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Intravitreal injection of ranibizumab (Lucentis) versus pan-retinal photocoagulation as a preoperative adjuvant before vitrectomy in management of proliferative diabetic retinopathy

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Abstract

Background
Diabetic retinopathy is a microvascular complication of diabetes mellitus, and it is the most common ophthalmic complication. Pan-retinal photocoagulation (PRP) has been the standard treatment for proliferative diabetic retinopathy (PDR) and can be used as an adjuvant before vitrectomy but has adverse effects. The use of intravitreal ranibizumab has been suggested as an alternative treatment or an alternative adjuvant before vitrectomy.

Aim
This study was conducted to study the effect of intravitreal injection of ranibizumab 10 mg/ml (Lucentis) versus PRP as an adjuvant before vitrectomy in the management of PDR.

Patients and methods
This study was performed on 40 eligible eyes, which were allocated into two groups: group A included 20 eyes that were injected by ranibizumab 10 mg/ml (Lucentis) intravitreally 4–7 days before vitrectomy and group B included 20 eyes that received argon laser photocoagulation (PRP) 1 month before vitrectomy.

Results
The study revealed highly statistically significant difference between both groups regarding the incidence of intraoperative bleeding, with patients in the PRP group showing less intraoperative bleeding, a lower need for intraoperative use of diathermy, a lower need for intraoperative use of both blunt and sharp dissection, as well as a need for a lower number of endolaser shots when compared with patients in the intravitreal injection of ranibizumab group. It can be concluded that treatment with ranibizumab was not associated with a higher incidence of postoperative bleeding or complications than PRP at 6 months postoperatively among eyes with PDR and that ranibizumab may be an appropriate alternative adjuvant for patients with PDR. However, more studies with longer-term follow-up are recommended to complement the current study results and demonstrate real clinical differences between the two adjuvant treatments.

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

Keywords: Pan-retinal photocoagulation, ranibizumab, vitrectomy

Introduction

Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus [1]. Furthermore, it is the most common and probably the most blinding ophthalmic

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complication of diabetes [2]. DR is a global health problem currently affecting ~100 million people worldwide [3]. Its severity is directly related to the duration and severity of hyperglycemia [4].

Long-term hyperglycemia results in vascular endothelial dysfunction with subsequent loss of endothelial cells and pericytes. This is followed by the development of retinal microaneurysms, intraretinal hemorrhages, and retinal ischemia (cotton-wool spots). At this point, the retinopathy is known as nonproliferative diabetic retinopathy (NPDR). With retinopathy progression, the vessels become further damaged; thus, retinal nonperfusion and more ischemia occur. Clinically, the retina has signs of vascular damage, including intraretinal microvascular abnormalities, venous beading, and severe hemorrhages. The retinopathy is classified as severe NPDR at this point. As the ischemic injury progresses, fragile new blood vessels' growth at the retina's inner surface is induced by compensatory chemical mediators, mainly vascular endothelial growth factors (VEGF). Furthermore, this stage is known as proliferative diabetic retinopathy (PDR), characterized by neovascularization of the optic disc and neovascularization elsewhere. Multiple serious complications can occur at this stage, including tractional retinal detachment, vitreous hemorrhage, and neovascular glaucoma [5].

The first line of treatment for PDR is laser treatment. Contrary to focal laser for macular edema where an area of leakage is treated, PDR requires a more global treatment, known as pan-retinal photocoagulation (PRP). PRP treats the peripheral retina and causes shrinkage of abnormal blood vessels. It minimizes the likelihood of bleeding and can result in up to 50% reduction in severe visual loss risk. Meanwhile, 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 [6].

PRP before pars-plana vitrectomy affects the vitreous level of multiple growth factors, especially interleukin-6, thereby reducing DR activity, reducing the time of surgery, and making the prognosis better [7].

Ranibizumab 10 mg/ml (Lucentis) is a drug that acts by inhibiting the VEGF and has been shown to slow DR progression and reduce its complications [8]. Moreover, when compared with PRP in PDR, ranibizumab resulted in visual acuity that was not inferior to PRP treatment achieved at 2 years, with fewer proliferative retinopathy complications [9].

