Journal of Medicine in Scientific Research

Volume 2 | Issue 2 Article 12

Subject Area:

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Recommended Citation

Ahmed, Mohammed S. (2019) "Panretinal photocoagulation versus intravitreal injection of bevacizumab as a preoperative adjuvant before vitrectomy in the management of proliferative diabetic retinopathy," *Journal of Medicine in Scientific Research*: Vol. 2: Iss. 2, Article 12.
DOI: https://doi.org/10.4103/JMISR.JMISR_6_19

Original Article

Panretinal photocoagulation versus intravitreal injection of bevacizumab as a preoperative adjuvant before vitrectomy in the management of proliferative diabetic retinopathy

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Abstract

Background

Proliferative diabetic retinopathy (PDR) characterized by neovascularization of the optic disk, retina, and/or iris may be an aberrant attempt to alleviate hypoxia in eyes with severe capillary closure or other retinal ischemia. The new vessels grow perpendicular to the plane of the retina into the scaffolding provided by the vitreous cortex, typically from venules at the junction of the perfused and nonperfused retina.

Objective

This work aims to study the effect of panretinal photocoagulation (PRP) versus intravitreal injection of bevacizumab (Avastin) before vitrectomy in the management of PDR.

Patients and methods

Our clinical study was conducted on 60 eyes in 40 patients with PDR with indications of vitrectomy (vitreous hemorrhage, tractional retinal detachment involving or threatening the macula, combined tractional/rhegmatogenous retinal detachment and fibrovascular membranes covering and distorting the macula, persistent macular edema with viteromacular traction) managed by parsplana vitrectomy after preoperative preparation by intravitreal injection of bevacizumab (Avastin) or PRP used as an adjunct was grouped into two groups: group A and group B; FFA was done previtrectomy for all cases.

Results

Intraoperative using of endodiathermy is reported as once in eight cases, twice in 15 cases, three times in seven cases in group A, while once in 14 cases, twice in six cases, and not used in 10 cases in group B. Intraoperative use of endolaser is reported as less than 1500 shoots in seven cases, and more than 1500 shoots in 23 cases in group A, while less than 1500 shoots in 29 cases, and more than 1500 shoots in one case in group B. Therefore, bevacizumab or PRP induces regression of active fibrovascular proliferation decreasing the extent of bleeding during tissue segmentation and delamination. The lesser intraoperative bleeding makes visualization of the surgical plane better, which in turn facilitates a precise separation of the proliferative tissue from the retina and helps avoid accidental retinal vascular damage and iatrogenic retinal breaks and make the surgery and the results better than conventional surgery (without using any adjuvants).

Conclusion

Use of both adjuvants before vitrectomy enhances the outcome of vitrectomy when best indicated rather than without using. The shorter time of surgery and less use of endodiathermy or endolaser is with the PRP group, although postoperative best-corrected visual acuity gaining is not significant. So, accurate clinical differences between two adjuvants need more researches.

Keywords: Bevacizumab, panretinal photocoagulation, vitrectomy

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Access this article online

Quick Response Code:

Website: www.jmsr.eg.net

DOI: 10.4103/JMISR.JMISR_6_19

How to cite this article: Ahmed MS. Panretinal photocoagulation versus intravitreal injection of bevacizumab as a preoperative adjuvant before vitrectomy in the management of proliferative diabetic retinopathy. J Med Sci Res 2019;2:157-67.

Introduction

Diabetic retinopathy is one of the microvascular complications of diabetes, and its severity is directly related to the severity and duration of hyperglycemia [1].

Diabetic retinopathy is the most common cause of blindness in adults in all industrialized countries [2].

Long-term hyperglycemia causes vascular endothelial dysfunction resulting in loss of endothelial cells and pericytes. The retina then develops microaneurysms, intraretinal hemorrhages, and focal areas of retinal ischemia (cotton-wool spots). At this point, the retinopathy is known as nonproliferative diabetic retinopathy (NPDR). As the retinopathy progresses, the vessels become further damaged, resulting in retinal nonperfusion and more ischemia. Clinically, the retina has signs of vascular damage including venous beading, intraretinal microvascular abnormalities, and severe hemorrhages. At this point, the retinopathy is classified as severe (NPDR). With further ischemic injury, compensatory chemical mediators 'most notably vascular endothelial growth factors (VEGF)' induce the growth of fragile new blood vessels at the inner surface of the retina. This stage is called proliferative diabetic retinopathy (PDR). It is characterized by neovascularization of the optic disk and neovascularization elsewhere. At this stage, multiple serious complications can occur like vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma [3].

Laser treatment is the first line of treatment for PDR. Unlike focal laser for macular edema where an area of leakage is treated, PDR requires a more global treatment. This is called panretinal photocoagulation (PRP). PRP treats the peripheral retina and causes the abnormal blood vessels to shrink. It lessens the likelihood of bleeding and can reduce the risk of severe visual loss by up to 50%. Vitrectomy surgery may be indicated in patients who develop a severe hemorrhage or traction retinal detachment, in which the vitreous gel, blood, and scar tissue are removed from the vitreous cavity [4].

PRP before parsplana vitrectomy influences the vitreous level of multiple growth factors especially interleukin-6, so it reduces the activity of diabetic retinopathy; hence it reduces the time of surgery and makes the prognosis better [5].

Bevacizumab (Avastin) is drug acting by inhibiting the VEGF. It has emerged as a promising treatment modality for PDR either singly, or with other regimens as, the combination with intravitreal injection of triamcinolone acetate, or with PRP [4].

Recently intravitreal injection of bevacizumab as a preoperative adjuvant before vitrectomy may be helpful in achieving the surgical and anatomical goals by reducing the time of surgery, the intraoperative and postoperative bleeding, and by reducing the use of silicone oil with subsequent reduction of second surgery [6].

Aim of the work

This work aims to study the effect of PRP versus intravitreal injection of Bevacizumab (Avastin) before vitrectomy in the management of PDR.

Patients and methods

Patient consent was taken. In our prospective clinical study, 60 eyes in 40 patients with PDR with indications of vitrectomy (vitreous hemorrhage, tractional retinal detachment involving or threatening the macula, combined tractional/hematogenous retinal detachment and fibrovascular membranes covering and distorting the macula) were managed by parsplana vitrectomy after preoperative preparation by PRP or intravitreal injection of bevacizumab (Avastin). The eyes were grouped into: group A, 30 eyes, who are injected by (1.25 mg in 0.05 ml) bevacizumab (Avastin) intravitreous from 7 to 10 days before vitrectomy (before starting of its tractional effect) and group B, 30 eyes, who receive argon laser photocoagulation 1 month before vitrectomy (to get maximum New vascularization (NV) regression). The patients were selected from the Outpatient Ophthalmology Clinic of Sohag Teaching Hospital and Al-Husein Hospital, Al Azhar University Hospital from 2016 to 2018. The protocol was revised and approved by our ophthalmology ethics committee.

