

The effect of different doses of intracameral bevacizumab on surgical outcomes of trabeculectomy for neovascular glaucoma

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PURPOSE. To prospectively evaluate the effect of 1.25 mg and 2.5 mg intracameral bevacizumab on surgical outcomes of trabeculectomy for neovascular glaucoma (NVG), with primary outcome measures being the regression of neovascularization of iris (NVI) and reduction of intraocular pressure (IOP).

METHODS. Consecutive patients with neovascular glaucoma from December 2006 to March 2007 were randomized into two cohorts assigned to receive 1.25 mg (Group 1) or 2.5 mg (Group 2) intracameral bevacizumab prior to undergoing mitomycin C (MMC) trabeculectomy. Surgical outcome measures were evaluated following initial injection and during follow-up post-surgery.

RESULTS. The most common causes for iris neovascularization were central retinal vein occlusion (47.3%) and proliferative diabetic retinopathy (36.8%). Following intracameral bevacizumab, there was a reduction in IOP compared to baseline in both treatment groups (Group 1, n=9: -10.4 ± 4.5 mmHg, $p=0.57$; Group 2, n=10: -12.1 ± 5.5 mmHg, $p=0.1$). The reduction in IOP was not statistically significant between the two groups ($p=0.55$). None of the eyes underwent further retinal ablation post trabeculectomy. Reappearance of NVI was seen in three eyes (Group 1, n=2; Group 2, n=1) after 3 months. There was no statistically significant difference in regression of NVI grade between the treatment groups ($p=0.1$).

CONCLUSIONS. The efficacy of an intracameral dose of 2.5 mg of bevacizumab prior to trabeculectomy for eyes with NVG is not significantly different from a 1.25 mg dose. Intracameral bevacizumab followed by trabeculectomy results in good surgical outcomes. Longer follow-up would be needed to evaluate differences in recurrence rates of iris neovascularization using different dosages. (*Eur J Ophthalmol* 2009; 19: 435-41)

KEY WORDS. Bevacizumab, Intracameral bevacizumab, Iris neovascularization, Neovascular glaucoma, Specular microscopy

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INTRODUCTION

Neovascular glaucoma (NVG) is a catastrophic sequel to a number of disease processes affecting the eye with a common inciting factor being retinal ischemia. The visual prognosis of these cases remains poor with management options limited to panretinal photocoagulation, filtering surgery

with antifibroblastic agents, shunts, and cyclodestructive procedures. However, these procedures are associated with delayed and incomplete regression of neovascularization, frequent recurrences, and postoperative complications.

Vascular endothelial growth factor (VEGF) plays a key role in the neovascularization processes in the eye (1-4). Recent studies have shown that the use of recombinant antibodies

against VEGF, including intravitreal bevacizumab, is effective for choroidal neovascularization, macular edema, and for regression of anterior segment neovascularization in various diseases like central retinal vein occlusion and diabetic retinopathy. Rates of adverse events reported with 7113 bevacizumab injections have been found to be less than 0.3% (5).

Intracameral route of administration of bevacizumab is being used increasingly for regression of anterior segment neovascularization. Using intracameral bevacizumab, Grisanti et al found regression of iris neovascularization in six eyes with NVG and suggested that treatment may be a useful adjuvant to retinal photocoagulation for iris rubeosis (6). No relapses of iris rubeosis were seen in the six patients over 4 weeks. The authors did not comment upon the effect of intraocular pressure (IOP) post intracameral injection of bevacizumab. Similar results were shown using intracameral bevacizumab by Chalam et al (7).

While there has been an upsurge in the use of intracameral bevacizumab for regression of iris neovascularization (6-8), there is no standardized dosage for intracameral route. Further, there is lack of prospective randomized studies comparing the therapeutic efficacy with different dosages or different routes of administration of bevacizumab for regression of iris neovascularization. No prospective studies are available to evaluate the surgical outcomes of trabeculectomy for NVG following bevacizumab injections. This study is aimed at prospectively evaluating the effect of 1.25 mg and 2.5 mg intracameral bevacizumab on regression of neovascularization of iris (NVI) and subsequent outcomes of filtering surgery in eyes with neovascular glaucoma.