Recently, intravitreal injection of ranibizumab 10 mg/ml (Lucentis) as a preoperative adjuvant before vitrectomy may help achieve the surgical and anatomical goals by reducing surgery time, reducing the intraoperative complications, and by sparing the need for silicone oil tamponade and postoperative retinal photocoagulation [10].

This study was conducted to study the effect of intravitreal injection of ranibizumab 10 mg/ml (Lucentis) versus PRP before vitrectomy in PDR management.

Patients and methods

Time frame

This study was conducted from January 2017 to June 2020 at the vitreoretinal unit of Sohag Teaching Hospital.

Study population

This study was conducted on 40 eligible eyes in 40 consecutive patients who attended the ophthalmology outpatient retinal clinic of Sohag Teaching Hospital during the study period.

Ethical approval

The study protocol received approval from the Institutional Review Board – our hospital. Administrative approval and official permissions were obtained before data collection. Informed consent was obtained from patients included in the study following a guarantee of data confidentiality to them.

Inclusion criteria

The following were the inclusion criteria:

(1) PDR with indications for vitrectomy (vitreous hemorrhage, tractional retinal detachment involving or threatening the macula, combined tractional/rhegmatogenous retinal detachment, and fibrovascular membranes covering and distorting the macula).

Exclusion criteria

The following were the exclusion criteria:

(1) Patients with visual acuity more than 6/60 (0.10) or less than hand movement.
(2) Previous vitrectomy.
(3) DR 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.

Patients were allocated into two groups:

(1) Group A: it included 20 eyes that were injected with intravitreal ranibizumab 10 mg/ml (Lucentis) 4–7 days before vitrectomy (before starting of its contraction tractional effect).
(2) Group B: it included 20 eyes that received argon laser photocoagulation 1 month before vitrectomy (to get maximum NV regression).

Methods

Cases were assessed preoperatively by history taking, including detailed medical history and detailed ocular history, such as duration of symptoms, trauma, previous anterior segment operations (cataract surgery), and previous posterior segment procedures (laser photocoagulation, previous intravitreal or subtenon injection, or previous vitrectomy). Visual acuity was evaluated by a nonaided and aided method after correcting refraction errors using ETDR charts. Anterior segment examination was performed using slit-lamp with intraocular pressure (IOP) measurement by slit-lamp mounted applanation tonometer. Detailed fundus examination was performed by indirect ophthalmoscope using 20 D lens and

scleral indentation with a thimble depressor and slit-lamp biomicroscopy by 78 D lenses with the assessment of the following: integrity of retinal vasculature, the integrity of retinal background, macular status, presence of vitreous hemorrhage, posterior vitreous face status, epiretinal membranes, retinal or choroidal detachment, and choroidal effusion. Fundus photography was performed for follow-up and documentation. Fundus fluorescein angiography was performed for proper diagnosis and followed up if needed. B-scan ultrasound examination was performed for cases with inadequate visibility owing to media opacity as vitreous hemorrhage. Moreover, optical coherence tomography was performed for proper diagnosis, adequate macula assessment, and follow-up if needed.

Intravitreal ranibizumab (Lucentis) injection

Intravitreal ranibizumab (Lucentis) injection in the group A was performed 4–7 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, washing of local betadine by BSS, application of benoxinate hydrochloride 0.4% as drops in the conjunctival sac, intravitreal injection of ranibizumab 10 mg/ml (Lucentis) 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.

The patients were examined the first day after injection to check for complications resulting from the intravitreal injection: slit-lamp examination, fundus examination, and IOP measurement. Patients were re-examined 5 days after the injection and just before the pars-plana vitrectomy: measurement of the best-corrected visual acuity (BCVA), IOP assessment, dilated fundus examination, and colored fundus imaging.

Pan-retinal photocoagulation

PRP in group B was performed 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 second session's superior half. PRP was done using the slit-lamp delivery system and the Mainster wide-field lens. Laser burns were applied to start at a circumference 500 μ from the disc and 2 DD from the fovea to the central retina wall. Laser settings were as follows: spot size = 200 μ, duration = 0.1–0.2 s, and 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 is a contact lens that provides excellent ophthalmoscopic resolution and images binocularity across the entire field of view. It allows an extensive range of slit-lamp magnifications to be used. Image magnification is × 0.68, and laser spot magnification is ×1.5, contact diameter is 16 mm, the lens height is 27.8 mm, and the field of vision is 118° static up to 127° dynamic [11].