Exclusion criteria

(1) Patients with visual acuity of more than 6/60 (0.10) or less than hand movement.
(2) Previous vitrectomy.
(3) Diabetic retinopathy with media opacification (dense cataract, corneal opacity).
(4) Double perforating trauma.
(5) Patients with chronic uveitis.
(6) Patients with intractable glaucoma or with rubeosis iridis.

Preoperative assessment of the cases

(1) History and demographic data:
Detailed medical history, detailed ocular history was taken including duration of symptoms, myopia, trauma, previous anterior segment operations (cataract surgery), and previous posterior segment procedures (laser photocoagulation, previous vitrectomy).
(2) Evaluation of visual acuity by:
(a) Nonaided and aided method after correction of errors of refraction using early treatment diabetic retinopathy (ETDR) decimal charts.
(3) Anterior segment examination by:
(a) Slit lamp with intraocular pressure (IOP) measurement by slit-lamp mounted aplanation tonometer.
(4) Detailed fundus examination:
By indirect ophthalmoscope using +20 D lens and scleral indentation with a thimble depressor, and slit-lamp bimicroscopy by 90 D lens with assessment of the following: integrity of retinal vasculature, integrity of retinal background, macular status, presence of vitreous hemorrhage, posterior vitreous face status, epiretinal

membranes, retinal or choroidal detachment, and choroidal effusion.
(5) Fundus photography for documentation and follow-up.
(6) Fundus fluorescein angiography for proper diagnosis and follow-up.
(7) B-scan ultrasound examination:
was performed for cases with inadequate visibility due to media opacity as vitreous hemorrhage.
(8) Optical coherence tomography for proper diagnosis, good assessment of the macula, and for follow-up.

Intravitreal bevacizumab injection

Intravitreal bevacizumab injection in group A was done 7–10 days before the vitrectomy. The following steps were done: topical anesthesia, sterilization with betadine for the eyelids, and betadine eye drops for the conjunctival cul-de-sac, application of sterile drapes, anterior chamber paracentesis to lower the IOP, intravitreal injection of bevacizumab (1.25 mg in 0.05 ml) in the lower temporal quadrant at 3.5–4 mm from the limbus, washing the conjunctival sac with betadine 5%, and postinjection topical antibiotic, steroid, and timolol eye drops.

Postinjection evaluation

All the patients were examined on the first day after injection to check for complications resulting from intravitreal injection: slit-lamp examination, fundus examination, and IOP measurement.

Then all the patients were reexamined 1 week after the injection and just before the parsplana vitrectomy: measurement of the best-corrected visual acuity (BCVA), IOP assessment, dilated fundus examination, and colored fundus imaging.

Panretinal photocoagulation

PRP was done in group B 1 month before vitrectomy. It involved applying laser burns over the entire retina sparing the central macular area. It was performed over two sessions, 1 week apart. In the first session, the inferior half of the retina was treated, followed by the superior half in the second session. PRP was done using the slit-lamp delivery system and the Mainster wide-field lens. Laser burns were applied starting at a circumference of 500 μ from the disk and 2 DD from the fovea to wall off the central retina.

Laser settings

(1) Spot size = 200 μ.
(2) Duration = 0.1–0.2 s.
(3) Power = 200–320 mW (sufficient to produce moderate intensity/gray–white burns).

The burns were placed one spot size apart, except in areas of neovascularization where the entire frond was treated. The procedure was continued peripherally to achieve ~ 800–1000 burns in each session, with a total of about 2000–3000 burns over two settings, 1 week apart.

Focal macular photocoagulation (for microaneurysms) was performed in the first session of PRP.

Mainster wide-field lens

This is a contact lens that provides excellent ophthalmoscopic resolution and image binocularity across the entire field of view. It allows a very wide range of slit-lamp magnifications to be used. Image magnification is × 0.68; laser spot magnification is ×1.5, contact diameter is 16 mm, lens height is 27.8 mm, and field of vision is 118° static up to 127° dynamic (Zein *et al*., 2006) [7-9].

Postpanretinal photocoagulation evaluation

All the patients were examined 1 month after PRP to check any complications before vitrectomy by: slit-lamp examination, fundus examination, IOP measurement, measurement of the BCVA, IOP assessment, and dilated fundus examination.

Parsplana vitrectomy

(1) General or local anesthesia.
(2) Sterilization with 'betadine' for the eyelids and 'betadine' eye drops for the conjunctival cul-de-sac.
(3) Application of sterile drapes.
(4) Incision of the conjunctiva at the sites of the three sclerotomies and application of diathermy. The incision is T-shaped temporally and L-shaped nasally.
(5) Three sclerotomies: one for the infusion cannula, one for the endo-illumination, and one for the vitrectomy probe or any other instrument as retinal forceps or scissors.
(6) Suturing of the infusion cannula after the first sclerotomy in the lower temporal quadrant.
(7) Core vitrectomy.
(8) Fenestration of the posterior vitreous cortex with a vitreous cutter and this fenestration extended for 360° in a ring-like manner to truncate the so-called conical anteroposterior traction. The peripheral margin of the posterior vitreous cortex (vitreous skirt) was trimmed, leaving a minimal amount attached to the vitreous base.
(9) Removal of the fibrovascular tissue (FVT): the posterior margin of the 360° fenestration was trimmed flush with the outer margin of the FVT. Conformal cutter delamination using a side approach was used to remove a significant portion of the FVT.
(10) The port was not oriented pointing toward the surgeon, nor was the cutter positioned under the FVT. The angle of attack was continuously modified so that the FVT could be fed into the port, while the port was rotated about 15° away from the retina. Some of the FVT was judged to be too adherent to the retina to remove with the vitreous cutter and was removed using inside-out scissors' delamination with curved scissors. The vascular attachment points were coagulated with the endodiathermy probe. Segmentation is primarily used as access to expose the dissection plane (potential space) for delamination.
(11) Perflurocarbon liquid (PFCL) injection on demand.
(12) Vitrectomy for the vitreous base was performed 360° with scleral indentation accomplished by the assistant.
(13) Endolaser PRP and endolaser to retinal breaks.
(14) PFCL/silicone oil exchange through the infusion cannula.
(15) Closure of two sclerotomies.
(16) Removal of the infusion cannula and closure of the third sclerotomy.

(17) Closure of the conjunctiva.
(18) Eye patching.

Intraoperative evaluation

(1) The effect of two adjuvants on the severity of intraoperative hemorrhage is evaluated.
(2) Using of intraoperative endodiathermy.
(3) Using of blunt and sharp dissections.
(4) Using of intraoperative endolaser.
(5) Meantime of surgery.

Postoperative follow-up

All the patients were regularly examined on the first day postoperatively, after 1 week, and then monthly for 6 months postoperatively. The following was examined:

(1) The BCVA.
(2) Anterior segment examination using a slit lamp to detect any postoperative complications such as reaction irido-cyclitis, or silicone oil in Anterior chamber (AC).
(3) Measurement of the IOP.
(4) Dilated fundus examination to detect postoperative vitreous hemorrhage and to evaluate the state of the retina.
(5) Silicone oil removal 3–6 months postoperatively.
(6) Colored fundus photography 1, 3, and 6 months postoperatively.