METHODS

Consecutive patients with NVG with persistently raised IOP, uncontrolled on maximum tolerable medical therapy, were included in the study. Patients were recruited from the glaucoma clinic of our tertiary care ophthalmic center from December 2006 to March 2007. Patients in whom IOP could not be recorded due to scarring of cornea, those with high blood pressure, or uncontrolled diabetes were excluded from the study.

Approval of use of bevacizumab for randomized controlled trial was obtained from our institutional review board prior to commencement. Informed consent was obtained from all patients following detailed discussion of the treatment op-

tions. The study adhered to the tenets of the Declaration of Helsinki. Each patient underwent a systemic evaluation with measurement of blood pressure and evaluation of diabetic status. Ocular evaluation including best-corrected visual acuity, slit-lamp biomicroscopy, gonioscopy, anterior segment photography, and applanation tonometry were conducted. These were performed at baseline, at 1 week, 1 month, 3 months, and 6 months after bevacizumab injection. Specular microscopy was performed at baseline and before trabeculectomy whenever possible.

Eyes were randomly assigned (by computer generated randomization) to receive 1.25 mg (Group 1) or 2.50 mg (Group 2) intracameral bevacizumab (Avastin; Genentech Inc., San Francisco, CA). One week prior to trabeculectomy with MMC, paracentesis of anterior chamber was performed under topical anesthesia and 1.25 mg (0.05 mL) or 2.5 mg (0.1 mL) of bevacizumab was injected into the anterior chamber. Patients were prescribed topical antibiotic, topical prednisolone, and antiglaucoma medications for a week. Trabeculectomy with MMC was performed by the same surgeon (V.G.) after 1 week in all cases to control IOP and/or relieve pain. Trabeculectomy was augmented with subconjunctival application of 0.4 mg/mL of MMC for 3 minutes. The scleral flap was sutured with two fixed 10-0 nylon sutures. Post trabeculectomy patients were prescribed topical antibiotics four times a day and topical prednisolone drops 2 hourly for 4 weeks; after that, topical prednisolone was reduced to 6 times a day depending on the bleb morphology. Following trabeculectomy, patients were followed up weekly for the first month and then every 4 weeks subsequently.

For control, we evaluated the outcomes of 16 patients with NVG who had undergone MMC augmented trabeculectomy (no bevacizumab) between January 2005 and January 2006 by the same surgeon. Surgical failure was defined as persistently elevated IOP >21 mmHg following surgery despite maximal topical antiglaucoma therapy.

Anterior segment photographs were taken for assessing NVI at baseline and at each follow-up (1 week, 1 month, 3 months, and 6 months post injection). Modified grading system described by Teich and Walsh for surface iris neovascularization was used to evaluate severity of NVI (9): Grade 0: Absence of surface neovascularization as seen on high magnification on slit lamp; Grade 1: Fine flat neovascularization of the pupillary zone of the iris involving less than two quadrants; Grade 2: Surface neovascularization of the pupillary zone of the iris involving more than two quadrants; Grade 3: In addition to neovascularization of pupillary zone, neovascularization of ciliary zone of the iris and/or ectropion

uveae involving one to three quadrants; Grade 4: Any feature of Grade 3 with ectropion uveae involving more than three quadrants.

Since ectropion uveae does not regress after therapy, we elected to grade the absence of surface neovascularization as seen on high magnification even in the presence of an ectropion uveae post therapy as Grade 0.

Primary outcome measures were to evaluate the effect on NVI regression and IOP control after trabeculectomy over 6 months.