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

Pars-plana vitrectomy

Following local or general anesthesia, sterilization was performed using 'betadine' for the eyelids and 'betadine' eye-drops for the conjunctival cul-de-sac, followed by application of sterile drapes. A 23-G torcher system was used to perform three torchers through the conjunctiva and sclera 3.5–4 mm from limbus: one for the infusion cannula, one for the endoillumination, one for the vitrectomy probe or any other instrument as retinal forceps or scissors. The infusion cannula should be examined inside mid-vitreous or not before beginning. Core vitrectomy was performed. Fenestration of the posterior vitreous cortex with the vitreous cutter extended for 360° in a ring-like fashion to truncate the conical so-called anteroposterior traction. The peripheral margin of the posterior vitreous cortex (vitreous skirt) was trimmed, leaving a minimal amount attached to the vitreous base. For removing the fibrovascular tissue (FVT), the posterior margin of the 360° fenestration was trimmed flush with the outer margin of the FVT, and conformal cutter delamination using a side approach was used to remove a significant portion of the FVT. 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 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 was primarily used as access to expose the dissection plane (potential space) for delamination. PFCL injection was performed on demand. Vitrectomy for the vitreous base was performed 360° with scleral indentation accomplished by the assistant or self-indentation if the chandelier is used. Endolaser PRP and endolaser to retinal breaks were performed, followed by PFCL/silicone oil exchange through the infusion cannula or PFCL/air exchange then air/silicon oil exchange. Finally, torchers are removed with massaging followed by closure of each one by one all through 8/0 vicryl suture and eye patching.

The intraoperative evaluation included evaluation of the effect of two adjuvants on the severity of intraoperative hemorrhage,

Table 1: Intraoperative bleeding in both groups

	Group A	Group B	Total	χ^2 test	
				χ^2	*P*
Intraoperative bleeding					
Minimal					
Count	6	9	15		
%	30	45	37.5		
Mild					
Count	10	4	14		
%	50.0	20.0	35.0	14.171	0.002
Moderate					
Count	4	0	4		
%	20	0.0	10		
No					
Count	0	7	7		
%	0.0	35	17.5		

Table 2: Intraoperative use of diathermy in both groups

	Group A	Group B	Total	χ^2 test	
				χ^2	*P*
Intraoperative diathermy					
1					
Count	6	9	15		
%	30	45	37.5		
2					
Count	10	4	14		
%	50.0	20.0	35.0	14.171	0.002
3					
Count	4	0	4		
%	20	0.0	10		
No					
Count	0	7	7		
%	0.0	35	17.5		

Table 3: Intraoperative using blunt or sharp dissection in both groups

	Group A	Group B	Total	χ^2 test	
				χ^2	*P*
Blunt/sharp dissection					
B					
Count	12	11	23		
%	60.0	55	57.5		
B/S					
Count	7	1	8	9.988	0.006
%	35	5	20.0		
No					
Count	1	8	9		
%	5	40.0	22.5		