Statistical analysis

IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp., USA) was used for data analysis. Data were expressed as mean ± SD for quantitative parametric measures in addition to median percentiles for quantitative nonparametric measures and both number and percentage for categorized data. The following tests were done: χ^2 test to study the association between each two variables or comparison between two independent groups as regards the categorized data. The probability of error at 0.05 was considered significant, while at 0.01 and 0.001 is highly significant.

Results

Our clinical prospective study of 60 eyes in 40 patients with PDR with indications of vitrectomy (vitreous hemorrhage, tractional retinal detachment involving or threatening the macula, combined tractional/rhegmatogenous retinal detachment, and fibrovascular membranes covering and distorting the macula, persistent macular edema with viteromacular traction) managed by parsplana vitrectomy after preoperative preparation by intravitreal injection of bevacizumab (Avastin) or PRP grouped into two groups: group A and group B.

Group A, 15 (50%) cases with mild bleeding, eight (26.7%) cases with minimal bleeding, seven (23.3%) cases with moderate bleeding, and 0 cases with no bleeding; group B, six (20%) cases with mild bleeding, 14 (46.7%) cases with minimal bleeding, 0 (0.0%) cases with moderate bleeding, and 10 (33.3%) cases with no bleeding, with statistically highly significant *P* value being 0.000 (Tables 1 and 2).

Group A, once in eight (26.7%) cases, twice in 15 (50%) cases, three times in seven (23.3%) cases, and not used in 0 cases, group B, once in 14 (46.7%) cases, twice in six (20%) cases, three times in 0 (0.0%) cases, and not used in 10 (33.3%) cases, with statistically highly significant *P* value is 0.000 (Tables 3–6).

Table 1: Cross-table showing grading of intraoperative bleeding in both groups

	A	B	Total
Intraoperative bleeding			
Mild			
Count	15	6	21
%	50.0	20.0	35.0
Minimal			
Count	8	14	22
%	26.7	46.7	36.7
Moderate			
Count	7	0	7
%	23.3	0.0	11.7
No			
Count	0	10	10
%	0.0	33.3	16.7
Total			
Count	30	30	60
%	100.0	100.0	100.0

Table 2: Pearson's χ^2 value for grading of intraoperative bleeding in both groups

	Value	*P*
Pearson's χ^2	22.494	0.000

Table 3: Cross-table showing using of intraoperative endodiathermy in both groups

	A	B	Total
Intraoperative diathermy			
1			
Count	8	14	22
%	26.7	46.7	36.7
2			
Count	15	6	21
%	50.0	20.0	35.0
3			
Count	7	0	7
%	23.3	0.0	11.7
No			
Count	0	10	10
%	0.0	33.3	16.6
Total			
Count	30	30	60
%	100.0	100.0	100.0

Group A, blunt dissection in 18 (60%) cases, blunt and sharp dissection in 11 (36.7%) cases, no dissection in one (3.3%) case; group B, blunt dissection in 17 (56.7%) cases, blunt and sharp dissection in one (3.3%) case, no dissection in 12 (40%) cases, with statistically highly significant *P* value being 0.000 [Table 6].

Group A, less than 1500 shoots in seven (23.3%) cases, more than 1500 shoots in 23 (76.7%) cases, group B, less than 1500 shoots in 29 (96.7%) cases, more than 1500 shoots in one (3.3%) case, with statistically highly significant *P* value being 0.000 (Tables 7 and 8).

Group A, flame-shaped hemorrhage in one (3.3%) case, preretinal hge in 11 (36.7%) cases, perifoveal hge in one (3.3%) case, no hge in 16 (53.3%) cases, peripapillary hge in one (3.3%) case, and spot hge zero (0.0%) cases; group B, flame-shaped hge in zero (0.0%) case, preretinal hge in one (3.3%) case, perifoveal hge in one (3.3%) case, no hge in 26 (86.7%) cases, peripapillary hge in one (3.3%) case, and spot hge one (3.3%) case, with statistically significant *P* value being 0.000 (Tables 9 and 10).

Group A, cellophane maculopathy in eight (26.7%) cases, ischemic maculopathy in 14 (46.7%) cases, ischemic maculopathy with pale optic disk in one (3.3%) case, pale optic disk in 0 (0.0%) case, macular pucker in one (3.3%) case, macular edema three (10.0%) cases, NPDR in one (3.3%) case, preretinal hge and RD in 0 (0.0%) case, tractional retinal detachement (RD) and rebleeding in one (3.3%) case, and no complications in one (3.3%) case; group B, cellophane maculopathy in eight (26.7%) cases, ischemic maculopathy in eight (26.7%) cases, ischemic maculopathy with pale optic disk in 0 (0.0%) case, pale optic disk in one (3.3%) case, macular pucker in 0 (0.0%) case, macular edema one (3.3%) cases, NPDR in four (13.3%) cases, preretinal hge and RD in one (3.3%) case, tractional RD and rebleeding in 0 (0%) case, and no complications in seven (23.3%) cases, with statistically nonsignificant *P* value being 0.125 (Tables 11 and 12, Figs 1–3).

Table 4: Pearson's χ^2 value for using of intraoperative diathermy in both groups

	Value	*P*
Pearson's χ^2	22.494	0.000

Table 5: Cross-table showing use of intraoperative blunt or sharp dissection in both groups

	A	B	Total
Sharp/blunt dissection			
B			
Count	18	17	35
%	60.0	56.7	58.3
B/S			
Count	11	1	12
%	36.7	3.3	20.0
No			
Count	1	12	13
%	3.3	40.0	21.7
Total			
Count	30	30	60
%	100.0	100.0	100.0

Table 6: Pearson's χ^2 value for use of intraoperative blunt or sharp dissection in both groups

	Value	*P*
Pearson's χ^2	17.670	0.000

Table 7: Cross-table showing use of intraoperative endolaser in both groups

	A	B	Total
Intraoperative endolaser			
<1500 shoots			
Count	7	29	36
%	23.3	96.7	60.0
>1500 shoots			
Count	23	1	24
%	76.7	3.3	40.0
Total			
Count	30	30	60
%	100.0	100.0	100.0

Table 8: Pearson's χ^2 value for use of intraoperative endolaser in both groups

	Value	*P*
Pearson's χ^2	33.611	0.000

Discussion

Diabetic retinopathy remains a major threat to sight in the working-age population in the developed world. Furthermore, it is increasing as a major cause of blindness in other parts of the world especially in developing countries [10].

In spite of all the scientific advances in medicine and the knowledge of the pathophysiology and treatment of diabetes over the past 25 years, diabetic retinopathy remains one of the leading causes of blindness in the industrialized working population [11].