Statistical Analysis

A sample size calculation was performed a priori for a 4 mmHg difference in mean IOP between the treatment groups using a two-tailed *t* test alpha error of 0.05 with 80% power. Six patients in each group would have to be recruited for statistical significance. Independent sample *t* test

was used to compare IOP between treatment groups. Non-parametric Mann Whitney *U* was used to compare difference in grade of NVI regression between the groups. Chi square test was used to compare the rates of complications with surgery between treatment groups and controls. Statistical analysis was performed using SPSS software (SPSS version 10.0 for Windows, SPSS Inc., Chicago, IL).

RESULTS

Nineteen eyes of 19 patients (M: F, 10:9) were recruited. Nine eyes received 1.25 mg and 10 received 2.5 mg intracameral bevacizumab. The clinical and demographic data of the two study groups are summarized in Tables I and II.

Mean age of the patients was not significantly different between the two groups ($p=0.65$). Nine out of the 19 (47.3%) eyes had central retinal vein occlusion (CRVO) while others

TABLE I - DEMOGRAPHIC AND CLINICAL FEATURES OF NVG EYES IN GROUP 1 (1.25 mg)

Patient no.	Age, yr	Gender	Diagnosis	Previous treatment	Visual acuity	Grade of NVI at baseline
1	60	Male	CRVO	None	LP	2
2	55	Male	PDR	PRP	HM	2
3	46	Male	Post uveitic glaucoma	None	HM	3
4	52	Female	CRVO	PRP	LP	1
5	41	Female	Post uveitic glaucoma	None	3/60	2
6	50	Female	CRVO	ARC	LP	2
7	56	Female	PDR	PRP	HM	1
8	50	Male	PDR	ARC	LP	4
9	50	Female	CRVO	ARC	LP	2

NVG = neovascular glaucoma; NVI = neovascularization of iris; CRVO = central retinal vein occlusion; LP = light perception; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; HM = hand movements; ARC = anterior retinal cryopexy.

TABLE II - DEMOGRAPHIC AND CLINICAL FEATURES OF NVG EYES IN GROUP 2 (2.5 mg)

Patient no.	Age, yr	Gender	Diagnosis	Previous treatment	Visual acuity	Grade of NVI at baseline
1	60	Female	CRVO	ARC	LP	4
2	60	Female	CRVO	ARC	CF	2
3	57	Male	CRVO	ARC+PRP	1/60	3
4	60	Male	PDR	ARC	LP	2
5	25	Male	Eales disease	ARC	LP	3
6	70	Male	PDR	PRP	CF	2
7	70	Male	PDR	PRP	LP	2
8	60	Female	CRVO	ARC	LP	4
9	51	Female	CRVO	ARC	HM	2
10	64	Male	PDR	None	LP –	2

NVG = neovascular glaucoma; NVI = neovascularization of iris; CRVO = central retinal vein occlusion; ARC = anterior retinal cryopexy; LP = light perception; CF = counting fingers; PRP = panretinal photocoagulation; PDR = proliferative diabetic retinopathy; HM = hand movements.

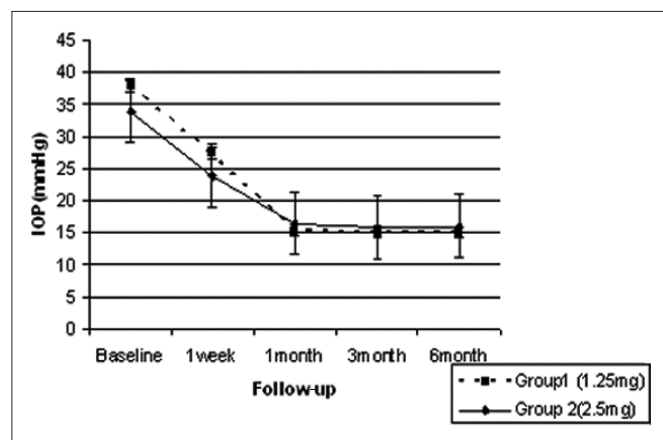


Fig. 1 - Comparative evaluation of intraocular pressure at baseline and over the follow-up between the two groups.

had proliferative diabetic retinopathy (PDR) (n=7), uveitis (n=2), and Eales disease (n=1). Fifteen out of 19 eyes (79%) had undergone previous retinal ablation with laser and/or anterior retinal cryopexy. Average duration between the retinal ablation and injection bevacizumab was 6±2.4 days in Group1 compared to 7±3.1 days in Group 2 (p=0.33).

