·Clinical Research·

Panretinal photocoagulation versus panretinal photocoagulation plus intravitreal bevacizumab for high-risk proliferative diabetic retinopathy

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Abstract

• AIM: To evaluate the effects of panretinal photocoagulation (PRP) compared with PRP plus intravitreal bevacizumab (IVB) in patients with high-risk proliferative diabetic retinopathy (PDR) according to the Early Treatment Diabetic Retinopathy Study criteria.

• METHODS: The data were collected retrospectively from the eyes of high-risk PDR patients, which were divided into two groups. After treated with standard PRP, the eyes were randomly assigned to receive only PRP (PRP group) or PRP plus intravitreal injection of 1.25 mg of bevacizumab (PRP-Plus group). Patients underwent complete ophthalmic evaluation, including best corrected visual acuity (BCVA), intraocular pressure (IOP), and new vessel size in fluorescein angiography (FA) and optical coherence tomography for the assessment of central subfield macular thickness (CSMT) at baseline and at weeks 12 (±2), 16 (±2), 24 (±2) and 48 (±2). Main outcome measures also included vitreous clear-up time and neovascularization on the disc (NVD) regression time. Adverse events associated with intravitreal injection were investigated.

• RESULTS: Thirty consecutive patients (*n*=36 eyes) completed the 48-week follow-up. There was no significant difference between the PRP and PRP-Plus groups with respect to age, gender, type or duration of diabetes, area of fluorescein leakage from active neovascularizations (NVs), BCVA or CSMT at baseline. The mean vitreous clear-up time was 12.1±3.4wk after PRP and 8.4±3.5wk after PRP combined with IVB. The mean time interval from treatment to complete NVD regression on FA examination was 15.2±3.5wk in PRP group and 12.5±3.1wk in PRP-Plus group. No significant difference in CSMT was observed between the groups throughout the study period. However, the total area of actively leaking NVs was significantly reduced in the PRP-Plus group compared with the PRP group (*P*<0.05). Patients received an average of 1.3 injections (range: 1-2). Ten eyes (27.8%) underwent 2 injections. Two eyes had ocular complication of PDR progression to dense vitreous hemorrhage (VH). No major adverse events were identified.

• CONCLUSION: The adjunctive use of IVB with PRP is associated with a greater reduction in the area of active leaking NVs than PRP alone in patients with high-risk PDR. Short-term results suggest combined IVB and PRP achieved rapid clearance of VH and regression of retinal NV in the treatment of high-risk PDR. Further studies are needed to determine the effect of repeated intravitreal bevacizumab injections and the proper number of bevacizumab injections as an adjuvant.

• KEYWORDS: panretinal photocoagulation; intravitreal bevacizumab; high-risk proliferative diabetic retinopathy; neovascularization on the disc

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INTRODUCTION

Diabetic retinopathy is the most common cause of vision loss in working-aged individuals in developed nations[1]. Retinal neovascularization (NV) represents an important risk factor for severe vision loss in patients with proliferative diabetic retinopathy (PDR). About 60% of patients with PDR respond to panretinal photocoagulation (PRP) with regression of NV within 3mo [2]. However, many patients require additional laser treatment, and 4.5% ultimately require pars plana vitrectomy despite PRP[3].

Although severe central vision loss because of PDR can be prevented with PRP in most cases, this destructive, often painful, laser procedure may be associated with decreased peripheral vision and an increased risk of macular edema. Besides additional laser photocoagulation, intravitreal injection of anti-vascular endothelial growth factor agents

have become an interesting alternative for new vessels regression, and more recently, regression of disc NVs was demonstrated after intravitreal injection of the antiangiogenic agent bevacizumab in the setting of PDR[4-11]. A small sample size and short duration of follow-up were limitations of these studies. Moreover, the effects of intravitreal bevacizumab (IVB) in high-risk PDR have not been sufficiently investigated. Therefore, we retrospectively evaluated the effectiveness of repeatedly intravitreally administered bevacizumab on functional [best-corrected visual acuity (BCVA)] and the proportions of adjuvant bevacizumab injection with PRP to reduce the risk of new vitreous hemorrhages (VHs) and macular edema during treatment of high-risk PDR patients.