The growth of new vessels in response to retinal ischemia (factor X) was initially proposed almost half a century ago [12].

But in 1994 Aiello and colleagues demonstrated that VEGF is the major mediator of PDR. He found high levels of VEGF in the vitreous of patients with PDR in response to retinal hypoxia.

Elevated expression of VEGF can be demonstrated in diabetic macular edema (DME), which suggests that a metabolic condition exists that has some properties in common with retinal hypoxia. VEGF is a potent inducer of vascular permeability and vessel dilatation [13].

Table 9: Cross-table showing postoperative bleeding in both groups

	A	B	Total
Postoperative bleeding			
Flame-shaped he			
Count	1	0	1
%	3.3	0.0	1.7
Preretinal he			
Count	11	1	12
%	36.7	3.3	20.0
Perifoveal he			
Count	1	1	2
%	3.3	3.3	3.3
No			
Count	16	26	42
%	53.3	86.7	70.0
Peripapillary he			
Count	1	1	2
%	3.3	3.3	3.3
Spot hge			
Count	0	1	1
%	0.0	3.3	1.7
Total			
Count	30	30	60
%	100.0	100.0	100.0

Table 10: Pearson's χ^2 value for postoperative bleeding in both groups

	Value	*P*
Pearson's χ^2	12.714	0.026

Then, over the next few years, evidence from both animal and human clinical studies has been accumulated to support the critical role of VEGF in ocular neovascularization. These findings provide the rationale behind anti-VEGF therapy in retinal vascular diseases associated with the formation of new vessels [14].

Retinal neovascularization represents an important risk factor for severe vision loss in patients with diabetes mellitus. Approximately 4.5% of patients with PDR require parsplana vitrectomy despite panretinal laser photocoagulation. Moreover, surgery may be challenging, especially when dealing with patients suffering from severe complications of PDR [15].

Intraoperative vitreous hemorrhage is a major problem of diabetic vitrectomy which renders the surgery more difficult due to obscuration of view intraoperatively. Meticulous surgical technique is essential to avoid intraoperative bleeding, but when it occurs, there are a lot of measures to be taken to manage this problem [16].

The first and most common method of stopping the bleeding is by raising the IOP through manipulation of the infusion line pressure [17]. The second method of controlling intraoperative

Table 11: Cross-table showing postoperative complications in both groups

	A	B	Total
Postoperative complications			
Cellophane maculopathy			
Count	8	8	16
%	26.7	26.7	26.7
Ischemic maculopathy			
Count	14	8	22
%	46.7	26.7	36.7
Ischemic maculopathy+pale optic disk			
Count	1	0	1
%	3.3	0.0	1.7
Pale disk			
Count	0	1	1
%	0.0	3.3	1.7
Macular pucker			
Count	1	0	1
%	3.3	0.0	1.7
Cystoid macular edema			
Count	3	1	4
%	10.0	3.3	6.7
No			
Count	1	7	8
%	3.3	23.3	13.3
NPDR			
Count	1	4	5
%	3.3	13.3	8.3
Sever preretinal hemorrhages			
Count	0	1	1
%	0.0	3.3	1.7
Tractional RD/rebleeding			
Count	1	0	1
%	3.3	0.0	1.7
Total			
Count	30	30	60
%	100.0	100.0	100.0

NPDR, nonproliferative diabetic retinopathy.

Table 12: Pearson's χ^2 value for postoperative complications in both groups

	Value	*P*
Pearson's χ^2	13.936	0.125

bleeding, when raising the infusion is ineffective, is by manual compression of the bleeding vessels [18]. The third method is heat-induced coagulation using either intraocular diathermy or argon laser endophotocoagulation [18]. The fourth method for hemostasis is by using fibrinogenic agents such as thrombin and hemocoagulase [19]. The fifth method is surgical tamponades which are used in intraoperative hemostasis including gas, viscoelastic agents, silicone oil, and perfluorocarbon liquids (Grigorian *et al*., 2003).

Then it was suggested by Chen and Park[20] to use preoperative intravitreal bevacizumab to reduce intraoperative bleeding

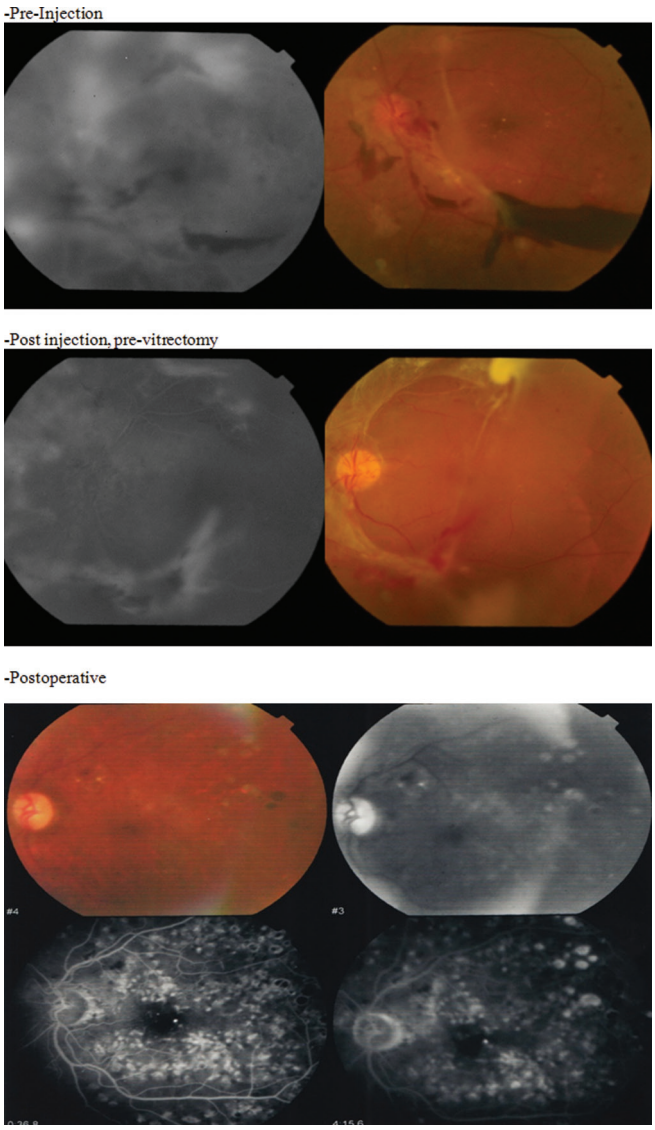

Figure 1: Case 2 preretinal hge, FVMs, NVDs, and NVEs.

depending on its anti-VEGF effect, to induce regression of neovascularization.

There was no increase in IOP postinjection. The results of the current study are consistent with data from other studies regarding the absence of any apparent association between intravitreal bevacizumab injection and increased IOP, cataract development or progression or increased rates of endophthalmitis related to the study drug [10].