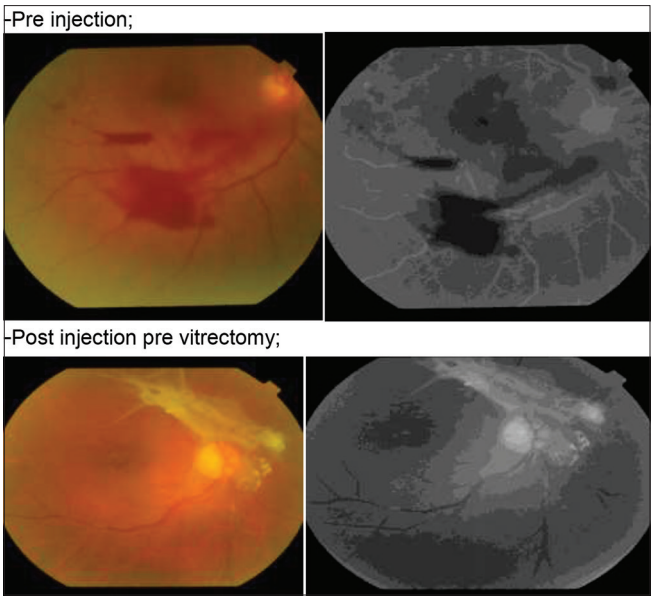

Figure 1: Preretinal, vitreous hemorrhage, and FVM. Preinjection; postinjection previtrectomy; postoperative. FVM, fibrovascular membrane.

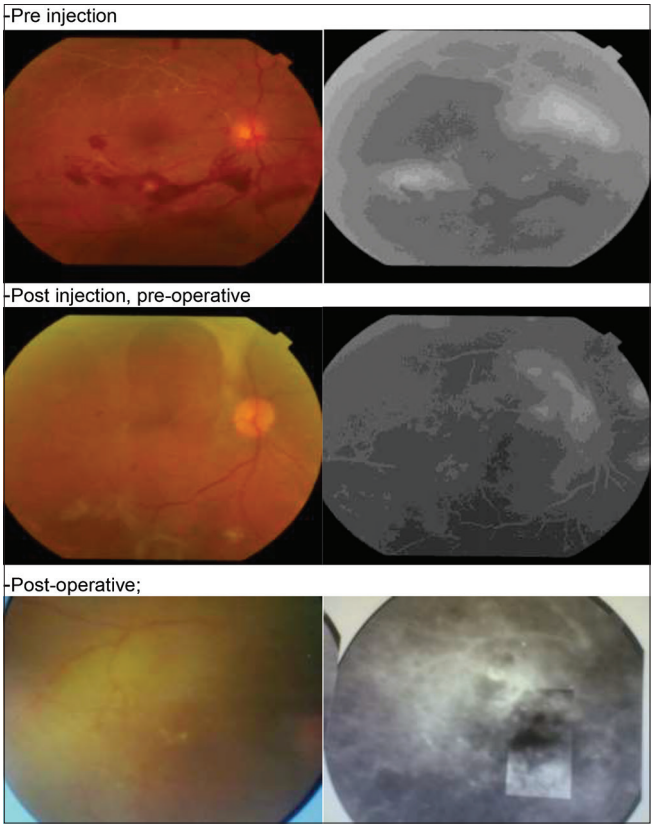

Figure 2: Preretinal hemorrhage, vitreous hemorrhage, FVMs, NVDs, and NVEs. Preinjection. Postinjection, preoperative. Postoperative. FVM, fibrovascular membrane; NVD, neovascularization of the optic disc; NVE, neovascularization elsewhere.

Table 4: Intraoperative using of endolaser in both groups

	Group A	Group B	Total	χ^2 test	
				χ^2	*P*
Intraoperative endolaser					
<1500 shoots					
Count	5	19	24		
%	25	95	60.0	20.417	0.001
>1500 shoots					
Count	15	1	16		
%	75	5	40.0		

Table 5: Postoperative bleeding in both groups

	Group A	Group B	Total	χ^2 test	
				χ^2	*P*
Postoperative bleeding					
Flame-shaped hemorrhage					
Count	1	0	1		
%	5	0.0	2.5		
Preretinal hemorrhage					
Count	7	1	8		
%	35	5	20.0		
Perifoveal hemorrhage					
Count	1	0	1	10.786	0.055
%	5	0.0	2.5		
Peripapillary hemorrhage					
Count	1	0	1		
%	5	0.0	2.5		
Spot hemorrhage					
Count	0	1	1		
%	0.0	5	2.5		
No					
Count	10	18	28		
%	50	92	70.0		

using of intraoperative endodiathermy, using of blunt and sharp dissections, using of intraoperative endolaser, and mean time of surgery.

