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Bevacizumab before Diabetic Vitrectomy

A Clinical Trial Assessing 3 Dosing Amounts

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Purpose: To evaluate the optimal dosing of preoperative intravitreal bevacizumab (IVB) in patients undergoing pars plana vitrectomy (PPV) for manifestations of proliferative diabetic retinopathy (PDR).

Design: Randomized clinical trial.

Participants: Two hundred six patients with severe manifestations of PDR underwent PPV at a single university-based hospital.

Methods: Patients were randomized into 1 of 3 treatment groups: group A received 0.625 mg IVB (0.025 ml) 1 to 10 days before PPV, group B received 1.25 mg IVB (0.05 ml) 1 to 10 days before PPV, and group C received 2.5 mg IVB (0.1 ml) 1 to 10 days before PPV.

Main Outcome Measures: The primary outcome was best-corrected visual acuity (BCVA) at 6 months. Secondary outcome measures were rates of perioperative tractional retinal detachment (TRD) development, intraoperative and postoperative complications, and incidence of unplanned PPV at 6 months.

Results: One hundred sixty-seven patients underwent PPV and completed 6 months of follow-up. There were no significant differences between treatment groups regarding baseline characteristics, final BCVA, intraoperative complications, postoperative complications, or unplanned PPV rates. There were no patients in group A (0.0%), 3 patients in group B (7.0%), and 5 patients in group C (8.5%) who demonstrated perioperative TRD after IVB administration, but before PPV ($P = 0.0283$). This difference was significant between groups A and B ($P = 0.0494$) and between groups A and C ($P = 0.0080$).

Conclusions: This randomized clinical trial demonstrated that patients receiving the 0.625-mg dose of IVB before PPV for the treatment of PDR-related manifestations showed similar visual acuity, but a lower incidence of perioperative TRD development compared with patients receiving the 1.25-mg and 2.5-mg doses. Clinicians should consider adopting the lowest effective dose, 0.625 mg, into clinical practice. The current study is limited by the lack of a control group receiving no IVB before PPV. *Ophthalmology Retina 2018;2:1010-1020 © 2018 by the American Academy of Ophthalmology*

The consequences of neovascularization and fibrovascular proliferation frequently result in profound vision loss in diabetic patients with proliferative diabetic retinopathy (PDR).[1,2] Pars plana vitrectomy (PPV) often is indicated when nonclearing vitreous hemorrhaging, extensive fibrovascular proliferation threatening or involving the fovea, or tractional retinal detachment (TRD) with or without rhegmatogenous retinal detachment occur in patients with PDR, and the visual prognosis may be guarded in these patients because of the relatively high incidence of intraoperative and postoperative complications.[3,4] Vitreous hemorrhaging is the most common complication after PPV in PDR patients, with an incidence ranging as high as 75% in some studies.[3–6]

Bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) is a full-length recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) and has demonstrated an ability to decrease the operating time, to reduce the rate of intraoperative complications, and to lower the incidence of postoperative vitreous hemorrhaging when given before surgery to PDR patients undergoing PPV.[7–11] The incidence of vitreous hemorrhaging after PPV in PDR patients receiving preoperative intravitreal bevacizumab (IVB) decreases to 13% to 25%.[10–12] Randomized controlled trial meta-analyses also support IVB as a preoperative adjunct.[13–15] However, few clinical data and no randomized comparative studies are available regarding the optimal amount of preoperative IVB to administer to PDR patients undergoing PPV. In this study, the authors compared the clinical outcomes of the standard IVB dose of 1.25 mg with a half dose (0.625 mg) and a double dose (2.5 mg) of IVB administered before surgery to patients with active PDR undergoing PPV for the indications of nonclearing vitreous hemorrhaging, TRD with or without rhegmatogenous retinal detachment, and extensive fibrous proliferation.

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Table 1. Evaluation of Dose Variation of Preoperative Bevacizumab Administration in Proliferative Diabetic Retinopathy Patients Undergoing Vitrectomy: Inclusion and Exclusion Criteria

Inclusion	Exclusion
Type I or II diabetes mellitus	Study eye was known to have a retinal or optic nerve disease otherwise unrelated to diabetes mellitus that, in the opinion of the examiner, was responsible for 2 lines or more of decreased Snellen visual acuity (macular degeneration, optic neuritis, glaucoma, amblyopia, etc.)
Age between 18 and 85 yrs	The study eye had a corneal opacity that, in the opinion of the examiner, was responsible for 2 lines or more of reduced Snellen visual acuity (corneal scar, ectasia, etc.)
Snellen best-corrected visual acuity between 20/40 and light perception with projection in the study eye during baseline examination	The study eye had a cataract that, in the opinion of the examiner, was responsible for 2 lines or more of reduced Snellen visual acuity
Active proliferative diabetic retinopathy evident in the study eye on clinical examination	An anterior or posterior vitrectomy in the study eye had been performed previously
Study eye required vitrectomy because of reduced visual acuity principally from a nonclearing vitreous hemorrhage, tractional retinal detachment with or without a rhegmatogenous retinal detachment, fibrous proliferation, or a combination of the 3 indications	A macula-involving retinal detachment more than 6 months in duration was documented in the study eye
	Patient received systemic or intravitreal anti-VEGF treatment to the study eye within 3 mos of anticipated enrollment
	Macular ischemia observed as foveal avascular zone enlargement on fluorescein angiography that, in the opinion of the examiner, was responsible for 2 lines or more of reduced Snellen visual acuity in the study eye
	Patient had elevated intraocular pressure >25 mmHg in the study eye secondary to neovascular glaucoma
	Uncontrolled hypertension (systolic, >200 mmHg; or diastolic, >120 mmHg) despite adherence to a multiple antihypertensive medication regimen

VEGF = vascular endothelial growth factor.