SUBJECTS AND METHODS

Between February 2013 and April 2015, all patients evaluated at the Department of Ophthalmology, the Second Affiliated Hospital of Medical College of Xi'an Jiaotong University, who presented with high-risk PDR and had not received any prior retinal laser treatment were in the study. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board, and all participants signed a written informed consent form. The nature of off-label use of this drug and its potential side effects of endophthalmitis, retinal detachment, and the possibility of thromboembolic events were discussed with patients before obtaining informed consent.

Patient Eligibility and Baseline Evaluation Patients were included if they had high risk PDR, which was defined according to the guidelines set forth by the Early Treatment Diabetic Retinopathy Study [12-13], as follows: 1) presence of moderate to severe neovascularization on the disc (NVDs) with 1/4-1/3 disc area in size or larger; 2) less extensive NVD, if vitreous or pre-retinal hemorrhaging was present; 3) NV of elsewhere (NVE) ≥1/2 disc area, if vitreous or pre-retinal hemorrhaging was present. Exclusion criteria included the following: 1) history of previous laser treatment, vitreoretinal surgery, or intravitreal injection; 2) history of another ocular disease other than PDR; 3) history of thromboembolic event-including myocardial infarction or cerebral vascular accident; 4) major surgery within the prior 6mo or planned within the next 48wk; 5) uncontrolled hypertension; 6) known coagulation abnormalities or current use of anticoagulative medication other than aspirin; 7) any condition affecting documentation; 8) PRP is impossible because of severe vitreous or pre-retinal hemorrhaging .

Study Design All patients underwent PRP performed at two time-points (at weeks 1 and 3) according to ETDRS guidelines (ETDRS Research Group 1987). Before PRP, topical anesthesia using 0.5% proparacaine (Alcaine®; Alcon Laboratories, Hunenberg, Switzerland) was dropped. Three hundred to four hundred argon laser (532 nm) burns with a spot size of 500 μm were made each time (800-1600 burns in total) using a fundus contact lens (Transequator®; Volk Optical, Mentor, OH, USA). PRP was executed in the inferior, nasal, superior, and temporal areas of eyes. PRP was performed by independent ophthalmologists unaware of this study. Retreatment was performed at weeks 8 and 12 if active new vessels were detected at fluorescein angiography (FA). Eyes in the PRP plus group received one intravireal injection of 0.05 mL (1.25 mg) of IVB and eyes in the PRP group received 500-μm additional spots per quadrant of active new vessels. For patients (n=6) presenting with high-risk PDR in both eyes, the eye with worse BCVA was selected to receive PRP plus IVB (6 eyes) and the fellow eye was treated with PRP alone (6 eyes). In the 24 eyes of 24 patients with unilateral high-risk PDR randomly selected to receive only PRP (PRP group) or PRP plus intravitreal injection of 1.25 mg of bevacizumab (PRP-plus group). One intravitreal injection of 1.25 mg (0.05 mL) bevacizumab was administered by a single retinal specialist (Zhou CJ). Injection technique: 1) the area around the eye was sterilized with 5% povidone iodine; 2) intravitreal Avastin® 0.05 mL (1.25 mg) was injected into the vitreous cavity *via* an insulin syringe with a 30 G needle inserted through the pars plana at a distance of 4.0 mm from the limbus at phakic eyes, and 3.5 mm in pseudophakic eyes, the needle was removed carefully using a sterile cotton applicator to prevent reflux; 3) patients were instructed to instill one drop of antibiotic eye drops into the injected eye four times daily for 1wk after the procedure. All injections were performed in the operating room. Patients visited an outpatient clinic for the examination of visual acuity, intraocular pressure (IOP), anterior segment, and fundus the day after treatment.