Visual acuity at presentation in the study eyes ranged from 3/60 to absent perception of light. No change in visual acuity was noted in any of the eyes at last follow-up.

Average baseline IOP was not significantly different between the two groups (37.7±15.3 mmHg in Group1, 33.9±12.5 mmHg in Group 2, p=0.6). There was a 10.4±4.5mmHg reduction of IOP compared to baseline in Group 1 (n=9, p=0.57) and 12.1±5.5 mmHg in Group 2 (p=0.1, n=10) after 1week of intracameral injection of bevacizumab. However, the difference in IOP reduction between the treatment groups was not statistically significant (p=0.55). All eyes were on maximum tolerable antiglaucoma treatment.

Specular microscopy was performed in five eyes prior to and 5 days after injection of intracameral bevacizumab; 2 eyes (22%) in Group 1 and 3 eyes (33%) in Group 2. The mean specular count decreased from 2528±510 to 2310±508/mm²; p=0.058.

Gonioscopy revealed 360 degree closure of the angle with peripheral anterior synechiae in all eyes at baseline. After intracameral injection, patients were followed up for a mean period of 6.6±1.2 months. One patient from Group 1 and one patient from Group 2 were lost to follow-up after 3 months.

Mean IOP at 1 month post surgery for Group 1 was 15.33±1.6 mmHg and for Group 2 was 16.4±1.9 mmHg. Mean IOP was significantly decreased at 1 month compared to baseline for both Groups 1 and 2 (p=0.004 and p=0.008, respectively). No further significant reduction in IOP was observed for both groups at 3 and 6 months (Fig. 1). The mean IOP at 6 months was not significantly different between the groups (Group 1 = 14±4.8 mmHg, Group 2 = 11.5±2 mmHg, p=0.30). Eight of 9 eyes in Group 1 achieved IOP <18 mmHg without antiglaucoma therapy. One eye required topical antiglaucoma therapy due to IOP of 20 mmHg at last follow-up. In Group 2, 9 of the 10 eyes had IOP of <18 mmHg free from topical therapy. One eye had an IOP of 40 mmHg needing a cyclodiode laser treatment. None of the patients in the study were administered 5-Fluorouracil injection in the postoperative period.

The 6-month results of trabeculectomy were compared to 16 control eyes that had undergone MMC augmented trabeculectomy for NVG without bevacizumab treatment. Mean reduction of IOP (22±17.3 mmHg) in the 19 eyes of the present study was not significantly different from that of controls (17.3±9.8 mmHg), p=0.5. The rates of complications of trabeculectomy in the two groups of the present study were comparable to those of the control group (Tab. III). Failure of

TABLE III - COMPLICATIONS OF TRABECULECTOMY WITH MITOMYCIN OVER A 6-MONTH PERIOD FOR NVG: COMPARING BEVACIZUMAB PREINJECTION WITH CONTROLS WHO DID NOT HAVE AN INJECTION OF BEVACIZUMAB

Complication	Trabeculectomy group 1 (n=9)	Trabeculectomy group 2 (n=10)	Trabeculectomy alone (controls) (n=16)
Persistent hyphema	1 (11%)	0 (0%)	4 (25%)
Failure	0 (0%)	1 (10%)	5 (31.2%)
Cataract	1 (11%)	2 (20%)	2 (12.5%)
Hypopyon	0 (0%)	1 (10%)	0 (0%)
Posterior synechiae	3 (33%)	4 (40%)	4 (25%)

NVG = neovascular glaucoma.

trabeculectomy was lower in eyes treated with prior intracameral bevacizumab compared with controls (5% and 31%, respectively, χ^2 $p=0.04$).