Methods

Study Design

This randomized patient- and surgeon-blinded clinical trial evaluated patients who underwent PPV for severe manifestations of PDR from November 2015 through July 2017 performed by a single surgeon (R.B.R.) at a university-based educational hospital in Montemorelos, Nuevo Leon, Mexico. The clinical trial was conducted in accordance with human research regulations and standards and followed the tenets of the Declaration of Helsinki. The study was in compliance with the Health Insurance Portability and Accountability Act. The protocol and consent forms of the clinical trial were approved by the institutional review boards of the University of Montemorelos and Panhandle Eye Group (identifier, IORG0008048), and written informed consent from each study participant was obtained before enrollment. The clinical trial was registered at ClinicalTrials.gov (identifier, NCT02590094; last accessed, March 5, 2018). The primary outcome measure of this clinical trial was best-corrected visual acuity (BCVA) at the 6-month follow-up. Secondary outcomes were rates of perioperative TRD development, intraoperative and postoperative complications, and incidence of unplanned PPV between treatment groups at 6 months.

Participants

Consecutive patients with severe manifestations of PDR were referred to the authors for study eligibility assessment. The criteria for inclusion and exclusion are summarized in Table 1. If a nonclearing vitreous hemorrhage was the primary indication for PPV, the hemorrhage was present by subjective history for a minimum of 12 weeks. If TRD was the primary indication for PPV, the TRD threatened (within 1 disc diameter) or involved the foveal center. If fibrous proliferation was the primary indication for PPV, it was extensive (>3 clock hours) and threatened (within 1 disc diameter) or involved the foveal center. Only 1 eye per patient was allowed into the study. If both eyes of a patient met the criteria for enrollment, then the eye with the lowest level of BCVA was selected.

Randomization and Masking

After enrollment, eligible patients were randomized into 1 of 3 possible treatment groups: group A received 0.625 mg IVB (0.025 ml) 1 to 10 days before PPV, group B received 1.25 mg IVB (0.05 ml) 1 to 10 days before PPV, and group C received 2.5 mg IVB (0.1 ml) 1 to 10 days before PPV. Simple randomization was used to assign patients to treatment groups. Visual acuity and intraocular pressure (IOP) measurements were recorded by masked technicians. Preoperative IVB injections were administered by unmasked retina fellows and department faculty members. Each study patient was masked to their treatment group assignment throughout the length of the clinical trial. The operating surgeon (R.B.R.) was masked to the identity of each patient's group assignment throughout the duration of the study, and the surgeon did not participate in either the preoperative or postoperative assessment of patients. Unmasked retina fellows and faculty retina specialists performed all preoperative and postoperative examinations.

Assessments and Interventions

All study patients underwent a complete ophthalmic examination at baseline, which included obtaining a past medical and ocular history, BCVA and IOP measurements, and slit-lamp assessments of the anterior and posterior segments. Gonioscopy was performed when the IOP was more than 25 mmHg or iris neovascularization was observed. In all phakic patients, an intraocular lens (IOL) power calculation was determined. Thorough B-scan ultrasonography was performed when a detailed view of the posterior segment was not possible by ophthalmoscopy secondary to vitreous hemorrhaging. When the ocular media was adequate for retinal photography, spectral-domain (SD) OCT (Zeiss Cirrus HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA) and fluorescein angiography (Visucam Pro NM; Carl Zeiss Meditec, Inc.) were performed. Fluorescein angiography was used to evaluate the perfusion status of the patient's macula, whereas SD OCT was used to assess for abnormal anatomic features of the retina such as the presence of intraretinal or subretinal fluid and preretinal membranes. Patients were considered to have fibrovascular proliferation when preretinal membranes exerted traction on the retina with or without intraretinal edema, but without subretinal fluid on B-scan ultrasonography or SD OCT. Patients were considered to have a TRD when preretinal membranes exerted traction on the retina, resulting in the presence of subretinal fluid on B-scan ultrasonography or SD OCT. Within 28 days from baseline examination, patients received the IVB injection 1 to 10 days before PPV.

A standard 23-gauge 3-port PPV using the Constellation Vision System (Alcon, Fort Worth, TX) and the Resight 500 (Carl Zeiss Meditec, Inc.) for visualization was performed on each study eye by a single fellowship-trained vitreoretinal specialist (R.B.R.) under peribulbar or retrobulbar anesthesia. Vitreous cutting rates of 5000 cuts/minute were applied. Endolaser photocoagulation was performed during the surgery until all 4 quadrants of the retina had laser burns that were 1 burn-length apart to the end of the mid-peripheral retina. Endodiathermy and fibrovascular membrane dissection were performed as required according to the needs of each individual patient. Indocyanine green dye-assisted internal limiting membrane peeling; vitreous substitution with fluid, air, gas, or silicone oil; and sub-Tenon triamcinolone administration at the end of each case was at the surgeon's discretion. Small-incision (2.4-mm) phacoemulsification with IOL implantation immediately before PPV was performed on all phakic patients during the same operating session. The operation start time was recorded after the initial PPV trocar incision, and the operation end time was recorded when the eyelid speculum was removed at the conclusion of the PPV. Vitreoretinal adhesion severity was graded during surgery according to the classification used by Ahn et al.[10] Briefly, grade 0 was absence of adhesion; grade 1 was focal adhesion at 3 or fewer sites; grade 2 was broad adhesion at 1 or more sites or adhesion at the disc, macula, and vascular arcades; and grade 3 was adhesion extending out to the peripheral retina. The following intraoperative occurrences were recorded: inability to reattach the retina fully during the operation, development of inadvertent posterior pole retinal holes, development of inadvertent peripheral retinal holes, suprachoroidal effusion or hemorrhage, and inability to finish all surgical maneuvers secondary to poor visualization from lack of hemostasis. Discrepancies between the preoperative indication for PPV and the intraoperative vitreoretinal adhesion grading were noted when present.

