# Intravitreal Bevacizumab to Treat Iris Neovascularization and Neovascular Glaucoma Secondary to Ischemic Retinal Diseases in 41 Consecutive Cases

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***Purpose:*** To evaluate the biologic efficacy of intravitreal bevacizumab (IVB) for iris neovascularization (INV) or neovascular glaucoma (NVG) in patients with ischemic retinal disorders.

***Design:*** Retrospective, consecutive, interventional case series.

***Participants:*** Thirty patients (41 eyes) with INV or NVG secondary to ischemic retinal disorders.

***Methods:*** Patients received IVB (1 mg) as the initial treatment for INV or NVG and were followed up for at least 6 months. Ophthalmic evaluations included measurement of visual acuity and intraocular pressure (IOP), a complete ophthalmic examination, and fluorescein angiography. Patients were divided into 3 subgroups: INV without elevated IOP (INV group), NVG with an open angle (O-NVG group), and NVG with angle closure (C-NVG group) for outcomes analysis.

***Main Outcome Measures:*** The controllability of IOP by IVB, incidence of recurrence, and requirement for surgery to treat NVG.

***Results:*** No significant ocular or systemic adverse events developed during follow-up (range, 6–22 months; mean, 13.3 months). The mean IOP levels were 14.7, 31.2, and 44.9 mmHg at baseline in the INV, O-NVG, and C-NVG groups, respectively. In the INV group (9 eyes), the INV regressed or resolved after 1 injection. Iris neovascularization recurred in 4 eyes by 6 months and stabilized after repeated injections without IOP elevation. In the O-NVG group (17 eyes), rapid neovascular regression with successful IOP normalization ($\leq$21 mmHg) occurred in 12 eyes (71%) within 1 week after 1 injection. Five (29%) of the 17 eyes required surgery by 6 months despite repeated IVB injections, and a total of 7 eyes (41%) underwent surgery during follow-up. In the C-NVG group (15 eyes), IVB caused INV resolution but failed to lower the IOP. Fourteen (93%) of 15 eyes required surgery by 2 months after initial IVB and achieved IOP stabilization. The mean interval between IVB and surgery was significantly shorter in the C-NVG group than in the O-NVG group ($P<0.001$).

***Conclusions:*** Intravitreal bevacizumab is well tolerated, effectively stabilized INV activity, and controlled IOP in patients with INV alone and early-stage NVG without angle closure. In advanced NVG, IVB cannot control IOP but may be used adjunctively to improve subsequent surgical results. Further evaluation in controlled randomized studies is warranted.

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Iris neovascularization (INV) and subsequent development of neovascular glaucoma (NVG) are serious complications for patients with proliferative diabetic retinopathy (PDR) and other ischemic retinal disorders.[1] Iris neovascularization often progresses to form a fibrovascular membrane in the chamber angle that impedes aqueous outflow and produces peripheral anterior synechiae (PAS) and progressive angle closure. The increased intraocular pressure (IOP) is difficult to control and frequently results in irreversible severe loss of vision.[1]

Iris neovascularization and NVG are highly correlated with retinal ischemia, which stimulates production of vascular endothelial growth factor (VEGF), a key molecule in ocular neovascularization.[2,3] Intravitreal injection of VEGF produces INV and NVG in a nonhuman primate, and inhibition of endogenous VEGF essentially is effective for suppressing the retinal ischemia-induced INV.[4,5] Currently, panretinal photocoagulation (PRP) is the only standard treatment of choice.[1,6–10] Vascular endothelial growth factor levels in patients with ischemic retinal pathologic features are reduced indirectly after laser photocoagulation.[3] However, in patients with media opacity such as cataract or vitreous hemorrhage, it is sometimes difficult to perform PRP. Furthermore, photocoagulation alone is not com-



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pletely successful in halting INV in every patient, especially those with severe and rapid neovascular progression.[1] Therefore, direct targeting of VEGF with anti-VEGF pharmacotherapy may be another possible therapeutic strategy to treat ocular neovascularization.[11]

Bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) is a full-length humanized monoclonal antibody that binds all isoforms of VEGF.[12,13] It has been approved by the Food and Drug Administration as an antiangiogenic agent for the treatment of metastatic colorectal cancer.[14] Recent studies using off-label intravitreal bevacizumab (IVB) injections have reported the short-term efficacy and safety of the treatment for IVN and NVG.[15–19] Rapid and marked regression and complete resolution of iris and angle neovascularization have occurred after IVB. The IOP was controlled in most cases, even in those with early-stage NVG.[15–19] Although encouraging, those early reports are limited in that they were small case series with relatively short follow-up periods. The recurrence rate, the efficacy of repeated injections, the requirement for subsequent intervention, and the adverse events related to IVB have not yet been clarified. The purpose of this study was to assess retrospectively the midterm results of IVB in preventing the development of INV to NVG and in controlling the increasing IOP in NVG in a large, consecutive series of cases.

## Patients and Methods

The authors retrospectively reviewed the charts of a consecutive series of 41 eyes of 30 patients who underwent IVB to treat INV (IOP ≤21 mmHg without antiglaucoma medication) or NVG (IOP >21 mmHg) caused by ischemic retinal disorders including PDR, central retinal vein occlusion, and ocular ischemic syndrome. All patients were treated at the Department of Ophthalmology, Osaka University Hospital, Osaka, Japan, from October 2005 to June 2007 and were followed up for at least 6 months. Initially, only patients with progressive INV or active NVG that was unresponsive to PRP were considered for IVB treatment. After favorable short-term outcomes were obtained from the initial 7 eyes of 5 consecutive patients,[18] IVB then was offered as the first treatment of choice to patients with INV or NVG regardless of whether traditional treatment was performed. If necessary, PRP was performed 1 or 2 weeks after the injection. The off-label use of bevacizumab was approved by the Institutional Review Board of Osaka University Medical School. Informed consent was obtained from all patients after discussing the benefits, potential risks, and alternative treatments.

Intravitreal bevacizumab was administered as an outpatient procedure under strict aseptic instructions.[20] A 50-μl aliquot of commercially available bevacizumab (25 mg/ml) was prepared for each patient and was placed in a tuberculin syringe with a 29-gauge needle and was refrigerated until use. After topical anesthesia was induced with 4% lidocaine eye drops and the conjunctiva was disinfected with 1.25% povidone-iodine solution, 40 μl bevacizumab (1 mg) was injected intravitreally via the pars plana. After injection, visual acuity (VA) testing and a fundus examination were performed immediately to verify perfusion of the optic nerve in all cases. In patients with increased IOP or an obscured fundus resulting from intraocular hemorrhage, paracentesis (100–200 μl) was performed to normalize the IOP. Patients were instructed to use topical antibiotics (either levofloxacin or gatifloxacin) for 1 week and were reexamined between 3 to 7 days after injection. Follow-up visits then were scheduled every month. On every visit including the initial visit, VA and IOP measurements, slit-lamp microscopic and gonioscopic examinations, and fundus microscopic examinations were performed. If necessary, fluorescein angiography and visual field measurements also were performed. Repeated injection of IVB was performed in patients if the IOP again increased to more than 30 mmHg despite antiglaucoma topical medications or prominent recurrence of INV. When the IOP remained at more than 30 mmHg despite IVB and additional PRP with the maximum tolerable antiglaucoma topical medications, antiglaucoma surgery was performed. Vitrectomy with extensive endolaser retinal photocoagulation to the ora serrata was considered simultaneously in the cases complicated with vitreous hemorrhage that did not resolve.