In our study, which was carried out on an Egyptian population shows prospective clinical study of 60 eyes in 40 patients with PDR with indications of vitrectomy (vitreous hemorrhage, tractional retinal detachment involving or threatening the macula, combined tractional/rhegmatogenous retinal detachment and fibrovascular membranes covering and distorting the macula) managed by parsplana vitrectomy after preoperative preparation by intravitreal injection of bevacizumab (Avastin) or PRP. The eyes were grouped into:

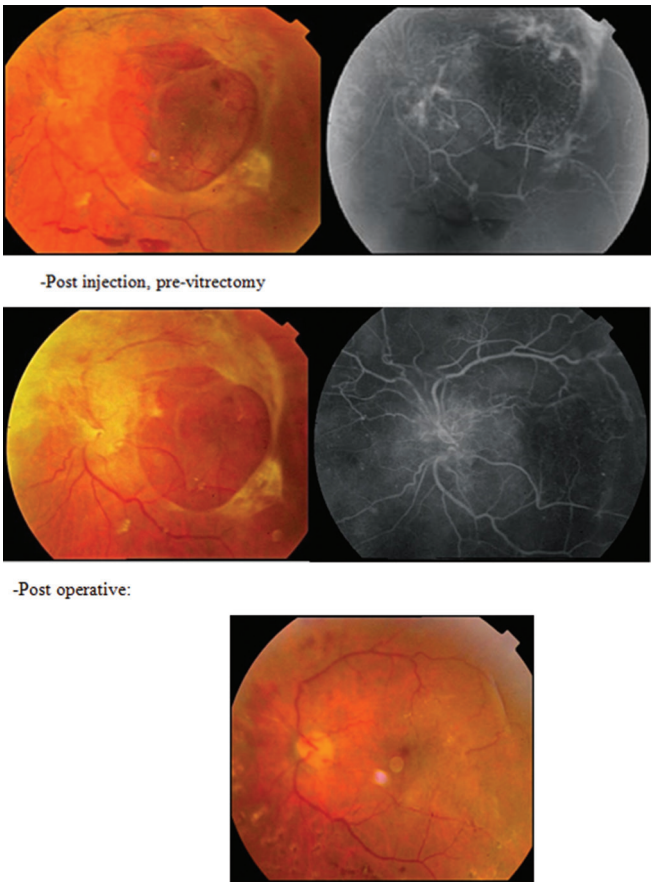

Figure 2: Case 3 FVMs, tractional RD, preretinal hge, tractional macular detachment.

group A, consisting of 30 eyes, which are injected by (1.25 mg in 0.05 ml) bevacizumab (Avastin) intravitreal from 7 to 10 days before vitrectomy and group B, consisting of 30 eyes, which received argon laser photocoagulation 1 month before vitrectomy.

Hattori *et al*.[21] showed the efficacy of 0.16 mg which was equivalent to a dose of 1.25 mg of intravitreal bevacizumab in reducing vitreous VEGF concentration and intraoperative bleeding when used before vitrectomy. However, they used this dose for a very short period before surgery (3 days) which is not a sufficient period to judge its actual effect on the macular thickness or its half-life in the vitreous cavity.

The rapid, dramatic response is seen with bevacizumab before vitrectomy due to its activity against all isoforms of VEGF. Its larger size gives it an advantage over the smaller ranibizumab due to less retinal penetration and a longer half-life [10].

A recent multicenter report has suggested that intravitreal injection of bevacizumab may precipitate tractional retinal detachment if vitrectomy was done after more than 10 days but did not occur if shorter time (5–7 days) postinjection [22].

Jonathan *et al*.[23] reported that at the time of surgery eyes treated with Avastin had significant regression of the vascular component of the fibrovascular complexes without progression

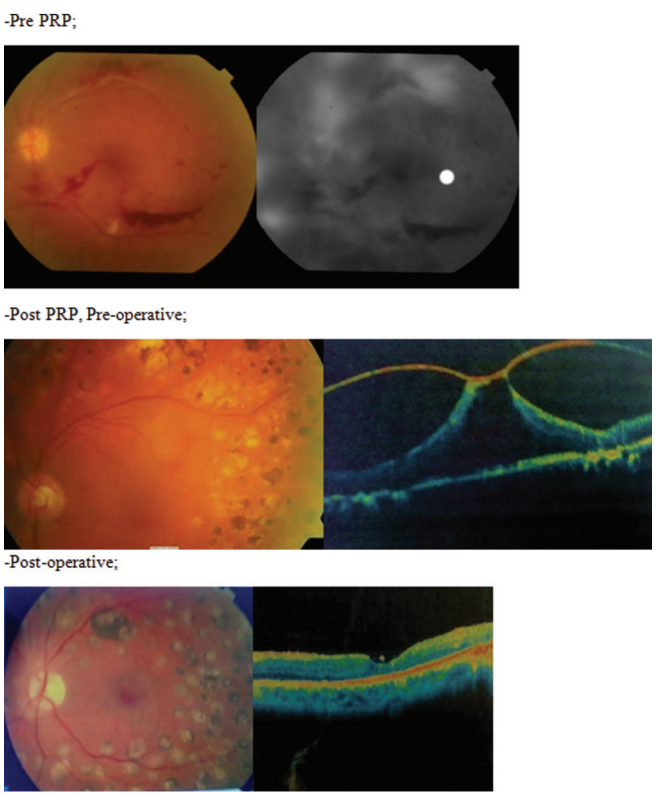

Figure 3: Case 5 severe NVDs, NVEs, preretinal hge, tractional macular detachment.

and thickening of the fibrous component and tractional retinal detachment (TRD). This made surgery technically easier, as the fibrovascular complex was readily separated from the retina with less intraoperative bleeding, which in turn provided better visualization. The relative ease of delamination after Avastin is difficult to be evaluated objectively and does not readily lend itself to a randomized, controlled study. However, the fibrovascular membranes, not adherent to the retina as would have been expected without preoperative Avastin, and they certainly did not bleed as much. They needed intraoperative diathermy in only six cases but would have expected to use it in the majority of similar diabetic cases. Whether improving the ease of surgery in this way results in a better outcome for the patient remains to be determined by larger studies.

In our study, time of surgery showing group A ranged from 55 to 88 min (with a mean duration of 71.8667 and SD 7.38467). Group B ranged from 48 to 85 min (with a mean duration of 66.4 and SD 8.57663). There was a statistically significant difference between both groups, *P* value is 0.011. Intraoperative use of endodiathermy showing group A, once in eight (26.7%) cases, twice in 15 (50%) cases, three times in seven (23.3%) cases, and not used in 0 cases; group B, once in 14 (46.7%) cases, twice in six (20%) cases, three times in 0 (0.0%) cases, and not used in 10 (33.3%) cases, with statistically highly significant *P* value being 0.000.