Patients were instructed to use topical prednisolone acetate 1% 4 times daily for 21 to 28 days, depending on their postoperative findings, and topical moxifloxacin 0.5% 4 times daily for a total of 7 days after surgery. Patients were assessed for data collection during 3 postoperative evaluations: the first ranged from 10 to 20 days after surgery, the second from 30 to 50 days after surgery, and the third from 170 to 200 days after surgery. Study patients were examined at nonstudy evaluations at the discretion of the examining clinician. The BCVA, IOP, development of any postoperative complication, and occurrence of any unplanned return to the operating room for a secondary PPV were recorded during each postoperative examination. When the ocular media was adequate for retinal photography, macular perfusion status by fluorescein angiography and central retinal thickness by SD OCT were assessed during the final postoperative examination. Specific postoperative complications recorded included recurrent retinal detachment (occurrence after an observed period of completely attached retina), new retinal detachment (development in an eye that previously did not have a retinal detachment), persistent vitreous hemorrhaging (observed from postoperative day 1 until beyond 90 days without clearing), recurrent vitreous hemorrhaging (occurrence of hemorrhage after an observed period of clearing), and development of neovascular glacouma (NVG) (IOP >30 mmHg with neovascularization of the iris, angle, or both). Specific indications for an unplanned return to the operating room for a secondary PPV during the clinical trial included new or recurrent retinal detachment formation threatening or involving the foveal center, persistent vitreous hemorrhaging to the extent that no more than the large vessels and optic disc were discernible on ophthalmoscopy (allowing >90 days for spontaneous postoperative resolution), and recurrent vitreous hemorrhaging to the extent that no more than the large vessels and optic disc were discernible on ophthalmoscopy (allowing >60 days for spontaneous postoperative resolution). Patients were not allowed to undergo anti-VEGF therapy for the treatment of active PDR during the study interval. Other postoperative complications not directly attributable to active PDR also were noted, including IOL problems such as posterior capsular opacification or IOL subluxation or dislocation, occurrence of endophthalmitis, corneal complications such as nonhealing corneal ulceration, elevated IOP not attributable to NVG, de novo epiretinal membrane formation, and the occurrence of diabetic macular edema (DME). Diabetic macular edema treatment with anti-VEGF therapy during the study interval was permitted in the postoperative period at the examining clinician's discretion only after 90 postoperative days had passed. Yttrium−aluminum−garnet capsulotomy was allowed during the study interval at the discretion of the clinician.

Statistical Analysis

With a study power of 80% and the assumption that the standard deviation of the BCVA is 0.5 logarithm of the minimum angle of resolution (logMAR) with a difference to detect of 0.3 logMAR among any of the 3 groups, a minimum sample size of 40 patients for each study group was determined. Comparative analysis for numerical outcome variables was performed using a 1-way analysis of the variance, and contingency analysis with likelihood ratios was used for the nominal outcome variables. JMP 11 statistical software from the SAS Institute (Cary, NC) was used to perform the analysis. Results were considered significant at the $\alpha < 0.05$ level. For analysis of perioperative TRD development after IVA but before PPV, patients with the surgical indication of vitreous hemorrhage alone were compared with the intraoperative findings according to the grading system described above. Tractional retinal detachment was considered to have developed in the perioperative period when grade 2 or 3 vitreoretinal adhesion with clinically evident subretinal fluid was encountered in such patients.