Ophthalmic Follow-up Examinations and Main Outcome Measures Throughout the study, measurement of BCVA was performed by a single, masked, certified examiner prior to any other study procedure. Ophthalmic evaluation was performed by a single retina specialist (Quan YL) and stereoscopic fundus photography and FA were performed by a single examiner (Yao J). Systemic and local adverse events were monitored throughout the study, including changes in IOP and lens status. Patients who did not completed the 48-week follow-up evaluation were excluded in this study.

Three main measures were used to evaluate the effects of bevacizumab: total area (mm^2) of fluoresce in leakage (FLA) from active NV was the primary outcome, if more than one site of active NV were found, the sum area, including all sites, was considered for analysis. The other two main outcome measures were BCVA and the central subfield macular thickness (CSMT) (μm). The secondary outcome measures were the vitreous clear-up time (VCUT) and NVD regression time. The VCUT was defined as clearly visible

Table 1 Clinical characteristics of the 30 patients enrolled in the current study *n* (%)

Characteristics	Patients of both eyes (*n*=6)	PRP group (*n*=12)	PRP-Plus group (*n*=12)
Gender (M/F)	4/2	7/5	5/7
Age of onset, $\bar{x} \pm s$ (a, range)	54.9±9.1 (37-70)	57.9±8.7 (42-74)	53.9±8.1 (45-65)
Duration of DM (a, $\bar{x} \pm s$)	12.5±5.8	15.1±7.5	11.5±8.1
Treatment regimen (no insulin/insulin)	2/4	3/9	2/10
HbA1c ($\bar{x} \pm s$)	9.1±1.5	9.3±0.7	8.9±1.4
Presence of hypertension	3 (50)	3 (25.0)	3 (25.0)
Presence of hyperlipidemia	3 (50)	2 (16.7)	1 (8.3)

HbA1c: Glycosylated hemoglobin; PRP: Panretinal photocoagulation; PRP-Plus: Panretinal photocoagulation and intravitreal injection of bevacizumab.

main retinal vessels and optic disc in the posterior pole with the peripheral retina clear enough for a successful PRP in at least 3 quadrants.

The NVD regression time was defined as the total absence of previous fluorescein leakage from the active NVD. The following results were also recorded to evaluate the effects of bevacizumab: number of patients who need second injection, rate of persistent or recurrent VH, and frequency of eyes underwent vitrectomy during follow-up.

Statistical Analysis Group comparisons at baseline were performed with one-way analysis of variance (ANOVA) and a *t*-test, while the effect of treatment (PRP and PRP-Plus) was compared within (Wilcoxon signed-rank test) and between (Wilcoxon rank-sum test) groups for the intraindividual differences of FLA, BCVA and CSMT values found after treatment minus baseline. All analyses considered $P<0.05$ as the level of significance.

RESULTS

A total of 30 consecutive patients (36 eyes) with high-risk PDR, complicated by VH or NVD, were enrolled and investigated in this study, all of who completed the 48-week follow-up evaluation. All patients involved in this study had type 2 diabetes mellitus. The baseline characteristics of the patients of two groups are summarized and shown in Table 1. Twenty-four patients with unilateral high-risk PDR were randomly assigned to receive either PRP or PRP plus IVB; in six patients with bilateral high-risk PDR, the eye with worse BCVA was included in the PRP-Plus group and the fellow eye was included in the PRP group [giving a total of 18 eyes in each treatment group (PRP and PRP-Plus groups)]. Of the 30 patients, 16 were female and 14 were male. Twenty-six eyes presented with VH, and 10 eyes presented with moderate to severe NVD. The mean age was 52.5±7.2y (age range: 37-74y). Nine patients had a history of hypertension (30%). Six patients had a history of hyperlipidemia (20%). There were no significant differences between the groups regarding gender, age or laterality.