The medical records of the patients were reviewed for age, gender, follow-up period, preexisting ischemic retinal disorders, previous treatments, changes in best-corrected visual acuity (BCVA) and IOP, the regression and recurrence rates of INV and NVG, the number of repeated injections of IVB, changes in the number of topical antiglaucoma medications if previously administered, the requirement for subsequent surgeries, and systemic and local adverse events related to the injection. Anterior segment fluorescein angiographic images, if available, were evaluated in a masked fashion on the basis of the iris angiography grading scale reported previously.[4,5,18]

Because there are 3 breakpoints along the disease continuum starting with INV and progressing through open-angle NVG to closed-angle NVG, the 41 eyes were divided into 3 categories for analysis: patients with INV without IOP elevation (≤21 mmHg; INV group); patients with IOP exceeding 21 mmHg with an open angle (O-NVG group), and patients with an angle closure (C-NVG group). The angle of all study eyes before IVB was evaluated by 2 glaucoma specialists using gonioscopy. Angle closure was defined as an angle closed 270° or more with PAS formation; an open angle was defined as an angle open more than 90°. Visual acuity was measured using the Landolt C acuity chart and was analyzed on a logarithm of minimal angle of resolution (logMAR) scale. For statistical analysis, counting fingers vision was assigned 0.01 (+2.0 logMAR) and hand movements was assigned 0.001 (+3.0 logMAR), according to methods published previously.[21]

The results were analyzed using a 1-way analysis of variance when quantitative parameters were compared among the 3 groups. If the parameter was not normally distributed, the nonparametric Kruskal-Wallis 1-way analysis of variance then was applied. Chi-square tests or the Fisher exact test were performed as appropriate to compare the proportions of the baseline characteristics and outcomes after IVB among the 3 groups. Kaplan-Meier survival analysis was conducted to estimate the success rate of IVB for each subgroup. Topical antiglaucoma medication and laser photocoagulation could be administered after IVB if necessary; however, oral carbonic anhydrase inhibitors were not prescribed after IVB. When surgical interventions such as filtrating surgery, transscleral cyclophotocoagulation, or pars plana vitrectomy were performed, IVB therapy was considered to have failed. The differences in the success rates among the groups were compared using the log-rank test. Statistical analysis was performed using SigmaStat software version 3.1 (SPSS, Inc., Chicago, IL) and SPSS software version 10.0J (SSPS, Inc.). $P \leq 0.05$ was considered statistically significant.

## Results

Of the 30 patients, 7 were women and 23 were men. The mean age was 57.3±9.6 years (range, 34–71 years). The mean follow-up period was 13.3±5.1 months (range, 6–22 months). Of 41 eyes, 9

Table 1. Patient Baseline Characteristics

| Parameter | Total (n = 41) | Iris Neovascularization Group (n = 9) | Open-Angle Neovascular Glaucoma Group (n = 17) | Angle-Closure Neovascular Glaucoma (n = 15) | *P* Value |
|---|---|---|---|---|---|
| No. eyes/patients | 41/30 | 9/7 | 17/15 | 15/14 | |
| Gender (F/M, no. patients) | 7/23 | 2/5 | 4/11 | 4/10 | 0.992 |
| Age (yrs) | | | | | |
| Mean±SD | 57.3±9.6 | 54.9±9.2 | 56.9±8.9 | 58.9±10.8 | 0.651 |
| Range | 34–71 | 41–64 | 41–70 | 34–71 | |
| Ischemic retinal disease, no. (%) | | | | | |
| PDR | 34 (83) | 7 (78) | 17 (100) | 10 (67) | |
| OIS | 5 (12) | 1 (11) | 0 (0) | 4 (27) | 0.116 |
| CRVO | 2 (5) | 1 (11) | 0 (0) | 1 (7) | |
| Baseline VA | | | | | |
| Mean (range) | 0.07 (HM–1.0) | 0.28 (0.01–1.0) | 0.09 (HM–1.0) | 0.02 (HM–0.9) | |
| LogMAR±SD | 1.18±0.95 | 0.59±0.64 | 1.03±0.92 | 1.69±0.91 | 0.006 |
| Baseline IOP (mmHg) | | | | | |
| Mean±SD | 32.6±14.9 | 14.7±3.1 | 31.2±5.7 | 44.9±15.0 | <0.001 |
| Range | 11–76 | 11–19 | 23–40 | 26–76 | |
| Previous treatment, no. (%) | | | | | |
| Complete PRP | 18 (44) | 3 (33) | 10 (59) | 5 (33) | 0.269 |
| PPV | 21 (51) | 3 (33) | 11 (65) | 7 (47) | 0.376 |
| None | 6 (15) | 2 (22) | 1 (6) | 3 (20) | 0.406 |
| Lens status, no. (%) | | | | | |
| Phakia | 14 (34) | 5 (56) | 4 (24) | 5 (33) | |
| Pseudophakia | 26 (63) | 4 (44) | 12 (71) | 10 (67) | 0.426 |
| Aphakia | 1 (2) | 0 (0) | 1 (6) | 0 (0) | |
| Preexisting VH | 2 (5) | 0 (0) | 0 (0) | 2 (13) | 0.162 |
| Preexisting hyphema | 2 (5) | 0 (0) | 0 (0) | 2 (13) | 0.162 |
| Follow-up (mos) | | | | | |
| Mean±SD | 13.3±5.1 | 15.1±6.2 | 14.2±5.2 | 11.4±4.0 | 0.150 |
| Range | 6–22 | 6–21 | 6–22 | 6–18 | |

CRVO = central retinal vein occlusion; F = female; HM = hand movements; IOP = intraocular pressure; M = male; OIS = ocular ischemic syndrome; PDR = proliferative diabetic retinopathy; PPV = pars plana vitrectomy; PRP = panretinal photocoagulation; SD = standard deviation; VA = visual acuity; VH = vitreous hemorrhage.

eyes were included in the INV group, 17 eyes in the O-NVG group, and 15 eyes in the C-NVG group. The patient demographics and baseline characteristics of each group are shown in Table 1. There was no significant difference in age, gender, the type of underlying ischemic retinal disease, previous treatments, lens status, or follow-up periods. However, there were significant differences in the VA ($P = 0.006$) and IOP ($P<0.001$) at baseline among the 3 groups. All patient data are shown in Table 2 (available at http://aaojournal.org).