For the postoperative follow-up, all patients were regularly examined on the first day postoperative, after 1 week, and then monthly for 6 months postoperatively. The following were examined: BCVA; anterior segment examination using the slit-lamp to detect any postoperative complications such as reaction iridocyclitis, or silicon oil in AC; measurement of IOP; dilated fundus examination to detect postoperative vitreous hemorrhage and to evaluate the state of the retina; silicone oil removal 3–6 months postoperatively; and colored fundus photography at 1, 3, and 6 months postoperatively.

Statistical analysis

Data were collected, revised, coded, tabulated, and analyzed using Statistical Package for Social Science IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. The data were presented as numbers and percentages. χ^2 test was used to study the association between two variables or compare between two independent groups regarding the categorized data. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the *P* value was considered significant at the level of less than 0.05.

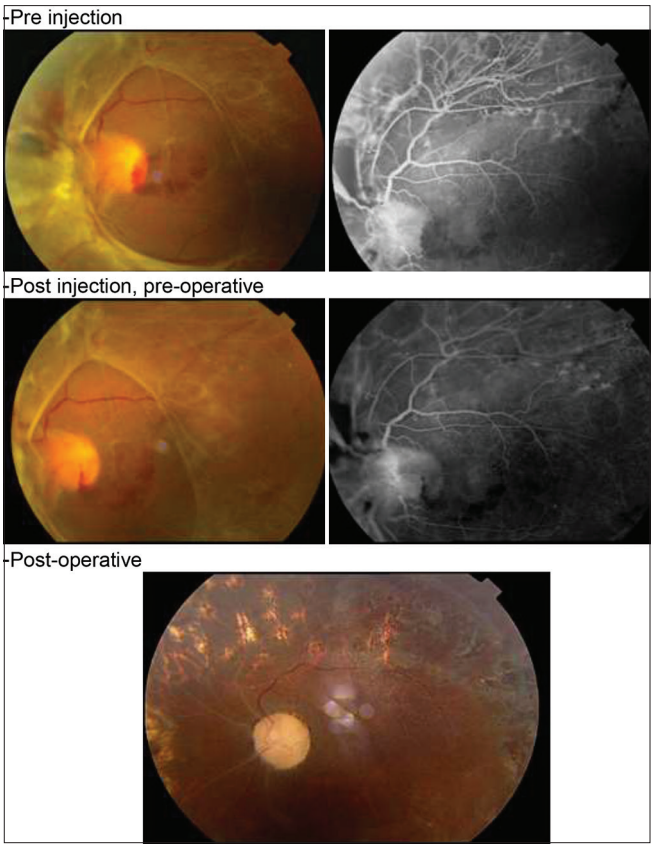

Figure 3: FVMs, tractional RD, preretinal hemorrhage. Preinjection. Postinjection, preoperative. Postoperative. FVM, fibrovascular membrane; RD, retinal detachment.

Results

This prospective clinical study included 40 eyes in 40 patients with PDR with indications of vitrectomy managed by pars-plana vitrectomy after preoperative preparation by intravitreal injection of ranibizumab (Lucentis) (group A patients) or PRP (group B patients).

The present study revealed a highly statistically significant difference between both groups regarding the incidence of intraoperative bleeding, with patients in group B showing less bleeding (Table 1).

The present study revealed a highly statistically significant difference between both groups regarding the need for using intraoperative diathermy, with patients in group B showing a lower need for intraoperative use of diathermy (Table 2).