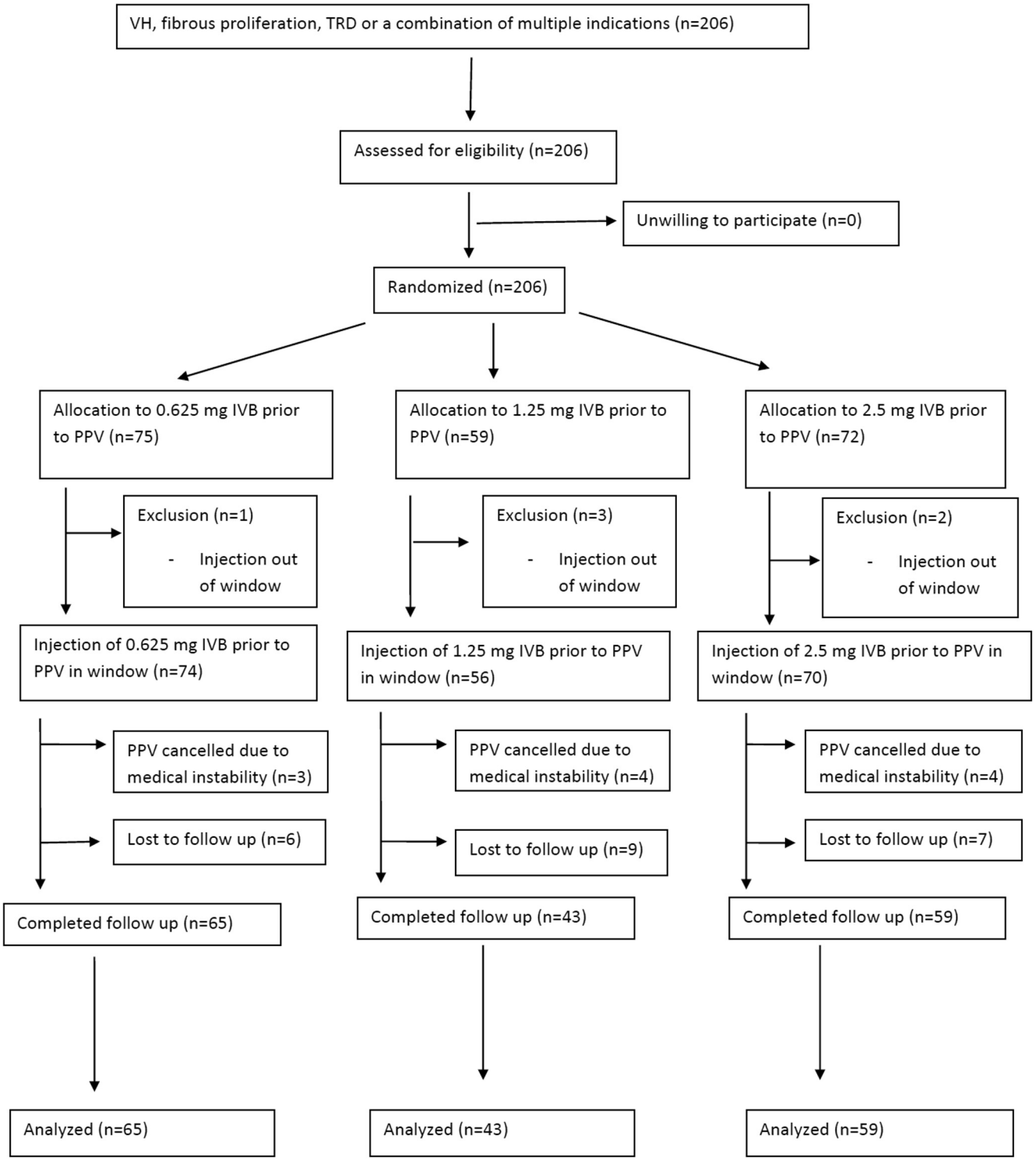

Figure 1. Flow chart showing the distribution of the study population. IVB = intravitreal bevacizumab; PPV = pars plana vitrectomy; TRD = tractional retinal detachment; VH = vitreous hemorrhage.

Results

Two hundred six patients were enrolled and randomized into the study. Six enrolled patients missed their preoperative IVB injection appointment or received IVB out of the proper treatment window, and thus were removed from the protocol. Eleven patients received preoperative IVB, but their surgery was canceled because they were declared medically unfit on the day of their scheduled

Table 2. Evaluation of Dose Variation of Preoperative Bevacizumab Administration in Proliferative Diabetic Retinopathy Patients Undergoing Vitrectomy: Baseline Demographic Features and Preoperative Characteristics of Treatment Groups

Baseline Characteristics	Group A (0.625 mg Intravitreal Bevacizumab before Vitrectomy)	Group B (1.25 mg Intravitreal Bevacizumab before Vitrectomy)	Group C (2.5 mg Intravitreal Bevacizumab before Vitrectomy)	P Value
Age (yrs)	57.3 (54.9–59.6)	55.6 (52.7–58.5)	56.3 (53.9–58.8)	0.6791
Gender	Female: 35 (53.9) Male: 30 (46.2)	Female: 28 (65.1) Male: 15 (34.9)	Female: 30 (50.9) Male: 29 (49.2)	0.3282
Diabetes type	Type 1: 2 (3.1) Type 2: 63 (96.9)	Type 1: 2 (4.7) Type 2: 41 (95.4)	Type 1: 4 (6.8) Type 2: 55 (93.2)	0.6267
Best-corrected visual acuity (logMAR)	1.91 (1.78–2.04)	1.92 (1.76–2.08)	1.88 (1.74–2.02)	0.9249
Lens status	Phakic: 52 (80.0) Pseudophakic: 13 (20.0)	Phakic: 39 (90.7) Pseudophakic: 4 (9.3)	Phakic: 55 (93.2) Pseudophakic: 4 (6.8)	0.0670
Subjective time of vision loss (mos)	8.1 (5.0–11.1)	8.9 (5.2–12.5)	10.1 (7.1–13.2)	0.6399
Use of 1 or more anticoagulant or antiplatelet agents for systemic disease	Yes: 6 (9.2) No: 59 (90.8)	Yes: 3 (7.0) No: 40 (93.0)	Yes: 10 (17.0) No: 49 (83.0)	0.2386
Presence of subfoveal fluid on OCT or B-scan ultrasonography	Yes: 12 (18.5) No: 53 (81.5)	Yes: 6 (14.0) No: 37 (86.0)	Yes: 12 (20.3) No: 47 (79.7)	0.6943
History of panretinal photocoagulation	Yes: 24 (36.9) No: 41 (63.1)	Yes: 18 (41.9) No: 25 (58.1)	Yes: 24 (40.7) No: 35 (59.3)	0.8539
Indication for surgery	Tractional retinal detachment: 2 (3.1) Nonclearing vitreous hemorrhage: 26 (40.0) Fibrovascular proliferation: 4 (6.1) Combination: 33 (50.8)	Tractional retinal detachment: 1 (2.3) Nonclearing vitreous hemorrhage: 17 (39.5) Fibrovascular proliferation: 6 (14.0) Combination: 19 (44.2)	Tractional retinal detachment: 1 (1.7) Nonclearing vitreous hemorrhage: 28 (47.4) Fibrovascular proliferation: 6 (10.2) Combination: 24 (40.7)	0.7878
No. of days intravitreal bevacizumab given before vitrectomy	5.0 (4.5–5.6)	4.2 (3.5–4.8)	4.8 (4.2–5.4)	0.1423

logMAR = logarithm of the minimum angle of resolution.
Data are mean (95% confidence interval) or no. (%), unless otherwise indicated.