The median grade of NVI at baseline was 2 for both groups (range 1–4 in Group 1 and range 2–4 in Group 2). Regression of NVI was observed after 1 week following intracameral bevacizumab injection in all eyes. No recurrence of NVI was observed for 3 months following treatment. The reduction in the grade of NVI post surgery was significant in both Group 1 ($p=0.007$) and Group 2 ($p=0.004$). The difference in the grade of NVI regression was not statistically significant between treatment groups ($p=0.1$). Recurrence of NVI was observed in three eyes (two in Group 1 had grade 1 and one in Group 2 which also had grade 1 NVI) between 3- and 6-month follow-up, needing repeat intracameral bevacizumab injections. None of the eyes underwent further retinal ablation post trabeculectomy.

DISCUSSION

Various modes of treatment have been tried for regression of anterior segment rubeosis in NVG, by targeting the ischemic retina to reduce the impetus for angiogenesis. These include panretinal photocoagulation (PRP), anterior retinal cryopexy (ARC), diode laser retinopexy, and panretinal diathermy (10–13). While PRP is the most effective treatment among these, its therapeutic effect becomes obvious after only a minimum period of 4 weeks, and total regression of NVI was rarely reported (13). Ehlers et al in a recent study recorded an average of 18 weeks for regression of NVI in eyes with NVG using PRP alone but only 12 days with PRP and intravitreal bevacizumab combination therapy (14). Mason et al also reported significant resolution of anterior segment neovascularization in patients after intravitreal bevacizumab (15). Oshima et al also found regression of NVI and significant reduction in IOP 2 months after intravitreal bevacizumab injection alone in 6 eyes (86%) with uncontrolled NVG (16).

The standard therapeutic intracameral or intravitreal dose for bevacizumab for treatment of NVI in neovascular glaucoma is not yet confirmed, though 1.25 mg and 2.5 mg doses have been used previously for various ocular indications (17, 18). Aqueous levels after intravitreal administration of drugs is variable. Bakri et al reported peak aqueous level of 37.7 μg at 3 days with a half life of 4.32 days after administration of 1.25 mg of intravitreal bevacizumab in an experimental study on rabbits (19). A higher dose of 2.50 mg intravitreal dose has been used previously (17); therefore we aimed to evaluate

whether a higher dose of 2.50 mg of bevacizumab has greater efficacy and more prolonged effect compared to the 1.25 mg dose. To our knowledge, this is the first prospective randomized clinical study comparing 1.25 and 2.5 mg doses of intracameral bevacizumab in NVG. Intracameral route of administration was chosen with the rationale of easy mode of administration and possibly earlier NVI regression. Furthermore, compared to intravitreal injection, one would expect less risk of lens injury and posterior segment complications with intracameral route of administration (20). Intravitreal bevacizumab may possibly lead to longer duration in the eye. It may also be argued that it may have a direct action on retinal lesions through this route in comparison to intracameral route; however, this has not been evaluated.

Specular microscopy performed in our study did not show a significant decline in the number of cells following intracameral bevacizumab. Recent experimental studies using up to 5 mg of bevacizumab found that even at higher doses it was non-toxic to cultured human corneal endothelial cells (21, 22).

Our study eyes with advanced NVG and extensive peripheral anterior synechiae showed significant decrease in IOP of more than 25% with intracameral bevacizumab alone within 1 week. This is compatible to the effect previously reported by Ehlers et al (14). This early response in IOP to intracameral bevacizumab injection may be mediated by mechanisms in addition to the reduction of neovascularization and vascular permeability. VEGF levels are known to be increased in the aqueous of NVG eyes early in the course of the disease (4, 23). In addition, bevacizumab has direct inhibitory effect on transforming growth factor (TGF) beta which is elevated in eyes with NVG and is important in causing contraction of inflammatory membrane that causes angle closure in NVG (3). Bevacizumab could also decrease IOP through reduction in anterior chamber inflammation (Dell’Omo; ARVO abstract 2008). Retinal photocoagulation or an anterior retinal cryopexy alone takes a longer time for regression of iris neovascularization and may also enhance ocular inflammation. Such a concomitant decrease in IOP with regression of new vessels could be of benefit to patients undergoing a trabeculectomy.