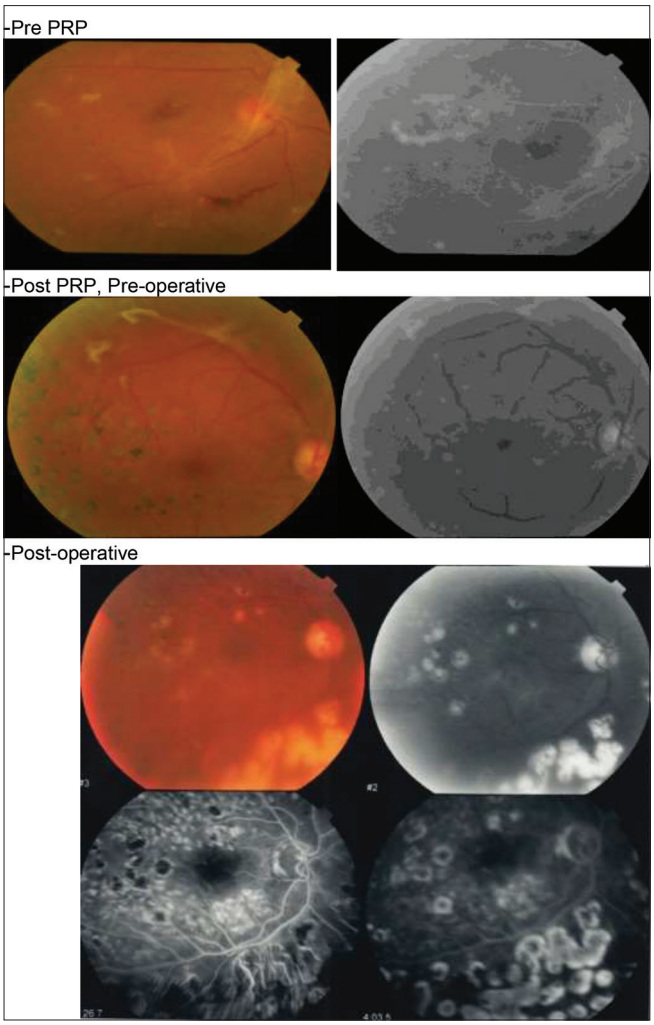

Figure 4: Preretinal hemorrhage., and FVMs: Pre-PRP. Post-PRP, Preoperative. Postoperative. FVM, fibrovascular membrane; PRP, pan-retinal photocoagulation.

The present study revealed a highly statistically significant difference between both groups regarding the need for intraoperative use of blunt and sharp dissection, with patients in group B showing a lesser need for intraoperative use of both blunt and sharp dissection (Table 3).

The present study revealed a highly statistically significant difference between both groups regarding the need for intraoperative use of endolaser, with patients in group B showing a need for a lower number of endolaser shoots (Table 4).

On the contrary, the present study revealed no statistically significant differences between both groups regarding the incidence of postoperative bleeding (Table 5) or postoperative complications (Table 6).

Group A: cases

Figs. 1–3.

Group B: cases

Figs. 4–6.