Table 3. Evaluation of Dose Variation of Preoperative Bevacizumab Administration in Proliferative Diabetic Retinopathy Patients Undergoing Vitrectomy: Intraoperative Details between Treatment Groups

Intraoperative Details	Group A (0.625 mg Intravitreal Bevacizumab before Vitrectomy)	Group B (1.25 mg Intravitreal Bevacizumab before Vitrectomy)	Group C (2.5 mg Intravitreal Bevacizumab before Vitrectomy)	*P* Value
Vitreoretinal adhesion grade	Grade 0: 16 (24.6) Grade 1: 18 (27.7) Grade 2: 13 (20.0) Grade 3: 18 (27.7)	Grade 0: 7 (16.3) Grade 1: 13 (30.2) Grade 2: 9 (20.9) Grade 3: 14 (32.6)	Grade 0: 12 (20.4) Grade 1: 15 (25.4) Grade 2: 14 (23.7) Grade 3: 18 (30.5)	0.9581
Vitreous substitute	Air: 7 (10.8) Fluid: 16 (24.6) Gas: 21 (32.3) Oil: 21 (32.3)	Air: 6 (14.0) Fluid: 7 (16.3) Gas: 13 (30.2) Oil: 17 (39.5)	Air: 5 (8.5) Fluid: 13 (22.0) Gas: 28 (47.5) Oil: 13 (22.0)	0.3405
Internal limiting membrane peeling	Yes: 48 (73.9) No: 17 (26.1)	Yes: 33 (76.7) No: 10 (23.3)	Yes: 48 (81.4) No: 11 (18.6)	0.6024
Sub-Tenon steroid injection	Yes: 50 (76.9) No: 15 (23.1)	Yes: 25 (58.1) No: 18 (41.9)	Yes: 40 (67.8) No: 19 (32.2)	0.1163
Intraoperative complications	Yes: 20 (30.8) No: 45 (69.2)	Yes: 21 (48.8) No: 22 (51.2)	Yes: 20 (33.9) No: 39 (66.1)	0.1464
Details of intraoperative complications	Failure to achieve complete hemostasis: 5 (25.0) Development of a peripheral retinal hole(s): 8 (40.0) Development of a posterior retinal hole(s): 5 (25.0) Inability to reattach retina: 2 (10.0)	Failure to achieve complete hemostasis: 0 (0.0) Development of a peripheral retinal hole(s): 10 (47.6) Development of a posterior retinal hole(s): 5 (23.8) Inability to reattach retina: 6 (28.6)	Failure to achieve complete hemostasis: 3 (15.0) Development of a peripheral retinal hole(s): 9 (45.0) Development of a posterior retinal hole(s): 5 (25.0) Inability to reattach retina =3 (15.0)	0.1491
Surgery time (min)	28.3 (25.5–31.1)	31.2 (27.8–34.6)	30.9 (28.1–33.8)	0.3078

Data are mean (95% confidence interval) or no. (%), unless otherwise indicated.

Table 4. Evaluation of Dose Variation of Preoperative Bevacizumab Administration in Proliferative Diabetic Retinopathy Patients Undergoing Vitrectomy: Postoperative Outcomes between Treatment Groups

Postoperative Outcomes	Group A (0.625 mg Intravitreal Bevacizumab before Vitrectomy)	Group B (1.25 mg Intravitreal Bevacizumab before Vitrectomy)	Group C (2.5 mg Intravitreal Bevacizumab before Vitrectomy)	*P* Value
Best-corrected visual acuity at 6 mos (logMAR)	0.94 (0.79–1.10)	0.82 (0.61–1.03)	0.92 (0.77–1.08)	0.6306
Elevation of intraocular pressure to >30 mmHg during postoperative period	Yes: 10 (15.4) No: 55 (84.6)	Yes: 6 (14.0) No: 37 (86.0)	Yes: 7 (11.9) No: 52 (88.1)	0.8490
Central macular thickness on spectral-domain OCT at 6 mos (μm)	288.4 (239.5–337.4)	268.7 (203.0–334.4)	288.5 (234.9–342.1)	0.8682
Postoperative complication*	Yes: 12 (18.5) No: 53 (81.5)	Yes: 7 (16.3) No: 36 (83.7)	Yes: 13 (22.0) No: 46 (78.0)	0.7542
Unplanned secondary vitrectomy during the postoperative period	Yes: 6 (9.2) No: 59 (90.8)	Yes: 2 (4.6) No: 41 (95.4)	Yes: 6 (10.2) No: 53 (89.8)	0.5468

logMAR = logarithm of the minimum angle of resolution.
Data are mean (95% confidence interval) or no. (%), unless otherwise indicated.
*Complications include persistent or recurrent vitreous hemorrhaging, new or recurrent retinal detachment, and neovascular glaucoma.

surgery, and thus were removed from the protocol. One hundred eighty-nine patients were enrolled, randomized, received IVB during the appropriate interval, and underwent PPV. During the study's 6-month postoperative follow-up period, 22 patients were excluded from analysis because of loss to follow-up (88.3% completion rate). All patients lost to follow-up missed 1 or more of the 3 scheduled data-collecting postoperative examinations, including the outcomes at the last follow-up examination, and thus were removed from the protocol. Therefore, for final data analysis, 65 patients in group A, 43 patients in group B, and 59 patients in group C were included. A flowchart of the distribution of the study population is presented in Figure 1.