We followed the bevacizumab injections by trabeculectomy in our protocol as patients came with advanced stage of NVG with complete angle closure. Though some case reports point to a dramatic reduction of IOP after bevacizumab injection in eyes with NVG (7, 18, 24), there is not enough follow-up in these reports to show how long this effect lasts. Once synechial closure of the angle is extensive, in advanced stages of the disease, it is unlikely that antiglaucoma medications alone would control IOP after bevacizumab injections, though

Yazdani et al (25) report two cases of NVG with complete synechial closure to have a stable IOP after 6 months of administration of 2.5 mg bevacizumab injections. Both their patients, however, needed repeat injections to control IOP over this period.

Trabeculectomy in NVG has variable success rates with many factors contributing to surgical outcomes. The extent of peripheral anterior synechiae and having a past history of vitrectomy are important negative predictors (26, 27). Despite modifications in the surgical procedure to improve success rate, failure rate and complications are still high in this patient group. Studies have shown less than 70% 6-month success rates with antifibrotic use during trabeculectomy, with hypHEMA being a major complication of surgery (28, 29). This study examined the effect of intracameral bevacizumab on surgical outcomes of trabeculectomy in NVG eyes. Higher rates of failure were found among eyes that had not previously had bevacizumab injections compared to those treated preoperatively with intracameral bevacizumab. Intracameral injection of bevacizumab caused initial reduction of IOP by 28% in Group 1 and 35% in Group 2, respectively. Further drop of 33% and 27% after MMC trabeculectomy at 1 month was observed in Group 1 and Group 2, respectively.

Regression of vessels was seen in all of our study eyes at 3-month follow-up. Sustained NVI regression up to 6 months was found in 85% of our eyes, while three recurrences of NVI were observed between 3- and 6-month follow-up. This is similar to a previous study by Arevalo et al (17) of 1.25 mg and 2.5 mg doses of intravitreal bevacizumab for diabetic macular edema that also found that most recurrences requiring reinjections occurred after 3 months, irrespective of the initial dose used. This decrease in efficacy over time may be related to gradual decrease of bevacizumab in ocular tissue following initial injection. The sustained effect of NVI regression up to 6 months in 85% of our eyes may be due to drop in IOP following trabeculectomy, which can have the effect of relieving retinal ischemia, thereby removing the stimulus for ongoing angiogenesis in NVG.

In terms of visual function, all eyes in this study were at advanced stage at presentation. None had postoperative decline of vision.

In this study there is no additional advantage of a higher dose of 2.5 mg of intracameral bevacizumab compared to 1.25 mg given prior to MMC trabeculectomy with regards to regression of iris rubeosis, recurrence rate, or IOP reduction in neovascular glaucoma. To our knowledge, this is the first prospective randomized clinical study comparing 1.25 and 2.5 mg doses of intracameral bevacizumab in NVG. While valuable conclu-

sions could be drawn by comparing the treatment groups with previous patients with NVG who had MMC trabeculectomy, one limitation of this study is the lack of a prospective control group. Specular microscopy also was unable to be performed in all study eyes. A comparative specular microscopy involving more eyes would provide more information on whether an increased dose of 2.5 mg of intracameral bevacizumab is detrimental to corneal endothelium. The number of patients involved in this study was not powered to examine this effect. Another consideration, and an interesting aspect that needs further prospective studies, is the long-term effect of injections alone on IOP in eyes with NVG. Since all eyes underwent trabeculectomy after the first week of injection in our study we were not able to evaluate this.

In conclusion, our study showed that intracameral injection of bevacizumab followed by MMC trabeculectomy resulted in good surgical outcomes within the first 6-month postoperative period, with significant reduction in NVI and good IOP control. Intracameral bevacizumab should be considered as a therapeutic alternative in eyes with neovascular glaucoma prior to filtering surgery for a better therapeutic effect with reduced complications.

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