Of the 9 eyes in the INV group, the mean IOP at the initial visit was 14.7±3.1 mmHg (range, 11–19 mmHg). In all eyes, the INV rapidly regressed or disappeared without an IOP elevation within 1 week after 1 injection. Although the INV recurred in 4 eyes (44%) during the first 6 months, the INV regressed after repeated injections and additional PRP (Table 3). The mean interval between the initial IVB and the recurrence in the 4 eyes during the first 6 months was 59±14 days (range, 46–78 days). Additional PRP was applied in 5 of 6 eyes in which the PRP was insufficient at the initial visit. However, no study eyes required any antiglaucoma medications to control the IOP throughout the follow-up periods. Furthermore, in the remaining 3 eyes in which PRP had been performed completely, the progression of the INV was halted

Table 3. Outcomes after Intravitreal Bevacizumab in 3 Groups at 6 Months

| | Iris Neovascularization (n = 9) | Open-Angle Neovascular Glaucoma (n = 17) | Angle-Closure Neovascular Glaucoma (n = 15) | *P* Value |
|---|---|---|---|---|
| IOP ≤21 mmHg after IVB without surgical intervention, no. (%) | 9 (100) | 10 (59) | 1 (7) | <0.001 |
| Repeated injection, no. (%) | 4 (44) | 12 (71) | 6 (40) | 0.183 |
| Total injection, no. ±SD (range) | 1.6±0.7 (1–3) | 2.2±1.1 (1–5) | 1.6±0.8 (1–3) | 0.147 |
| Additional PRP, no. (%) | 5 (56) | 12 (71) | 6 (40) | 0.220 |
| Interval between initial IVB and recurrence (days) | | | | |
| Mean±SD | 59.0±13.7 | 58.4±32.2 | NA | 0.312 |
| Range | 46–78 | 29–120 | | |

IOP = intraocular pressure; IVB = intravitreal bevacizumab; NA = data not available; PRP = panretinal photocoagulation; SD = standard deviation.

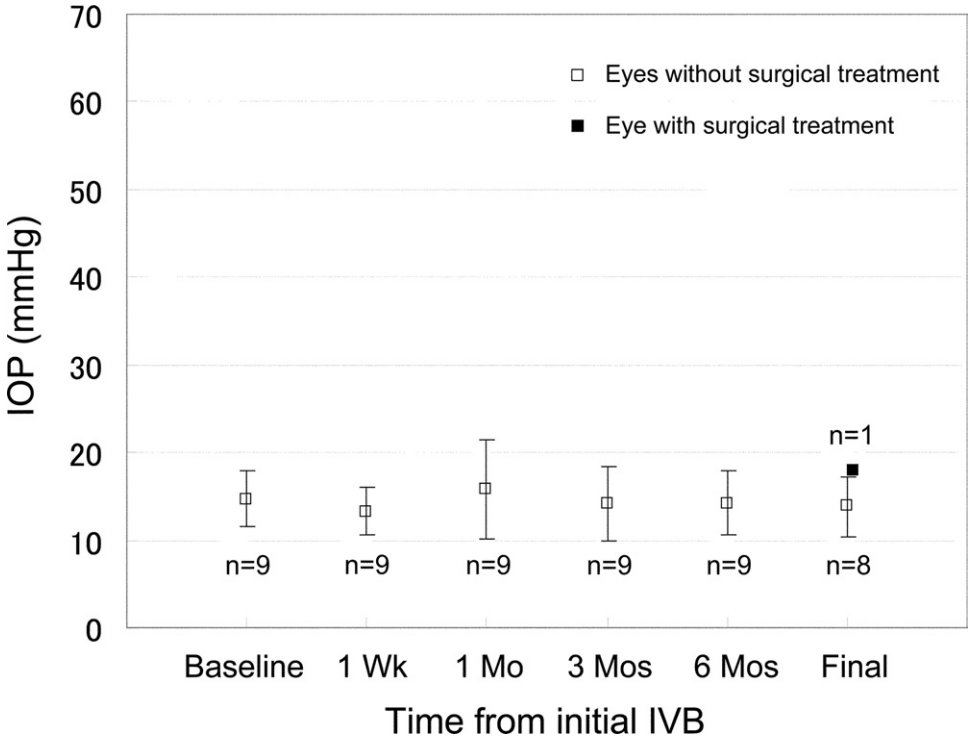


**Figure 1.** Graph showing the intraocular pressure (IOP; mean±standard deviation) after intravitreal bevacizumab (IVB) in eyes with iris neovascularization with (closed squares) and without (open squares) surgical intervention.

with IVB monotherapy without an IOP elevation. The IOP remained stable with a mean of 14.2±3.7 mmHg at the 6-month examination and 14.2±3.6 mmHg at the final visit (Fig 1). No study eyes in the INV group required antiglaucoma surgery to control IOP. Although a subsequent vitrectomy was required in 1 eye (11%) 12 months after IVB, the surgery was not related to recurrence of iris and gonioneovascularization, but rather to an unresolved vitreous hemorrhage.

Of the 17 eyes in the O-NVG group, the mean IOP before IVB was 31.2±5.7 mmHg (range, 23–40 mmHg). Rapid neovascular regression with successful IOP normalization (≤21 mmHg) was achieved in 12 eyes (71%) within 1 week after 1 injection. The mean IOP in the 12 eyes 1 week after IVB was 16.4±2.1 mmHg (range, 12–20 mmHg). However, recurrence of INV with another elevation of IOP was observed in 7 (58%) of the 12 eyes and required another injection of bevacizumab. Repeated injections were performed in a total of 12 eyes (71%) by the 6-month time point in this group (Table 3). Additional PRP was applied in 12 eyes in which the PRP was insufficient at the initial visit by the 6-month visit (Table 3). The mean interval between the initial IVB and recurrences was 58±32 days (range, 29–120 days). Despite repeated IVB injections, 5 eyes (29%) required surgery by 6 months after initial IVB, and a total of 7 eyes (41%) in this group underwent surgery throughout the follow-up period because the IOP increased along with progression of PAS formation (Tables 3 and 4). The mean IOP in the 10 eyes that did not undergo any surgical interventions at the final visit was 17.3±3.6 mmHg (range, 14–26 mmHg; Fig 2). Patients in the O-NVG group had received antiglaucoma topical medications an average of 2.5±0.9 items before being referred to the authors' institute. The mean number of medications had decreased to 1.2±1.3 ($P<0.001$) at the final follow-up visit. Of the 7 eyes that underwent surgery, the mean interval between the initial IVB and surgery was 195±168 days (range, 54–538 days). The mean IOP in the 7 eyes stabilized at a mean of 11.9±4.5 mmHg (range, 7–19 mmHg; Fig 2). The details of the surgeries performed in the 7 eyes are shown in Table 4.

Several predictive parameters were analyzed to determine the characteristic differences in the eyes requiring surgical intervention in the O-NVG group (Table 5, available at http://aaojournal.org). Repeated injections by the first 3 months after the initial IVB were the only risk factor that reached significance ($P = 0.050$) between the eyes with and without subsequent surgery in this group. However, the difference in the final VA between the eyes with and without surgery was not significant ($P = 0.48$).