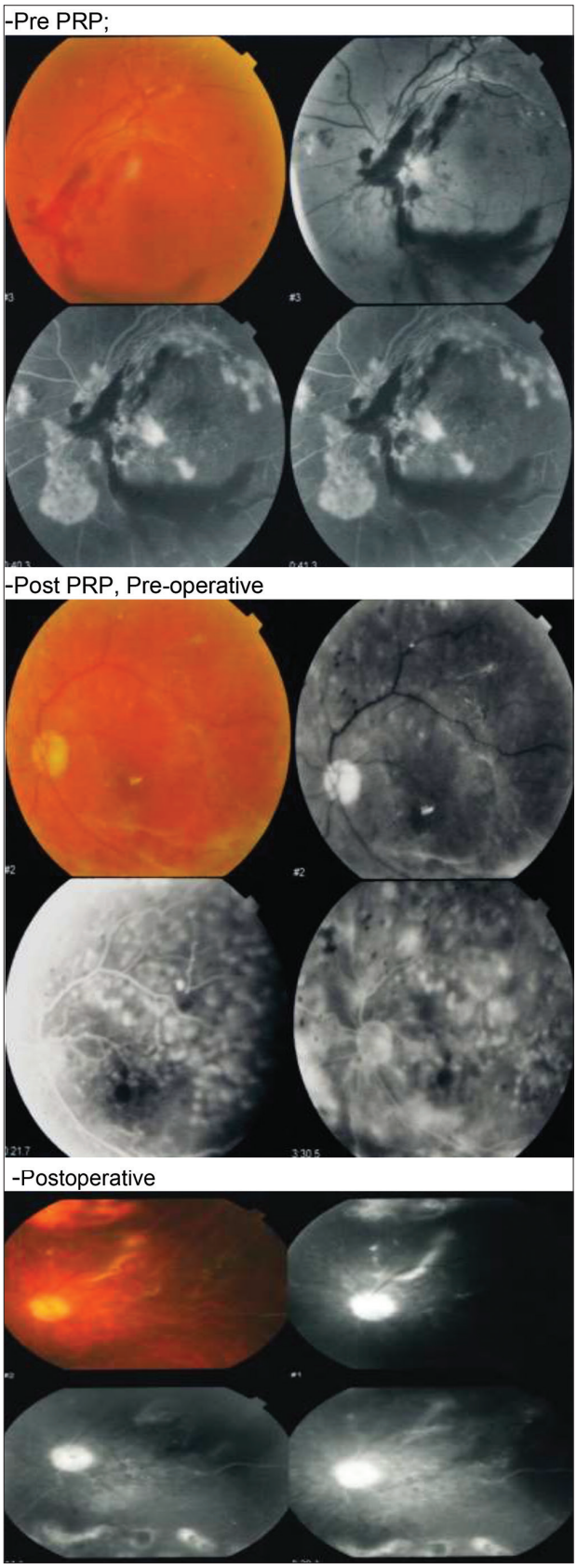

Figure 5: FVMs, tractional RD, preretinal hemorrhage., and vitreous hemorrhage. Pre-PRP; post-PRP, preoperative. Postoperative. FVM, fibrovascular membrane; PRP, pan-retinal photocoagulation; RD, retinal detachment.

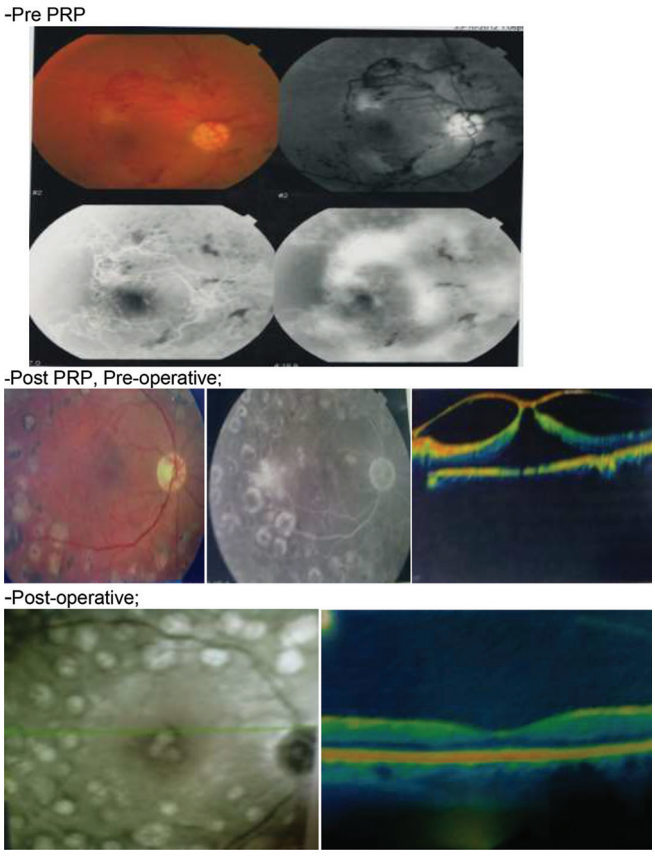

Figure 6: Severe NVDs, NVEs, preretinal hemorrhage. Tractional macular detachment. Pre-PRP. Post-PRP, preoperative; postoperative. NVD, neovascularization of the optic disc; NVE, neovascularization elsewhere; PRP, pan-retinal photocoagulation.

Discussion

PDR is a leading cause of vision loss in patients with diabetes mellitus [12]. Without treatment, nearly 50% of patients with high-risk PDR experience severe vision loss within 5 years. PRP has been the standard treatment for PDR [13]. PRP before pars-plana vitrectomy influences the vitreous level of multiple growth factors, especially interleukin-6, so it reduces DR; hence, it reduces the time of surgery and makes the prognosis better [7]. However, PRP can cause permanent peripheral visual field loss, decrease night vision, and may exacerbate diabetic macular edema, making alternative treatments desirable [14].