Mason *et al*.[24] report that at the time of surgery, they observed that eyes treated with bevacizumab had significant regression of the vascular component of the fibrovascular complexes without progression and thickening of the fibrous component and TRD. This made surgery technically easier, as the fibrovascular complex was readily separated from the retina with less intraoperative bleeding, which in turn provided better visualization. Preoperative Avastin seems to be particularly useful in eyes in which there is still a significant vascular component to the fibrovascular proliferation despite full PRP. Eyes that are in the fibrotic stage of proliferative disease are unlikely to benefit to the same extent.

In our study, intraoperative bleeding showing group A, 15 (50%) cases with mild bleeding, eight (26.7%) cases with minimal bleeding, seven (23.3%) cases with moderate bleeding, and 0 cases with no bleeding; group B, six (20%) cases with mild bleeding, 14 (46.7%) cases with minimal bleeding, 0 (0.0%) cases with moderate bleeding, and 10 (33.3%) cases with no bleeding, with statistically highly significant, *P* value is 0.000.

Gibran *et al*.[25] presented six severe PDR cases, which were successfully treated with a combination of vitrectomy and advanced intravitreal bevacizumab. In the vitrectomy of severe PDR, they often encounter sustained bleeding that obscures surgical field and prolongs surgical time, which results in the increase of the risk of accidental retinal damages. They demonstrated the efficacy of bevacizumab for the treatment of PDR, which remarkably attenuates the activity of fibrovascular membrane (FVM) at a week postadministration. Their cases showed minimum bleeding in surgical excisions of FVM even after 3 days of administration. However, the excessive fibrosis of FVM may increase tissue traction.

A study by Rizzo *et al*.[22] was conducted on 22 eyes with severe PDR. Out of the 22 patients enrolled, 11 underwent intravitreal bevacizumab (1.25 mg in 0.05 ml) 5–7 days before pars plana vitrectomy (PPV) (group A), while 11 received direct surgery (group B). In this study, the intraoperative bleeding during FVP removal occurred five times in group A versus 16 times in group B. Hemorrhage was controlled by increasing infusion pressure or by mechanical pressure with a blunt tool three times in group A versus seven times in group B. Endodiathermy was applied twice in group A and nine times in group B.

In our study, intraoperative dissection of FVM showing: group A, blunt dissection in 18 (60%) cases, blunt and sharp dissection in 11 (36.7%) cases, no dissection in one (3.3%) case; group B, blunt dissection 17 (56.7%) cases, blunt and sharp dissection in one (3.3%) case, no dissection in 12 (40%) cases, with statistically highly significant *P* value being 0.000. Intraoperative use of endolaser showing group A, less than 1500 shoots in seven (23.3%) cases, more than 1500 shoots in 23 (76.7%) cases, group B, less than 1500 shoots in 29 (96.7%) cases, more than 1500 shoots in one (3.3%) case, with statistically highly significant *P* value being 0.000.

Anti-VEGF agents have been effectively used for the reduction of neovascularization related to PDR and to decrease

intraoperative bleeding, allowing for better visualization and dissection of epiretinal membranes with less incidence of iatrogenic breaks. This was evidenced by the significant reduction in neovessels expressing the panendothelial marker CD34, which was noted from day 5 postinjection and became consistently low from day 10 onwards if surgery is delayed, or these increasing traction forces cannot be monitored and it might risk endangering the macula, central vision, or final visual outcome by progression of TRD [20].

Avery *et al*.[10] conducted a retrospective, interventional, consecutive case series of 45 eyes in 32 patients with retinal and/or iris neovascularization secondary to diabetes mellitus treated with intravitreal bevacizumab (6.2 μg–1.25 mg). No significant ocular or systemic adverse events were observed. Complete resolution of angiographic leakage of NV of the disk was noted in 73% of the eyes, and leakage of iris NV completely resolved in 82% of eyes. Leakage was noted to diminish as early as 24 h after injection. Short-term results suggested that intravitreal bevacizumab was well tolerated and was associated with a rapid regression of iris and retinal NV even with the lowest dose (6.2 μg).

In a study by Peters *et al*.[26] the intravitreal peak concentration, as well as the antiedematous effects on the choriocapillaris, was found to be present on day 4, obviously paralleling the situation in the anterior chamber. The ciliary body shows an intense immune-reactivity for bevacizumab, even on day 14.

A pharmacokinetic study showed that after intravitreal injection, bevacizumab can be detected within the choroids and the inner retina as early as 1 day postoperatively. Bevacizumab rapidly spreads to the outer retina and choroid in the days following the injection and is present at detectable levels in the retinal tissue 14 days after intravitreal injection [27].

In other words, in the study of Yang *et al*.[28] one may expect some bevacizumab effect in the early postoperative days. This residual effect may decrease the likelihood of prompt new vessel proliferation after surgery. However, since the effect is only temporary, this single preoperative dose may not be sufficient to prevent late-onset recurrent vitreous hemorrhage secondary to new blood-vessel growth at the sclerotomy sites or vitreous base.

It has been suggested that intravitreal bevacizumab injection at the end of surgery may decrease postoperative vitreous hemorrhage since it can potentially reduce bleeding from residual FVT [29].

In our study, postoperative bleeding showing: group A, flame-shaped hge in one (3.3%) case, preretinal hge in 11 (36.7%) cases, perifoveal hge in one (3.3%) case, no hge in 16 (53.3%) cases, peripapillary hge in 1 (3.3%) case, and spot hge In zero (0.0%) case; group B, flame-shaped hge in zero (0.0%) case, preretinal hge in one (3.3%) case, perifoveal hge in one (3.3%) case, no hge in 26 (86.7%) cases, peripapillary hge in one (3.3%) case, and spot hge In one (3.3%) case, with statistically significant *P* value being 0.000.

A study conducted by Itakura *et al*.[30] demonstrated that a high level of VEGF in the vitreous was maintained in the vitreous cavity after vitrectomy in eyes with PDR. This suggests that VEGF is secreted into the vitreous cavity even after vitrectomy. Their results suggested that intraretinal production of VEGF is maintained before and after vitrectomy.

In spite of this, there was no regrowth of new vessels in our study in both groups A or B. This could be attributed to the Good dissection of epiretinal membranes due to reduced intraoperative bleeding and improved intraoperative visualization, the effect of PRP, the prolonged effect of bevacizumab, or due to the short postoperative follow-up period (6 months).