In the 15 eyes in the C-NVG group, the mean IOP before injection was 44.9±15.0 mmHg (range, 26–76 mmHg). Intravitreal bevacizumab resulted in rapid regression of INV but failed to normalize the elevated IOP in most cases despite additional application of PRP (Table 3). Fourteen (93%) of 15 eyes underwent emergent antiglaucoma surgery to control the highly elevated IOP despite IVB. In the 1 eye that did not require surgery, the INV completely regressed with repeated IVB followed by additional PRP, and the IOP eventually was stabilized to 20 mmHg at the final visit. The mean preoperative IOP in the 14 eyes was 47.2±9.2 mmHg (range, 30–66 mmHg; Table 4). The mean interval between IVB and surgery was 11±15 days. After surgery, the mean IOP in the 14 eyes stabilized at a mean of 12.0±3.8 mmHg (range, 7–21 mmHg; Fig 3). The details of the surgery performed in the 14 eyes are shown in Table 4. Of all study eyes, topical antiglaucoma medication had been administered at another medical practice an average of 2.9±0.3 items before the patients were referred to the authors. At the final follow-up examination, an average of 1.1±0.3 topical antiglaucoma medications were administered in 7 (47%) eyes.

The Kaplan-Meier survival curves (Fig 4) illustrate the success rate of IOP control by IVB combined with or without additional PRP. The surgery-free rates differed significantly among the 3

Table 4. Details of Surgical Intervention after Intravitreal Bevacizumab in the Open-Angle Neovascular Glaucoma and the Angle-Closure Neovascular Glaucoma Groups

| | Open-Angle Neovascular Glaucoma (n = 17) | Angle-Closure Neovascular Glaucoma (n = 15) | *P* Value |
|---|---|---|---|
| Eyes that underwent surgery during the first 6 mos, no. (%) | 5 (29) | 14 (93) | <0.001 |
| Eyes that underwent surgery during the entire follow-up period, no. (%) | 7 (41) | 14 (93) | 0.006 |
| IOP before surgery during entire follow-up period (mmHg), mean±SD (range) | 41.3±13.8 (27–60) | 47.2±9.2 (30–66) | 0.412 |
| Interval between initial IVB and surgery during the entire follow-up period (days), mean±SD (range) | 195±168 (54–538) | 11±15 (1–46) | <0.001 |
| Total number of surgeries during the entire follow-up period | 10 | 21 | |
| PPV | 3 | 5 | |
| Trabeculectomy | 4 | 8 | |
| PPV+trabeculectomy | 1 | 4 | |
| TSCPC | 2 | 3 | |
| STA-MCA bypass | 0 | 1 | |

Data were determined at 6 months and at the last follow-up examination after initial IVB.
IOP = intraocular pressure; IVB = intravitreal bevacizumab; PPV = pars plana vitrectomy; SD = standard deviation; STA-MCA = superficial temporal artery to middle cerebral artery; TSCPC = transscleral cyclophotocoagulation.

groups ($P<0.001$). Although antiglaucoma surgery was necessary in both the O-NVG and the C-NVG groups, the mean interval between IVB and surgery was significantly shorter in the C-NVG group (11±15 days) than in the O-NVG group (195±168 days; $P<0.001$; Table 3).

The VA levels in the 41 study eyes before and after treatment are shown in Figure 5. The mean VA before and after treatment in each group did not differ significantly ($P = 0.091$). The visual improvements are shown in Figure 6. The final VA improved by 3 lines or more in 14 eyes (34%), remained unchanged in 19 eyes (46%), and deteriorated by 3 lines or more in 8 eyes (19%). In the INV group, the final BCVA improved in 3 eyes (33%), was unchanged in 5 eyes (56%), and deteriorated in 1 eye (11%). In the O-NVG group, the final BCVA improved in 5 eyes (29%), remained unchanged in 9 eyes (53%), and deteriorated in 3 eyes (18%). In the C-NVG group, the final BCVA improved in 6 eyes (40%), remained unchanged in 5 eyes (33%), and deteriorated in 4 eyes (27%). There were no significant differences in visual changes among the 3 groups ($P = 0.76$).

No adverse systemic and local complications related to IVB, such as hypertension, myocardial or cerebral infarction, cataract

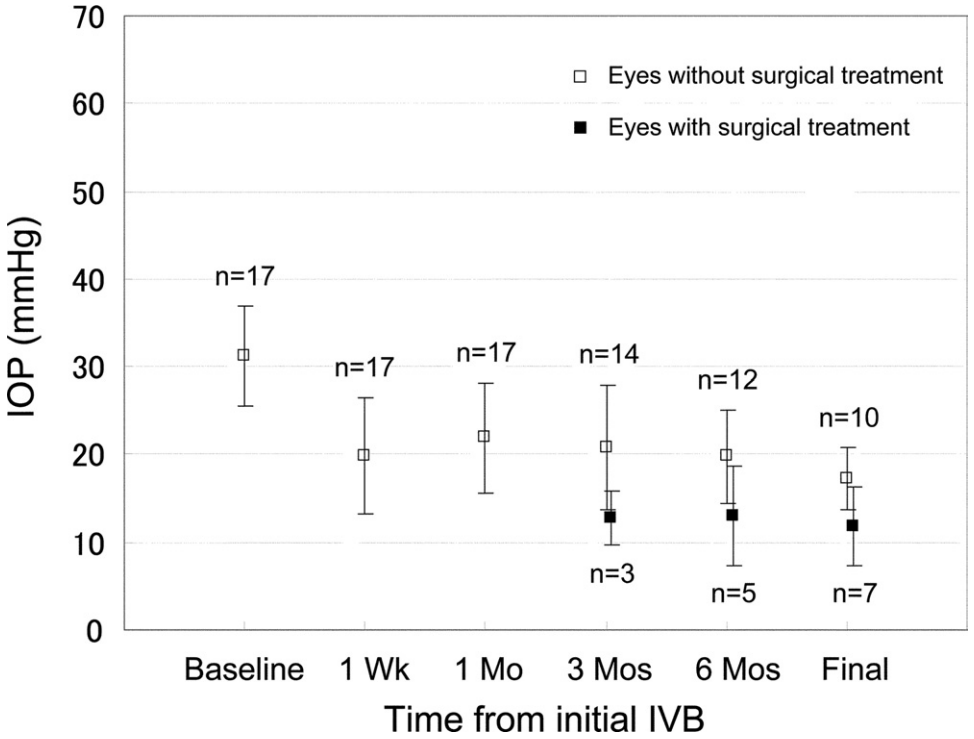


**Figure 2.** Graph showing the intraocular pressure (IOP; mean±standard deviation) after intravitreal bevacizumab (IVB) in eyes with open-angle neovascular glaucoma with (closed squares) and without (open squares) surgical intervention.