No serious drug-related adverse events were observed in the 18 eyes (18 patients) treated with bevacizumab in this study. Overall, the intravitreal injection procedure was well tolerated, and no clinical evidence of uveitis, endophthalmitis or ocular toxicity was observed. Two had mild anterior uveitis that occurred one day after injection. These patients were prescribed antibiotic eye drops for seven days. No definite cell in the anterior chamber was found after one week in either patient. Further, no significant changes in IOP or lens status were observed in any of the 18 injected eyes during the 48-week follow-up period. Minor local adverse events related to the treatment procedure, such as subconjunctival hemorrhage and foreign body sensation, were reported in one (5.6%) and three (16.7%) patients, respectively. These events were transient and resolved in all patients by three days after injection. Partially reperfused retinal NV with minor preretinal hemorrhage was observed in 5 eyes (27.8%) one months after the first injection, and resolved after repeated bevacizumab injections. Patients received an average of 1.3 injections during follow-up (range: 1-2). The 27.8% of eyes (5 eyes) underwent repeated injections.

Table 2 Clinical outcomes of the eyes from PRP group and PRP-Plus group

Clinical outcome	PRP group (*n*=18)	PRP-Plus group (*n*=18)
Complication		
NVD	4	6
VH	14	12
IOP (mm Hg, $\bar{x} \pm s$)	15.3±4.5	14.5±5.1
No. of IVB (mean)	0	1.3
Time of NVD regression (wk, $\bar{x} \pm s$)	15.2±3.5	12.5±3.1
VCUT without vitrectomy (wk, $\bar{x} \pm s$)	12.1±3.4	8.4±3.5
Eyes underwent vitrectomy within one year	2	0
Eyes with persistent DME	5	2
Baseline FLA (mm^2)	8.5±1.4	8.9±0.8 (P=0.1462)
Baseline BCVA	0.42±0.06	0.31±0.05 (P=0.8650)
Baseline CSMT (μm)	251.5±51.3	317.3±62.2 (P=0.2433)

DME: Diabetic macular edema; NVD: Neovascularization on the disc; VH: Vitreous hemorrhage; IOP: Intraocular pressure; IVB: Intravitreal injection of bevacizumab; VCUT: Vitreous clear-up time; BCVA: Best-corrected visual acuity; FLA: Area (mm^2) of fluorescein leakage; CSMT: Central subfield macular thickness. Statistical analysis of the difference baseline FLA (mm^2); BCVA and CSMT (μm) between PRP group and PRP-Plus group was performed using the Wilcoxont test: $P>0.05$ ($P<0.05$ was considered statistically significant).

In 26 eyes of high-risk PDR complicated with VH, the mean VCUT was 12.1±3.4wk after PRP and 8.4±3.5wk after PRP combined with intravitreal injections of bevacizumab (Table 2). Disease progression was found in two patients one year after the treatment. Both patients had VHs in the