Anti-VEGF agents have been effectively used to reduce neovascularization related to PDR and 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 pan-endothelial marker CD34, noted from day 5 after injection, and became consistently low from day 10 onward. If surgery is delayed or these increasing traction forces cannot be monitored, it might risk endangering the macula, central vision, or final visual outcome by the progression of TRD [15]. Many reports regarding the effects

Table 6: Postoperative complications in both groups

	Group A	Group B	Total	χ^2 test	
				χ^2	*P*
Postoperative complications					
Cellophane maculopathy					
Count	4	5	9		
%	20	25	22.5		
Ischemic maculopathy					
Count	9	5	14		
%	45	25	35		
Ischemic maculopathy + pale optic disc					
Count	1	0	1		
%	5	0.0	2.5		
Pale disc					
Count	0	1	1		
%	0.0	5	2.5		
Macular bucker					
Count	1	0	1	9.387	0.402
%	5	0.0	2.5		
Cystoid macular edema					
Count	2	1	3		
%	10.0	5	7.5		
NPDR					
Count	1	3	4		
%	5	15	10		
Sever preretinal hemorrhage					
Count	0	1	1		
%	0.0	5	2.5		
Tractional RD/rebleeding					
Count	1	0	1		
%	5	0.0	2.5		
No					
Count	1	4	5		
%	5	10	12.5		

NPDR, nonproliferative diabetic retinopathy; RD, retinal detachment.

of anti-VEGF agents on PDR have been published, suggesting that preoperative intravitreal anti-VEGF injection might be helpful to facilitate vitrectomy in severe PDR cases [15,16]. Furthermore, intravitreal injection of bevacizumab 1 week before vitrectomy was found to reduce the need for vitrectomy significantly [17].

Based on the previous study results, we conducted this prospective clinical study to study PRP's effect versus intravitreal injection of ranibizumab 10 mg/ml (Lucentis) before vitrectomy in managing PDR.

The present study revealed a highly statistically significant difference between both groups regarding the incidence of intraoperative bleeding, intraoperative use of diathermy, intraoperative use of both blunt and sharp dissection, and number of endolaser shots, with patients in the PRP group showing less intraoperative bleeding, a lower need for intraoperative use of diathermy, a lower need

for intraoperative use of both blunt and sharp dissection, as well as a need for a lower number of endolaser shots when compared with patients in the intravitreal injection of ranibizumab group. However, compared with direct vitrectomy, patients who received intravitreal injection of ranibizumab 4–7 days before vitrectomy had shorter surgical duration, fewer intraoperative complications, less silicone oil internal tamponade, and less need for postoperative retinal laser coagulation, alleviating these patients' suffering from repeated surgical treatment [10].

On the contrary, the present study revealed no statistically significant differences between both groups regarding the incidence of postoperative bleeding or postoperative complications. Intravitreal injection of bevacizumab 4–7 days before vitrectomy was found to reduce the incidence of early postoperative hemorrhage in patients with DR [18,19]. This is nearly similar to the results of the present study. Gross *et al*. [9]. performed a similar study and reported no significant differences between both groups regarding the incidence of postoperative adverse events apart from inflammation, whose incidence was significantly higher in the PRP group. This difference between results might be attributed to the longer follow-up period, of 2 years, in their study. Otherwise, the present study results regarding the incidence of postoperative complications are consistent with other studies [14,20,21].

Several limitations related to the study design and conduct are significant when interpreting these results. These limitations include the allocation of patients into groups and masking of testers. Furthermore, the short follow-up period of 6 months cannot provide a complete evaluation of the difference between both pretreatments.

Conclusion

Among eyes with PDR, treatment with ranibizumab was not associated with a higher incidence of postoperative bleeding or complications when compared with PRP at 6 months postoperative. Using both adjuvants before vitrectomy enhances the outcome of vitrectomy when best indicated rather than without using. The shorter time of surgery and less endodiathermy or endolaser use are with the PRP group, although postoperative BCVA gaining is not significant. So, real clinical differences between the two adjuvants need more research studies.

Recommendations

More studies with longer-term follow-up are needed to complement the current study results and demonstrate real clinical differences between the two adjuvant treatments.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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