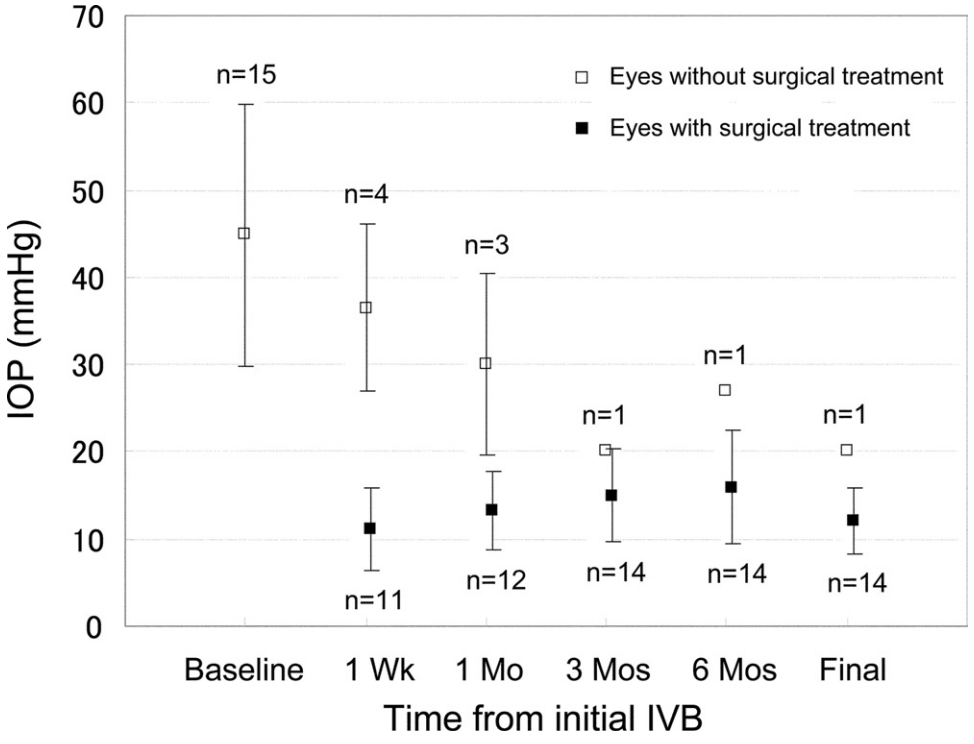


**Figure 3.** Graph showing the intraocular pressure (IOP; mean±standard deviation) after intravitreal bevacizumab (IVB) in eyes with angle-closure neovascular glaucoma with (closed squares) and without (open squares) surgical intervention.

progression, uveitis, or endophthalmitis, were observed in any study patients throughout the follow-up periods.

## Discussion

Recent encouraging results from several small case studies of IVB in the treatment of INV, NVG, or both promoted the authors to consider the drug as the first treatment of choice not only for INV but also for more severe NVG secondary to ischemic retinal disorders.[22] The rapid biologic effect of bevacizumab is favorable and is not surprising because preclinical primate studies have shown that intravitreal VEGF antibodies are sufficient to halt the experimentally induced INV by vein occlusion.[4,5] However, the effect of bevacizumab on regression of

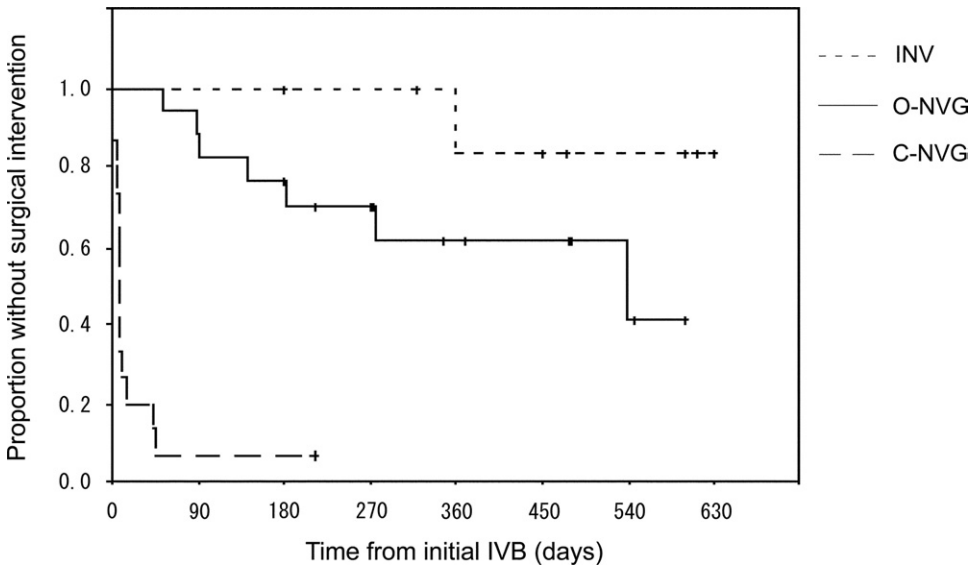


**Figure 4.** Kaplan-Meier survival curve showing the difference in the proportion of eyes that did not undergo surgery between eyes with iris neovascularization (INV), eyes with open-angle neovascular glaucoma (O-NVG), and eyes with angle-closure neovascular glaucoma (C-NVG). The differences are statistically significant ($P<0.001$, log-rank test). IVB = intravitreal bevacizumab.

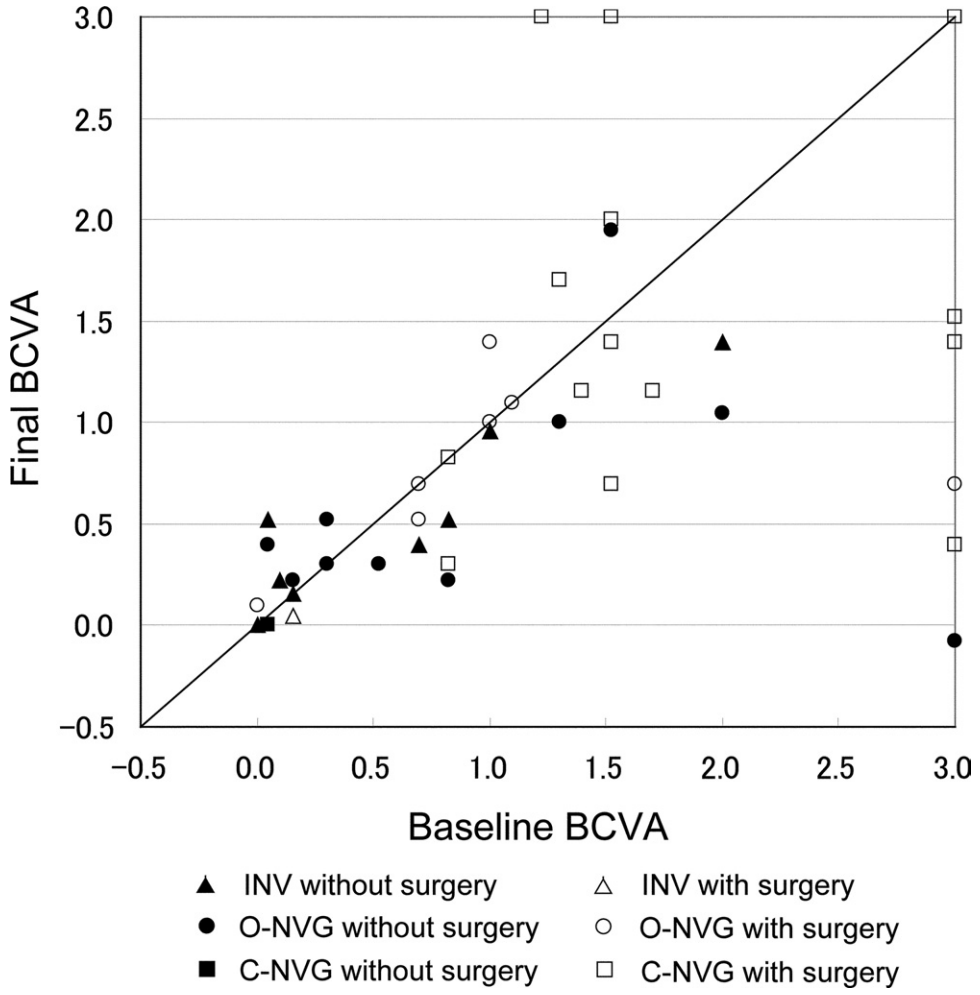


**Figure 5.** Scatterplot showing the changes in baseline and final best-corrected visual acuity (BCVA) after intravitreal bevacizumab in each group. The visual acuity was converted to logarithm of the minimum angle of resolution units. There are no statistical differences between the baseline BCVA and the final BCVA in each group. C-NVG = neovascular glaucoma with a closed angle; INV = iris neovascularization; O-NVG = neovascular glaucoma with an open angle.