Baseline Data

The baseline data for treatment groups A, B, and C are summarized in Table 2. There were no significant differences in age, gender, diabetes type, BCVA, lens status, subjective time of vision loss, history of panretinal photocoagulation (PRP), use of 1 or more anticoagulant or antiplatelet agent for systemic disease, presence of subfoveal fluid, indication for surgery, or preoperative IVB injection interval between treatment groups.

Outcomes

The final BCVA at 6 months of follow-up was 0.94 ± 0.71 logMAR (20/174) for group A, 0.82 ± 0.48 logMAR (20/132) for group B, and 0.92 ± 0.58 logMAR (20/166) for group C. There was not a significant difference in final BCVA between treatment groups ($P = 0.6306$). All 3 treatment groups showed a significant improvement in BCVA from baseline to 6 months: group A showed an improvement of 0.97 logMAR, group B showed an improvement of 1.1 logMAR, and group C showed an improvement of 0.96 logMAR ($P < 0.0001$ for each group). The change in BCVA from baseline to 6 months was not significant between treatment groups ($P = 0.1278$). There was no significant difference between treatment groups in the likelihood of losing 1 or more logMAR lines of BCVA from baseline ($P = 0.6116$). The intraoperative details for the treatment groups are summarized in Table 3. There were no significant differences in vitreoretinal adhesion grade, surgery time, intraoperative complications, vitreous substitution, internal limiting membrane peeling, and sub-Tenon steroid administration between treatment groups.

The postoperative data for treatment groups are summarized in Table 4. There were no significant differences in the incidence of postoperative complications, unplanned PPV, elevation of IOP to more than 30 mmHg, or central retinal thickness on SD OCT at 6 months between treatment groups. Postoperative complications for group A included 10 cases of persistent or recurrent vitreous hemorrhaging, 1 case of new or recurrent retinal detachment, and 1 case of NVG development. Postoperative complications for group B included 4 cases of postoperative persistent or recurrent vitreous hemorrhaging, 1 case of new or recurrent retinal detachment, and 2 cases of NVG development. Postoperative complications for group C included 9 cases of postoperative persistent or recurrent vitreous hemorrhaging, 3 cases of new or recurrent retinal detachment, and 1 case of NVG development.

Table 5. Evaluation of Dose Variation of Preoperative Bevacizumab Administration in Proliferative Diabetic Retinopathy Patients Undergoing Vitrectomy: Adverse Events among Treatment Groups

Adverse Event	Group A (0.625 mg Intravitreal Bevacizumab before Vitrectomy)	Group B (1.25 mg Intravitreal Bevacizumab before Vitrectomy)	Group C (2.5 mg Intravitreal Bevacizumab before Vitrectomy)
Partial intraocular lens subluxation	0	2	0
De novo epiretinal membrane formation	2	1	4
Postoperative macular hole formation	1	0	0
Glaucoma filtration procedure for medically uncontrolled intraocular pressure	1	1	0
Posterior capsular opacification requiring YAG capsulotomy	0	2	2
Neurotrophic corneal ulceration	0	0	1
Intravitreal bevacizumab therapy for the treatment of diabetic macular edema during the postoperative period	7	3	4
Retinal detachment resulting in final visual acuity worse than baseline visual acuity	1	0	1
Development of neovascular glaucoma resulting in final visual acuity worse than baseline visual acuity	1	1	0
Macular ischemia resulting in final visual acuity worse than baseline visual acuity	1	0	0

YAG = yttrium–aluminum–garnet.

Perioperative Tractional Retinal Detachment Formation

No patients in group A (0.0%), 3 patients in group B (7.0%), and 5 patients in group C (8.5%) showed a preoperative indication for PPV of vitreous hemorrhage alone (without TRD or fibrous proliferation), but were found during surgery to have grade 2 or 3 vitreoretinal adhesion with TRD with or without an associated rhegmatogenous retinal detachment ($P = 0.0283$). This difference was significant between groups A and B ($P = 0.0494$) and between groups A and C ($P = 0.0080$). Further subset analysis showed that the 8 patients with perioperative TRD were more likely to receive intraoperative silicone oil tamponade ($P = 0.0138$), to experience an intraoperative complication ($P = 0.0194$), and to demonstrate an intraoperative retinal break ($P = 0.0108$) when compared with all other patients in the study who demonstrated a preoperative indication for PPV of vitreous hemorrhage alone. The study was not powered adequately in this subset analysis to determine if there was a difference in the BCVA at the last follow-up examination among these groups.

Other Adverse Events

Table 5 presents the other adverse events that occurred during the study interval. There were no patients in the study who ended up with no light perception at 6 months of follow-up. There were no cases of endophthalmitis or suprachoroidal hemorrhaging during the clinical trial.