Yang *et al*.[28] concluded that local factors related to clear-up speed of the vitreous after vitrectomy for PDR include the amount of residual blood clots on the retinal surface at the end of operation, which will inevitably lyse and cause temporary vitreous opacity before reabsorption; retained blood in the peripheral vitreous skirt, which may dissolve and shed into the fluid vitreous cavity; bleeding from surgically injured retinal blood vessels; bleeding from unreleased FVT; and fibrin and inflammatory cells within the vitreous. Meticulous suction and trimming of the vitreous base with a vitreous cutter may minimize residual peripheral blood, and adequate and timely use of topical or regional steroids may control excessive inflammation. Despite the above measures, delay of vitreous clear-up time may still occur and can be attributable to blood clot lysis or ruptured vessels in the retina or from residual FVT. It was found that intraoperative bleeding and subsequent blood clots that remained at the end of the surgery were significantly less in the bevacizumab pretreated group, ensuring shortened reabsorption time for clot lysis. The regression of active fibrovascular proliferation by the action of bevacizumab decreases the extent of bleeding during tissue segmentation and delamination. The lesser intraoperative bleeding makes visualization of the surgical plane better for the surgeon, who in turn facilitates a precise separation of the proliferative tissue from the retina and helps avoid accidental retinal vascular damage and iatrogenic retinal breaks. As the factors causing a delay of vitreous clear-up are specifically and properly targeted and treated, the vitreous clear-up time can be shortened.

In our study, postoperative bleeding showing: group A, flame-shaped hge in one (3.3%) case, preretinal hge in 11 (36.7%) cases, perifoveal hge in one (3.3%) case, no hge in 16 (53.3%) cases, peripapillary hge in one (3.3%) case, and spot hge in zero (0.0%) case, group B, flame-shaped hge in zero (0.0%) case, preretinal hge in one (3.3%) case, perifoveal hge in one (3.3%) case, no hge in 26 (86.7%) cases, peripapillary hge in one (3.3%) case, and spot hge In one (3.3%) case, with statistically significant *P* value being 0.000.

PRP has been the mainstay for the treatment of PDR, and its suppressive effect on retinal nerve fibres (RN) has been well documented. However, substantial regression of new vessels may take weeks after completion of PRP, and in up to one-third of cases, new vessels continue to grow despite initial PRP. In

these cases, vitreous hemorrhage may induce visual loss and prevent complete laser. Moreover, macular edema may increase after PRP that may be transient or persistent [20].

Scatter (panretinal) photocoagulation is a type of laser surgery for PDR, in which laser is delivered in a scatter pattern throughout the peripheral fundus and is intended to lead to regression of neovascularization. The primary goal of laser photocoagulation for PDR is to prevent vision loss from tractional retinal detachment, vitreous hemorrhage, and neovascular glaucoma [31].

The cells of the RPE produce growth-stimulating and growth-inhibiting factors and the response of these cells to photocoagulation injury may change the balance of these factors [32].

PRP before parsplana vitrectomy influences vitreous level of multiple growth factors especially interleukin-6, so it reduces the activity of diabetic retinopathy. Hence it reduces the time of surgery and makes the prognosis better [5].

The most important method of treatment in advanced PDR is the application of panretinal laser photocoagulation. Surgery is a commonly accepted method of treatment after completing laser photocoagulation. The objective of preoperative photocoagulation is to facilitate control of the vascular proliferative process. The outcomes of vitreous surgery in eyes where intensive photocoagulation has been applied are more satisfactory. In the advanced stages of DR, the external laser photocoagulation treatment could no longer be applied in the presence of preretinal and vitreous hemorrhage and intensive fibrovascular vitreoretinal tractions. Despite the intensive photocoagulation applied preoperatively, the proliferations were observed to continue in 70.83% of the cases. At this stage, vitreoretinal surgery and additional intraoperative endolaser photocoagulation were necessary [33].

Yorston *et al*.[5] in their study 'predictive clinical features and outcomes of vitrectomy for PDR' used a preexisting argon laser group in their study in the form of PRP in 65 (43%) patients, and they reported that eyes with preoperative laser had no increased risk of vitreous cavity hemorrhage or washout; 57% of cases achieved a vision 6/60 or better in cases with preoperative macular detachment while in cases without preoperative macular detachment 84% of cases achieved a vision 6/60 or better; five (3.0%) cases complicated with retinal detachment due to iatrogenic break, postoperative hemorrhage occurred in 22% of eyes. Also, they reported that there was no association between visual outcome and patient age, insulin use, duration of diabetes mellitus, hypertension, or preoperative laser treatment. They conclude that the outcome of vitrectomy for PDR remains unpredictable, but the great majority of patients will regain or retain useful vision.

In the study by Rizzo *et al*. [22], the mean preoperative BCVA was 1.87 log MAR in the bevacizumab group and 2.04 log MAR in group B, which is not significantly different ($P = 0.7$ Wilcoxon's two-sample test). Mean postoperative BCVA at 6 months was 0.88 log MAR in group A and log MAR 2.01 in control group B, significantly different ($P = 0.01$ Wilcoxon's two-sample test). Postoperative BVCA improved in the bevacizumab group from the preoperative value ($P = 0.15$ slightly significant), while in the control group there was a nonsignificant increase ($P = 0.96$).

In our study, baseline BCVA showing: group A, ranged from 0.008 to 0.08 (with a mean VA of 0.032533, median 0.023 and SD 0.02556). Group B ranged from 0.016 to 0.1 (with a mean VA of 0.0484, median 0.05, and SD 0.0282325). There was a statistically significant difference between both groups, *P* value is 0.014, and preoperative BCVA showing group A, ranged from 0.008 to 0.1 (with a mean VA of 0.041067, median 0.03, and SD 0.0265056). Group B ranged from 0.016 to 0.1 (with a mean VA of 0.063067, median 0.06, and SD 0.0285209). There was a statistically highly significant difference between both groups, *P* value is 0.003.

Postoperative BCVA after 1-month showing group A ranged from 0.016 to 0.1 (with a mean VA of 0.06147, median 0.06, and SD 0.027215); group B ranged from 0.016 to 0.15 (with a mean VA of 0.10853, median 0.1, and SD 0.034176). There was a statistically highly significant difference between both groups, *P* value is 0.00.

Postoperative BCVA after 3 months is showing: group A ranged from 0.016 to 0.15 (with a mean VA of 0.07147, median 0.08, and SD 0.035525). Group B ranged from 0.016 to 0.25 (with a mean VA of 0.11787, median 0.1, and SD 0.044287). There was a statistically highly significant difference between both groups, *P* value is 0.00.

Postoperative BCVA after 3 months is showing: group A ranged from 0.05 to 0.15 (with a mean VA of 0.104, median 0.1, and SD 0.03158); Group B ranged from 0.06 to 0.25 (with a mean VA of 0.1887, median 0.15, and SD 0.05746). There was a statistically highly significant difference between both groups, *P* value is 0.00.