INV may be transient because of the drug's short half-life.[23] Another concern is that the panisoform inhibition of VEGF may increase its side effects in normal retinal tissue and circulation.[24,25]

In the current study, the results after the use of IVB as the initial treatment of INV and NVG were reviewed retrospectively in a consecutive series of 41 eyes. To the best of the authors' knowledge, this is the first report of a large series

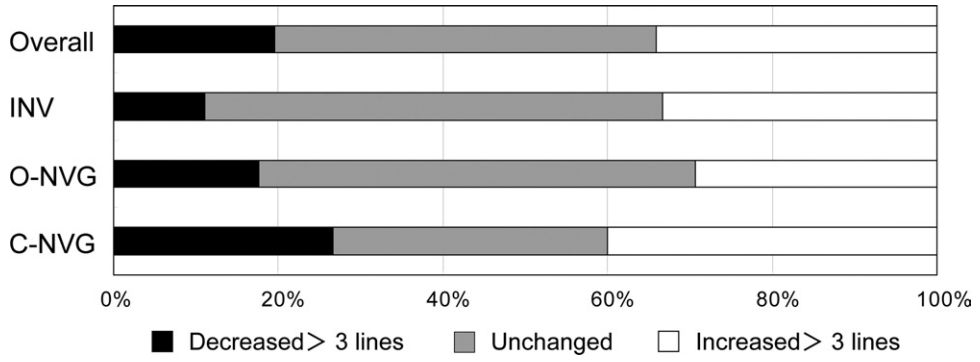


**Figure 6.** Bar graph showing the changes in the best-corrected visual acuity (BCVA) after intravitreal bevacizumab in the 3 study groups. Visual changes are defined as changes of 0.3 logarithm of the minimum angle of resolution units or more. C-NVG = neovascular glaucoma with a closed angle; INV = iris neovascularization; O-NVG = neovascular glaucoma with an open angle.

of eyes to elucidate the benefits and limitations of IVB according to the preexisting stage of INV and NVG. In the current 41 eyes, the mean VA and IOP at baseline that differed significantly among the 3 subgroups may well influence the differences in the clinical severity of these 3 breakpoints in the same pathologic conditions.

Intravitreal bevacizumab has a beneficial effect in eyes with INV without elevated IOP. In this series, rapid regression or disappearance of INV was achieved in all eyes with 1 injection of IVB. Recurrence of INV (44% by 6 months) is highly possible, but it was not prominent in most cases. Recurrent INV can be resolved by repeated administrations of IVB and additional PRP in all cases without development of NVG. The mean IOP in the 9 eyes remained stable throughout the more than 6-month follow-up period, suggesting that IVB with application of additional PRP may be a good combination therapy to reduce the risk of rapid development of NVG through the anti-VEGF efficacy of bevacizumab and to control the longer-term stability by PRP. Intravitreal bevacizumab can be a powerful treatment option instead of laser photocoagulation to stabilize the neovascular activities in eyes complicated with cataract or vitreous hemorrhage that obscures visualization of the fundus. Intravitreal bevacizumab monotherapy also may be effective for patients who have undergone PRP and in whom INV nevertheless developed, as in the study eyes.

In patients with NVG with an open angle, IVB seems to be partially effective for permanently stabilizing the elevated IOP. In this stage of NVG in which aqueous outflow has not yet been impeded completely by the neovascular membrane, 1 injection of IVB stabilized the elevated IOP into the normal range with rapid regression of INV in approximately 70% of the study eyes. The recurrence rate of 71% by 6 months of follow-up in the O-NVG group is much higher than that of 44% in the INV group, indicating that IVB may be effective but insufficient to treat eyes in this pathologically advanced stage. Nevertheless, the IOP decreased rapidly to a near-normal level by IVB monotherapy or IVB with topical antiglaucoma medication in 9 eyes (53%) during a mean follow-up of 13.3 months, suggesting the efficacy of IVB in selected cases in this group. Although 41% of the study eyes eventually required subsequent surgical intervention because of gradual advancement of fibrovascular membrane proliferation and PAS formation at the chamber angle resulting in reelevation of IOP, the duration from the initial visit to surgery can be prolonged to at least more than 2 to 3 months by repeated administration of IVB in this group. The increased IOP was controlled successfully by filtering surgery in all operated eyes after repeated IVB without intraoperative and postoperative bleeding complications, because the active neovascularization was stabilized already. There was no significant difference in the final VA between the eyes that did and did not undergo surgery in this group, which encouraged us to consider that, in addition to the conventional topical treatment, IVB may be another candidate as the first treatment of choice or as the emergent treatment of choice for eyes with NVG with an open angle.

In the current study, we could not elucidate the strong predictive factors necessitating subsequent surgery because of the small sample size. However, repeated injections to stabilize the reelevation of IOP with recurrent INV were found to be a significant risk factor leading to eventual antiglaucoma surgery ($P = 0.05$). Further study is necessary to determine the appropriate frequency of IVB and optimal timing of surgery for IOP stabilization in patients in this subgroup.

The efficacy of bevacizumab for achieving rapid and marked regression of iris and gonio neovascularization in patients in the C-NVG group was similar to that in patients in the INV and O-NVG groups. However, IVB failed to decrease the elevated IOP in most cases in the C-NVG group. In the Kaplan-Meier survival curves (Fig 4), 11 eyes (73%) required early surgical intervention within 1 week after the initial IVB injection, and a total of 14 eyes (93%) underwent surgery to stabilize the markedly elevated IOP by the first 2 months of follow-up. The duration from the initial IVB to the surgery in this group was significantly shorter than in the other 2 groups.