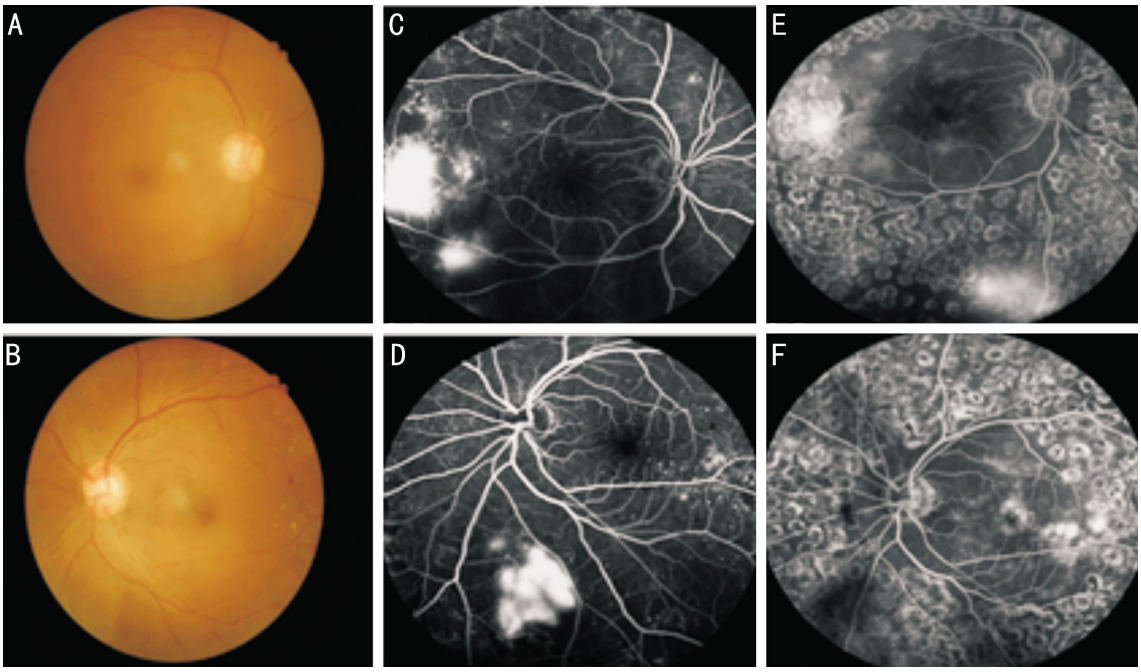

Figure 1 A 53-year-old female patient with bilateral high-risk PDR A-D: Actively leaking new vessels were observed in both eyes at baseline. She presented with sever NVE and a little VH in the both eyes, and FA showed large regions of NVE leakage compatible with the diagnosis of high-risk PDR. She received the standard PRP in both eyes. After 1mo, in both eyes, VH remarkably cleared, and visual acuity improved from 0.3 at baseline to 0.5. An obvious FLA reduction was found in both eyes but no NVE completely regression. IVB injection was added to the treatment of her left eye and supplemental photocoagulation for her right eye. E: At week 12, a marked decrease of leakage was noted in the left eye. F: In her right eye, leakage from NV was slightly decreased but still actively persistent. Six months after bevacizumab injection, VH completely cleared up and FA disclosed no more fluorescein leakage from NVE in the left eye.

PRP only eye. The VHs were not absorbed spontaneously, so vitrectomies were performed for both patients. A patient with high-risk PDR in both eyes, who presented NVE ⩾1/2 disc area and VH was present in peripheral retina, were treated with PRP plus an intravitreal injection of bevacizumab in the left eye and single PRP therapy in the right eye and is shown in Figure 1. In 10 eyes of high-risk PDR complicated with moderate to severe NVD, the mean time interval from treatment to complete NVD regression on FA examination was 15.2±3.5wk in PRP group and 12.5±3.1wk in PRP-Plus group. One patient presented with high-risk PDR and severe NVD and who was treated with PRP plus injection of bevacizumab is shown in Figure 2. During one-year follow-up, complete regression of neovessels elsewhere occurred in 100% (PRP-Plus) and 83.3% (PRP) and for NVD in 55% (PRP-Plus) and 30% (PRP).

There was no statistically significant difference between the groups in baseline BCVA. The mean±SD BCVA was 0.42±0.06 in the PRP group and 0.31±0.05 in the PRP-Plus group (P=0.8650). A BCVA increase of 0.10 compared with baseline was observed at 16 and 24wk after treatment in the PRP-Plus group (P<0.05), while no statistically significant change in BCVA was observed in the PRP group at any study visit (P>0.05). Between-group analysis showed significantly better BCVA in the PRP-Plus group compared with the PRP group at the week 24 (P<0.05) (Figure 3, Table 3).

Table 3 Mean±SD intraindividual difference (values found after treatment minus baseline) for FLA, BCVA and CSMT in both groups for all eyes n=18

Outcome	Weeks	PRP	PRP-Plus	[1]P
FLA (mm^2)	12	-2.6±0.5	-4.3±0.5	0.0110
	16	-3.0±0.6	-5.4±0.5	0.0033
	24	-3.4±0.7	-6.4±0.5	0.0243
BCVA	12	0.02±0.03	0.08±0.03	0.1411
	16	0.04±0.02	0.11±0.03	0.0744
	24	0.03±0.02	0.10±0.02	[2]0.0173
CSMT (μm)	12	33.5±35.2	-16.1±32.5	0.3079
	16	25.7±21.1	-38.7±30.6	0.0921
	24	7.3±26.1	-17.2±26.2	0.5116

BCVA: Best-corrected visual acuity; CSMT: Central subfield macular thickness; FLA: Total area (mm^2) of fluorescein leakage from active neovascularization; PRP: Panretinal photocoagulation; PRP-Plus: Panretinal photocoagulation plus intravitreal injection of 1.25 mg of bevacizumab. [1]P-values for between-group comparisons analyses using Wilcoxon test; [2]Mean difference between PRP group and PRP-Plus group. Statistical significance was tested by Wilcoxon test.