Discussion

Anti-VEGF therapy with IVB is effective at regressing neovascularization secondary to PDR,[16,17] and preoperative IVB administration before performance of surgical maneuvers in patients with PDR undergoing PPV can improve surgical visualization through reduction in intraoperative hemorrhaging and can facilitate more complete fibrovascular membrane removal with fewer iatrogenic breaks.[7,9–12] However, development or extension of TRD shortly after preoperative IVB administration has been reported.[18,19] Therefore, the optimal dosing for preoperative IVB administration in patients with PDR undergoing PPV should maximize the antiangiogenic effects of IVB while minimizing the negative consequences of fibrovascular contraction at the least toxic amount.

Peak concentrations of bevacizumab occur 1 day after intravitreal injection,[20] and the half-life after a single injection of 1.25 to 1.5 mg bevacizumab into a nonvitrectomized eye has been reported to range from 6.7 to 9.82 days, with levels higher than the median inhibitory concentration for 78 days.[21,22] Clinically, examiners have described substantial neovascular regression during the first week after treatment with the typical dose of 1.25 mg IVB in patients with PDR.[17,23] Intravitreal bevacizumab at doses ranging from 0.16 to 2.5 mg have been injected from 1 to 33 days before PPV in patients with PDR.[7–14,24–27] In a recent meta-analysis, 7 of the 8 randomized controlled trials included in the analysis used the standard 1.25-mg bevacizumab dose before PPV.[14] Only the study by Modarres et al[27] used the 2.5-mg bevacizumab dose, and their results were broadly comparable with the outcomes of the other trials. Presently, there are no randomized controlled trials evaluating the 0.625-mg dose.

To our knowledge, this is the first randomized clinical trial to compare different doses of IVB administered before surgery to patients with PDR undergoing PPV. The 2 higher doses of IVB did not confer any clinical advantages over the lowest dose of IVB used in our study. All 3 doses apparently were equally effective at regressing neovascularization enough to provide a good operating view and to facilitate

safe surgical maneuvers, thereby resulting in a significant improvement in visual acuity for the overall study population. However, differences were observed in the rates of perioperative TRD development after administration of preoperative IVB between treatment groups. Patients receiving the 2 higher doses were observed to have some cases of TRD after IVB, whereas there were no cases observed in the 0.625-mg dosing group. Indeed, the difference in the incidence of perioperative TRD formation was significantly higher in patients receiving the 2.5-mg and the 1.25-mg doses when compared with those receiving the 0.625-mg dose in our study. This suggests the possibility of a dose-dependent relationship in TRD formation risk, with greater doses conferring the highest risk of development. Higher doses of IVB may result in more rapid neovascular involution with accelerated fibrosis and posterior hyaloidal contraction as a response to reduced levels of VEGF, thereby provoking TRD formation to a greater degree than lower doses. In support of this observation, a retrospective study by Arevalo et al[19] reported rates of TRD development or progression after IVB in 3% of patients who received the 1.25-mg dose, whereas the rate was 8.3% in patients who received the 2.5-mg dose. The time from injection to TRD occurrence had a mean of 11 ± 7.5 days (range, 5−32 days) and time from IVB administration to PPV had a mean of 18.8 ± 11.5 days (range, 5−37 days) in the study by Arevalo et al,[19] who did not report any patients with TRD development or progression before 5 days after IVB administration. Development of TRD occurred much sooner after IVB injection (average, 3.75 days) in our study. However, all of the patients in the study by Arevalo et al[19] underwent full PRP at least 2 months before IVB administration and were considered by the researchers to be refractory to PRP. Only approximately 40% of our overall study population had undergone PRP before PPV, and 75% of patients who went on to demonstrate a perioperative TRD after IVB administration were without PRP before PPV. This suggests that an early PPV (1−3 days after IVB administration) may be prudent in patients without prior PRP if they are to receive either the 1.25-mg or 2.5-mg dose.

A limitation of our study is that our sample size was relatively small and not specifically powered to detect the infrequent complication of TRD development or progression after IVB but before PPV. Another limitation is that our study for preoperative TRD and fibrovascular proliferation assessment relied heavily on B-scan ultrasonography, which presently does not have a standardized grading system. However, researchers have reported excellent correlation and agreement between preoperative B-scan ultrasonography and intraoperative findings when evaluating for TRD in patients with PDR.[28] Perioperative TRD determination was made by comparing baseline B-scan ultrasonography results in patients whose indication for surgery was nonclearing vitreous hemorrhage alone with the encountered vitreoretinal adhesion grade during PPV. The authors included for this assessment only patients with vitreous hemorrhage without any discernible preretinal membranes, subretinal fluid on preoperative B-scan ultrasonography, or both, but who were found to have vitreoretinal adhesion grades of 2 or 3 with TRD (the presence of clinically evident subretinal fluid) during PPV. Therefore, it is possible that our study actually underreports the true incidence of TRD development or progression because we may be overlooking patients with lower-grade vitreoretinal adhesion (grade 1) development or progression of a lower-grade vitreoretinal adhesion to a higher grade. The authors also recognize that it is possible that TRD development may have occurred in some of our study patients after the baseline examination, but before IVB was injected, because our protocol allowed for up to 28 days from the baseline examination to the preoperative IVB injection.