These data taken together suggest that the role of bevacizumab in the treatment of advanced NVG is limited to halting the neovascular activities. Patients in whom angle-closure NVG had already developed required early trabeculectomy, other antiglaucoma surgery, or both to control IOP. However, trabeculectomy alone and other shunt-tube drainage procedures for NVG are well-known challenging situations because neovessels tend to bleed easily and are associated with inflammation.[26–28] Fortunately, the patients in the current series obtained remarkably stable surgical results without bleeding complications because of marked regression of the iris and angle neovascularization after IVB. Less postoperative bleeding and inflammation in the bevacizumab-assisted trabeculectomy also may help to maintain a well-functioning bleb. Therefore, the postoperative IOP in the 14 eyes could be well controlled throughout the postoperative follow-up. Not only IOP normalization but also visual stabilization seems to be much better in this series than that reported previously without bevacizumab.[26–28] Although its effect is limited, bevacizumab may be a useful adjunct in the surgical treatment of NVG in this advanced stage because of its rapid and dramatic suppressive activity against neovascularization.[29] A prospective, randomized, comparative study with an appropriate follow-up should be considered to evaluate the benefits of adjunctive injection of bevacizumab followed by antiglaucoma surgery for advanced NVG.

The overall visual outcomes in the current study are acceptable or better than those reported previously, especially in eyes with angle-closure NVG.[30,31] According to a previous large case series of 32 patients who underwent aggressive surgeries including vitrectomy with cyclophotocoagulation and silicone oil tamponade to treat the uncontrolled NVG, VA worse than hand movements developed in 69% of eyes 3 months after surgery, and 10 eyes (31%) lost light perception at the final examination.[30] A more recent study of 25 diabetic eyes with NVG showed that trabeculectomy combined with vitrectomy and extensive endolaser photocoagulation controlled the elevated IOP but failed to avoid vision loss in 25%.[31] Postoperative vitreous hemor-

rhage and hyphema were the major surgical complications. In contrast to these reports, the current results are encouraging because no eyes lost light perception and 38 eyes (93%) had a final VA exceeding 0.01. However, analysis showed that each group had eyes with gradual visual impairment. In cases of iris or retinal neovascularization in which bevacizumab was not used, regression or progression of neovascularization is the critical indicator enhancing the severity of retinal ischemia. In eyes treated with IVB, the progression and the severity of retinal ischemia may be underestimated or masked by bevacizumab-induced regression of neovascularization. Although no adverse local and systemic events occurred in this series, panisoform inhibition of VEGF by bevacizumab may increase the toxicity to normal retinal and vascular tissues,[24,25] perhaps leading to gradual visual disturbance. Retinal ischemia should be evaluated, and sufficient PRP must be considered even after bevacizumab is applied as the initial treatment of choice.

The limitations of the current study are its retrospective nature, the absence of a control group, and the nonstandardized protocols for treatment and follow-up care. Nevertheless, the total sample size of 41 eyes and the follow-up periods ranging from 6 to 22 months are considerably larger than those of previous reports. The data presented in this study suggested that IVB offers several effective treatment options depending on the severity of the NVG, that is, IVB facilitates regression or resolution of anterior segment neovascularization to stabilize IOP in early-stage NVG with an open angle, and it may improve the quality and safety of antiglaucoma surgery in advanced NVG with angle closure, thus providing long-term IOP control in both stages. However, because the long-term results have not yet been clarified, more research and a large, prospective, randomized, controlled clinical trial would elucidate further the appropriate use of bevacizumab in combination with other treatments for managing NVG.

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## Footnotes and Financial Disclosures

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Table 2. Forty-one Cases of Iris

| Case No. | Diagnosis | Eye | Age (yrs) | Gender | Stage | Baseline Intraocular Pressure (mmHg) | Baseline Visual Acuity | Intraocular Pressure 1 wk after Intravitreal Bevacizumab (mmHg) |
|---|---|---|---|---|---|---|---|---|
| 1 | PDR | R | 43 | M | O-NVG | 32 | 0.2 | 32 |
| 2 | PDR | R | 63 | F | O-NVG | 36 | 0.1 | 32 |
| 3A | PDR | L | 56 | M | INV | 12 | 0.1 | 14 |
| 4A | PDR | R | 61 | F | INV | 18 | 0.7 | 15 |
| 4B | PDR | L | 61 | F | INV | 19 | 0.8 | 19 |
| 3B | PDR | R | 56 | M | INV | 13 | 0.2 | 13 |
| 5 | PDR | R | 56 | M | O-NVG | 30 | 0.03 | 17 |
| 6 | PDR | R | 52 | M | O-NVG | 24 | 1.0 | 25 |
| 7 | PDR | L | 57 | F | O-NVG | 40 | 0.1 | 13 |
| 8 | PDR | R | 71 | M | C-NVG | 45 | 0.15 | 49† |
| 9 | PDR | L | 58 | M | O-NVG | 25 | 0.9 | 16 |
| 10A | OIS | R | 58 | F | C-NVG | 40 | 0.03 | 56† |
| 11A | PDR | R | 70 | M | O-NVG | 26 | 0.3 | 14 |
| 10B | OIS | L | 58 | F | INV | 18 | 0.01 | 10 |
| 11B | PDR | L | 70 | M | O-NVG | 37 | 0.5 | 20 |
| 12A | PDR | R | 41 | M | INV | 16 | 0.9 | 14 |
| 13A | PDR | R | 59 | F | C-NVG | 65 | 0.04 | 65† |
| 13B | PDR | L | 59 | F | C-NVG | 76 | 0.02 | 53† |
| 12B | PDR | L | 41 | M | C-NVG | 42 | HM | 55† |
| 14A | PDR | L | 64 | M | C-NVG | 34 | 0.03 | 45† |
| 15A | PDR | L | 70 | F | O-NVG | 36 | 0.2 | 30 |
| 16 | PDR | L | 41 | M | O-NVG | 38 | 0.01 | 18 |
| 17 | CRVO | R | 70 | M | C-NVG | 31 | 0.03 | 31 |
| 18 | OIS | R | 58 | M | C-NVG | 27 | 0.06 | 36 |
| 19A | PDR | R | 56 | F | O-NVG | 24 | 0.15 | 15 |
| 20 | PDR | L | 69 | M | O-NVG | 32 | 0.08 | 17 |
| 15B | PDR | R | 70 | F | C-NVG | 49 | HM | 41† |
| 14B | PDR | R | 64 | M | INV | 12 | 0.7 | 11 |
| 21A | PDR | R | 59 | M | O-NVG | 30 | HM | 17 |
| 22A | PDR | L | 55 | M | C-NVG | 32 | 0.05 | 50† |
| 23 | PDR | R | 51 | M | O-NVG | 23 | 0.7 | 15 |
| 21B | PDR | L | 59 | M | O-NVG | 27 | HM | 19 |
| 24 | PDR | L | 56 | M | C-NVG | 49 | HM | 43† |
| 25 | OIS | R | 68 | M | C-NVG | 26 | 0.9 | 29 |
| 22B | PDR | R | 55 | M | O-NVG | 39 | 0.05 | 12 |
| 19B | PDR | L | 56 | F | C-NVG | 64 | HM | 66† |
| 26 | OIS | R | 65 | M | C-NVG | 38 | 0.03 | 38† |
| 27 | PDR | R | 54 | M | O-NVG | 32 | 0.5 | 26 |
| 28 | PDR | L | 43 | M | INV | 13 | 1.0 | 14 |
| 29 | PDR | R | 34 | M | C-NVG | 56 | 0.15 | 30† |
| 30 | CRVO | L | 61 | M | INV | 11 | 0.15 | 10 |

