant side effects in their study and showed a significant IOP decrease with mild inflammation.

Kahook et al. have reported a case of bleb needling revision using bevacizumab, demonstrating that the bleb was noted to be more diffuse with a decrease in surface neovascularization [36]. They suggested that the drug may be an effective medication for rescuing failing filtering blebs that exhibit neovascularization. In our study, it was noted that the number and caliber of vessels over the bleb significantly decreased after the surgery, unlikely what would be expected in cases of NVG. We believe that after the injection of bevacizumab, part of the drug diffuses through the sub-Tenon space resulting in decreased stimulus for neovascularization and bleb failure. A longer period of follow-up time is necessary to confirm this hypothesis. Iliev et al. evaluated glaucoma control in eyes with NVG following retinal vein occlusion after intravitreal injection of bevacizumab.[37] The authors observed rapid regression of iris and angle neovascularization and suggested further studies using VEGF inhibitors as adjunct therapy in the management of NVG. Recent reports described similar results and suggested new perspectives in the treatment of this type of refractory glaucoma [38, 39]. Our study confirmed those findings and also addressed one of its potential uses in glaucoma management.

One limitation of our study was the lack of a control group. Nevertheless, trabeculectomy with antimetabolites and bevacizumab should be compared with a control group without bevacizumab. However, since it is well known that trabeculectomy (even with adjunctive MMC) has high risk of failure in NVG, a comparative study using a group without bevacizumab would face ethical issues. Alternatively, a comparative study with tube implants would be biased for using a completely different surgical modality. Due to the lack of a control group, we cannot speculate whether the observed results are due to the intracameral use of bevacizumab or the PRP combined with the use of MMC intraoperatively. Based on our experience and on the available literature, the success rates of trabeculectomy even with adjunctive use of antimetabolites are very low (approximately 58% in 2 years) [13]. It is possible that the transitory anti-VEGF effect of the drug might have contributed to success by reducing inflammation and inhibiting excessive bleb vascularization, which are the main causes of failure in these eyes. Despite the growing use of monoclonal VEGF inhibitors in retinal disease, it is consensus that PRP should always be considered as first choice treatment in neovascular retinal diseases, as it has been validated by the major clinical trials in the area [3, 4].

We also used a high concentration of MMC (0.5 mg/ml) in these eyes, which may have also contributed to the avascular appearance of the bleb during follow-up.

In summary, intracameral injection of bevacizumab during trabeculectomy in this sample of patients with NVG resulted in satisfactory IOP control during a mid-term follow-up period with minor complications. Further prospective case-control studies are necessary to confirm these results.

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