One more limitation of our clinical trial was that DME, a confounding variable on BCVA measurements, was not assessed for particularly and was recorded specifically only when study patients underwent anti-VEGF treatment in the postoperative period for this indication. Because treatment of DME was left to the judgment of the surgeon during surgery and to the examining clinician after surgery, the study population's incidence of DME cannot be evaluated accurately. One of the main factors in which the operating surgeon administered sub-Tenon triamcinolone during PPV was intraoperative recognition of DME, and the relatively high rate of sub-Tenon steroid administration (68% for the overall study population) suggests that DME may have been encountered commonly and was treated at the time of surgery. The treatment groups showed similar rates of sub-Tenon steroid administration, and the incidence of anti-VEGF treatment for DME during the postoperative period was low for all treatment groups. Sub-Tenon triamcinolone has a long duration of action in a vitrectomized eye, and this may explain the low rate of DME treatment with anti-VEGF medications during the postoperative period. The postoperative central retinal thickness on SD OCT was just 283.9 ± 100.6 μm for the overall study population at 6 months, further indicating that DME was encountered during the postoperative period at a low incidence throughout the study.

In summary, this clinical trial, the first of its kind to compare 3 doses of IVB for preoperative administration in patients with PDR undergoing PPV, found that patients receiving the 0.625-mg dose showed similar visual outcomes at 6 months, but a lower rate of perioperative TRD development, compared with patients receiving the 1.25-mg and 2.5-mg doses. The patients who demonstrated a perioperative TRD in our study were more likely to experience an intraoperative complication and require silicone oil tamponade compared with the patients who did not experience this perioperative complication. The authors therefore recommend that the lowest effective dose, 0.625 mg, be considered for adoption into clinical practice. Clinicians should exercise caution when using the higher doses of IVB before PPV if PRP has not been performed previously. Future clinical trials should evaluate if an even lower dose of preoperative IVB may be as safe and effective as the 0.625-mg dose, as well as the optimal timing for administering preoperative IVB at lower-than-standard doses.

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **DME** = diabetic macular edema; **IOL** = intraocular lens; **IOP** = intraocular pressure; **IVB** = intravitreal bevacizumab; **logMAR** = logarithm of the minimum angle of resolution; **NVG** = neovascular glacouma; **PDR** = proliferative diabetic retinopathy; **PPV** = pars plana vitrectomy; **PRP** = panretinal photocoagulation; **SD** = spectral-domain; **TRD** = tractional retinal detachment; **VEGF** = vascular endothelial growth factor.

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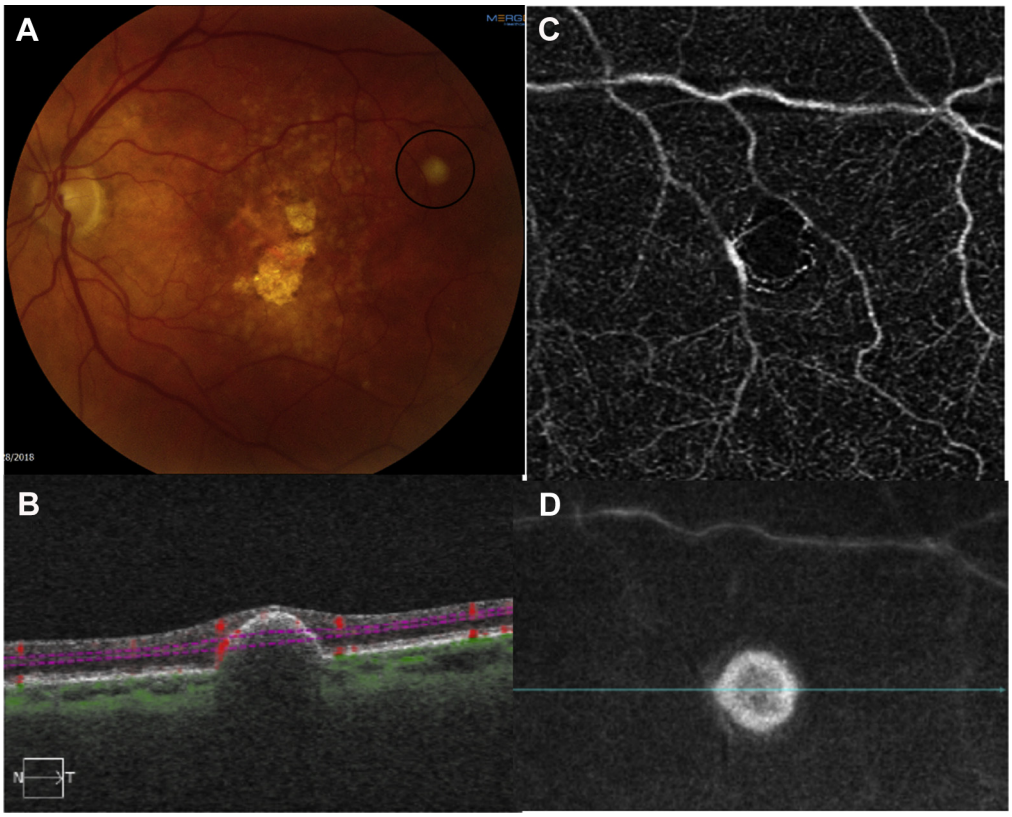
Pictures & Perspectives



Solitary Circumscribed Retinal Astrocytic Proliferation Imaged with OCT Angiography

An 84-year-old woman with age-related macular degeneration presented with a chronic asymptomatic pearl-white lesion in the left temporal macula (Fig 1**A**) consistent with solitary circumscribed retinal astrocytic proliferation. OCT angiography of the deep capillary plexus shows no intrinsic vascularity (Fig 1**C**). The associated B scan reveals a mass arising from the outer retina or retinal pigment epithelium with inward retinal compression (Fig 1**B**). The structural mid-retina enface image is shown (Fig 1**D**). The lesion seems to be fibrotic and originate from the deep retina or retinal pigment epithelium, which supports updated nomenclature for this entity.

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