C-NVG = angle-closure neovascular glaucoma; CRVO = central retinal vein occlusion; F = female; HM = hand movements; INV = iris proliferative diabetic retinopathy; PPV = pars plana vitrectomy; PRP = panretinal photocoagulation; R = right; STA-MCA = superficial temporal
*IOP after surgery.
†IOP just before surgery.

| Intraocular Pressure 3 mos after Intravitreal Bevacizumab (mmHg) | Intraocular Pressure 6 mos after Intravitreal Bevacizumab (mmHg) | Additional Panretinal Photocoagulation | Surgical Treatment | Length of Follow-up (mos) | Intraocular Pressure at Last Visit | Visual Acuity at Last Visit |
|---|---|---|---|---|---|---|
| 16* | 16* | Yes | Trabeculectomy | 22 | 17* | 0.3 |
| 18 | 21 | Yes | Trabeculectomy | 22 | 8* | 0.1 |
| 10 | 13 | Yes | None | 21 | 14 | 0.1 |
| 21 | 16 | Yes | PPV | 20.5 | 18* | 0.9 |
| 19 | 19 | Yes | None | 20.5 | 19 | 0.6 |
| 14 | 13 | Yes | None | 20 | 12 | 0.4 |
| 17 | 17 | Yes | None | 20 | 20 | 0.01 |
| 33 | 34 | No | PPV | 19.5 | 19* | 0.6 |
| 27 | 20* | No | Trabeculectomy, TSCPC | 18 | 7* | 0.04 |
| 10* | 12* | No | PPV, trabeculectomy | 18 | 12* | 0.15 |
| 24 | 19 | Yes | None | 18 | 18 | 0.4 |
| 15* | 19* | No | PPV, trabeculectomy | 18 | 11* | 0.01 |
| 12 | 18 | Yes | None | 16 | 14 | 0.5 |
| 13 | 12 | Yes | None | 16 | 18 | 0.04 |
| 13 | 18 | Yes | None | 16 | 16 | 0.3 |
| 17 | 18 | Yes | None | 15 | 14 | 0.3 |
| 18* | 15* | No | PPV + trabeculectomy | 14 | 17* | 0.07 |
| 18* | 20* | No | PPV + trabeculectomy | 14 | 13* | 0.07 |
| 18* | 32* | No | PPV, TSCPC | 14 | 7* | HM |
| 14* | 8* | No | PPV+trabeculectomy | 13.5 | 11* | 0.2 |
| 10* | 9* | Yes | PPV, trabeculectomy | 13 | 12* | 0.2 |
| 18 | 16 | Yes | None | 12.5 | 16 | 0.09 |
| 7* | 14* | Yes | Trabeculectomy | 12 | 21* | HM |
| 21* | 24* | No | STA-MCA bypass, trabeculectomy | 11.5 | 7* | HM |
| 34 | 17 | Yes | None | 11.5 | 15 | 0.6 |
| 18 | 6* | Yes | PPV+ trabeculectomy, TSCPC | 11.5 | 10* | 0.08 |
| 28* | 13* | No | PPV, TSCPC | 11 | 14* | 0.04 |
| 14 | 18 | Yes | None | 10.5 | 14 | 0.7 |
| 12* | 14* | Yes | PPV | 10 | 10* | 0.2 |
| 11* | 8* | Yes | PPV, Trabeculectomy | 10 | 11* | 0.02 |
| 18 | 16 | Yes | None | 9 | 16 | 0.6 |
| 19 | 18 | Yes | None | 9 | 18 | 1.2 |
| 15* | 19* | No | Trabeculectomy, TSCPC | 8.5 | 12* | 0.03 |
| 20 | 27 | Yes | None | 7 | 20 | 1.0 |
| 14 | 17 | Yes | None | 7 | 14 | 0.1 |
| 11* | 14* | No | Trabeculectomy | 6 | 10* | 0.4 |
| 14* | 14* | No | PPV+trabeculectomy | 6 | 14* | 0.04 |
| 26 | 26 | Yes | None | 6 | 26 | 0.5 |
| 9 | 9 | Yes | None | 6 | 9 | 1.0 |
| 9* | 10* | No | Trabeculectomy | 6 | 8* | 0.5 |
| 10 | 10 | No | None | 6 | 10 | 0.3 |

neovascularization; IOP = intraocular pressure; L = left; M = male; OIS = ocular ischemic syndrome; O-NVG = open-angle neovascular glaucoma; PDR = artery to middle cerebral artery; TSCPC = transscleral cyclophotocoagulation; VA = visual acuity.

Table 5. Comparison of Demographic Characteristics between Eyes with and without Surgical Treatment after Intravitreal Bevacizumab in the Open-Angle Neovascular Glaucoma Group

| Parameter | Open-Angle Neovascular Glaucoma Group | | P Value |
|---|---|---|---|
| | *Eyes with Surgical Treatment (n = 7)* | *Eyes without Surgical Treatment (n = 10)* | |
| Age | 59.0±9.5 | 55.1±8.0 | 0.408 |
| Baseline VA (logMAR±SD) | 1.07±0.93 | 1.00±0.96 | 0.877 |
| Baseline IOP | 32.9±5.1 | 30.1±6.1 | 0.344 |
| PAS ratio, no. (%) | | | |
| <1/4 | 6 (86) | 9 (90) | |
| 1/4–2/4 | 1 (14) | 1 (10) | 1.000 |
| 2/4–3/4 | 0 | 0 | |
| >3/4 | 0 | 0 | |
| Previous treatment, no. (%) | | | |
| Complete PRP | 5 (71) | 5 (50) | 0.622 |
| PPV | 6 (86) | 5 (50) | 0.304 |
| None | 0 | 1 (10) | 1.000 |
| Lens status, no. (%) | | | |
| Phakia | 0 | 4 (40) | |
| Pseudophakia | 7 (100) | 5 (50) | 0.084 |
| Aphakia | 0 | 1 (10) | |
| IOP after IVB (mmHg), mean±SD | | | |
| 1 wk | 23.7±8.0 | 17.2±3.9 | 0.130 |
| 1 mo | 25.4±5.5 | 19.5±5.7 | 0.068 |
| Repeated injections during the first 3 months, no. (%) | 6 (86) | 3 (18) | 0.050 |
| Total injections during the first 3 months, no.±SD (range) | 2.1±0.7 (1–3) | 1.4±0.7 (1–3) | 0.063 |
| Total injections during the entire periods, no.±SD (range) | 5.1±3.4 (2–10) | 2.3±0.8 (1–3) | 0.142 |
| Final VA (logMAR±SD) | 0.79±0.42 | 0.59±0.61 | 0.476 |
| Follow-up periods (mos) | | | |
| Mean±SD | 16.6±5.0 | 12.5±4.8 | 0.112 |
| Range | 10–22 | 6–20 | |

IOP = intraocular pressure; IVB = intravitreal bevacizumab; logMAR = logarithm of the minimum angle of resolution; PAS = peripheral anterior synechiae; PPV = pars plana vitrectomy; PRP = panretinal photocoagulation; SD = standard deviation; VA = visual acuity.