Conclusion

Use of both adjuvants before vitrectomy enhances the outcome of vitrectomy when best indicated rather than without using. The shorter time of surgery and less using of endodiathermy or endolaser is with the PRP group, although postoperative BCVA gaining is not significant. So, accurate clinical differences between two adjuvants need more researches.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Rajala U, Pajunpää H, Koskela P, Keinänen-Kiukaanniemi S. High cardiovascular disease mortality in subjects with visual impairment caused by diabetic retinopathy. Diabetes Care 2000; 23:957–996.
2. Blum M, Eichhorn M, Vilser W. Hemodynamics and diabetic

retinopathy. Klin Monatsbl Augenheilkd 2005; 222:463–470.
3. Massin P, Chabouis A, Erginay A, Viens-Bitker C, Lecleire-Collet A, Meas T, *et al*. OPHDIAT: a telemedical network screening system for diabetic retinopathy in the Ile-de-France. Diabetes Metab 2008; 34:227–234.
4. Rema M, Sujatha P, Pradeepa R. Visual outcomes of panretinal photocoagulation in diabetic retinopathy at one-year follow-up and associated risk factors. Indian J Ophthalmol 2005; 53:93–99.
5. Yorston D, Wickham L, Benson S, Bunce C, Sheard R, Charteris D. Predictive clinical features and outcomes of vitrectomy for proliferative diabetic retinopathy. Br J Ophthalmol 2008; 92:365–368.
6. Arevalo JF, Maia M, Flynn HW, Saravia M, Avery RL, Farah ME, *et al*. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. Br J Ophthalmol 2008; 92:213–216.
7. Zein WM, Baha'n NO, Jurdi FA, Schakal A, Bashshur ZF. Panretinal photocoagulation and intravitreal triamcinolone acetonide for the management of proliferative diabetic retinopathy with macular edema. Retina 2006; 26:137–42.
8. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, *et al*. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994; 331:1480–7.
9. Grigorian RA, Castellarin A, Bhagat N, Priore LD, Von Hagen S, Zarbin MA. Use of viscodissection and silicone oil in vitrectomy for severe diabetic retinopathy. In Seminars in ophthalmology. Taylor & Francis; 2003; 18:121–126.
10. Avery RL, Pearlman J, Pieramici DJ, Rabena M, Castellarin A, Nasir M, *et al*. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology 2006; 113:1695–1705.
11. Kempen JH, O'Colmain BJ, Leske MC, Haffner SM, Klein R, Moss SE, *et al*. The prevalence of diabetic retinopathy among adults in the United States. Arch Ophthalmol 2004; 122:552–563.
12. Michaelson IC. Retinal circulation in man and animals. Am J Ophthalmol 1954; 38:419–20.
13. Soliman W, Sander B, Jorgensen TM. Enhanced optical coherence patterns of diabetic macular edema and their correlation with the pathophysiology. Acta Ophthalmol Scand 2008; 85:613–617.
14. Adamis AP, Miller JW, Bernal MT, D'amico DJ, Folkman J, Yeo TK, Yeo KT. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. Am J Ophthalmol 1994; 118:445–450.
15. Flynn HWJr, Chew EY, Simons BD, Barton FB, Remaley NA, Ferris FL. Pars plana vitrectomy in the early treatment diabetic retinopathy study. ETDRS report number 17. Ophthalmology 1992; 99:1351–1357.
16. Gardner TW, Blankenship GW. Proliferative diabetic retinopathy: principles and techniques of surgical treatment. In: Ryan SJ, ed. *Retina*. 2nd ed. St Louis: Mosby; 1994. 515–539.
17. Parel JM, Parish RK, Nose I. An intraoperative intraocular pressure monitor. Ophthalmic Surg 1987; 18:371–374.
18. Chow DR, De Bustros S. Control of perioperative bleeding in vitreoretinal surgery. In: Ryan SJ, ed. *Retina*. 4th ed. St. Louis: Mosby; 2006. 2451–2461.
19. Thompson JT, Auer CL, de Bustros S, Michels RG, Rice TA, Glaser BM. Prognostic indicators of success and failure in vitrectomy for diabetic retinopathy. Ophthalmology 1987; 93:290–295.
20. Chen E, Park CH. Use of intravitreal bevacizumab as a preoperative adjunct for tractional retinal detachment repair in severe proliferative diabetic retinopathy. Retina 2006; 26:699–700.
21. Hattori T, Shimada H, Nakashizuka H, Mizutani Y, Mori R, Yuzawa M. Dose of intravitreal bevacizumab used as preoperative adjunct therapy for proliferative diabetic retinopathy. Retina 2010; 30:761–764.
22. Rizzo S, Genovesi-Ebert F, Di Bartolo E, Vento A, Miniaci S, Williams G. Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative diabetic retinopathy (PDR). Graefe's Arch Clin Exp Ophthalmol 2008; 246:837–842.
23. Jonathan Y, Williams C, Allen P, Buttery R, Chiu D, Clark B, *et al*. Avastin as an adjunct to vitrectomy in the management of severe proliferative diabetic retinopathy. Clin Exp Ophthalmol 2008; 36:449–454.
24. Mason J, Nixon P, White M. Intravitreal injection of bevacizumab (Avastin) as adjunctive treatment of proliferative diabetic retinopathy. Am J Ophthalmol 2006; 142:685–688.
25. Gibran SK, Sachdev A, Stappler T, Newsome R, Wong D, Hiscott P. Histological findings of a choroidal neovascular membrane removed at the time of macular translocation in a patient previously treated with intravitreal bevacizumab treatment (Avastin). Br J Ophthalmol 2007; 5:602–604.
26. Peters S, Heiduschka P, Julien S, Bartz-Schmidt KU, Schraermeyer U. Immuno-histochemical localization of intravitreally injected bevacizumab in the anterior chamber angle, iris and ciliary body of the primate eye. Br J Ophthalmol 2008; 92:541–544.
27. Heiduschka P, Fietz H, Hofmeister S, Schultheiss S, Mack AF, Peters S, *et al*. and The Tübingen Bevacizumab Study Group. Penetration of bevacizumab through the retina after intravitreal injection in the monkey. Invest Ophthalmol Vis Sci 2007; 48:2814–2823.
28. Yang C-M, Yeh P-T, Yang C-H, Chen M-S. Bevacizumab pretreatment and long-acting gas infusion on vitreous clear-up after diabetic vitrectomy. Am J Ophthalmol 2008; 146:211–217.
29. Charles S, Rosenfeld PJ, Gayer S. Medical consequences of stopping anticoagulant therapy before intraocular surgery or intravitreal injections. Retina 2007; 27:813–815.
30. Itakura H, Kishi S, Kotajima N, Murakami M. Persistent secretion of vascular endothelial growth factor into the vitreous cavity in proliferative diabetic retinopathy after vitrectomy. Ophthalmology 2004; 111:1880–1884.
31. Goff M, Mcdonald H, Ai E. Photocoagulation for Diabetic Macular Edema and Diabetic Retinopathy. In: I. Scott H. Flynn, Smiddy W, ed. Diabetes and Ocular Disease, 2nd ed. New York: Oxford University Press; 2010. p. 183–206.
32. Danis RP, Davis MD. Proliferative diabetic retinopathy. In Diabetic Retinopathy. Humana Press; 2008. p. 29-65.
33. Diabetic Retinopathy Vitrectomy Study Research Group. Early vitrectomy for severe proliferative diabetic retinopathy in eyes with useful vision. Clinical application of results of a randomized trial. DRVS report 4. Ophthalmology 1988; 95:1321–1334.