There was no statistically significant difference of FLA between in the PRP and PRP-Plus groups at baseline. Mean±SD FLA was 8.5±1.4 mm^2 in the PRP group and 8.9±0.8 mm^2 in the PRP-Plus group (P=0.1462; t-test). A within-group statistically significant FLA reduction compared with baseline was found at weeks 12, 16 and 24 in both groups (P<0.05). Intragroup comparison showed a significantly larger reduction in FLA at weeks 12, 16 and 24 in the PRP-Plus group compared with the PRP group (Figure 3, Table 3).

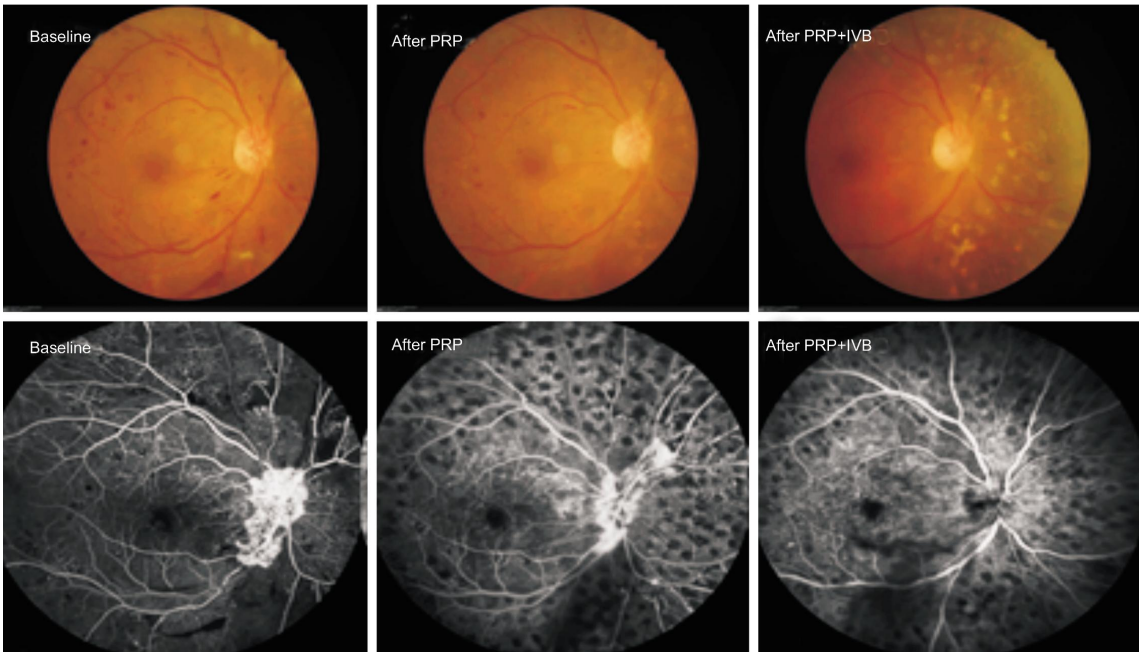

Figure 2 A 57-year-old male patient presented with high-risk PDR and severe NVD The eye with severe NVD was compatible with the diagnosis of high-risk PDR. FA showed profuse NVD leakage and a large area of capillary dropout. The NVD was slightly decreased but still actively persistent after PRP. Complete NVD regression without any fluorescein leakage was noted one month after one intravireal injection of bevacizumab at the week 8.

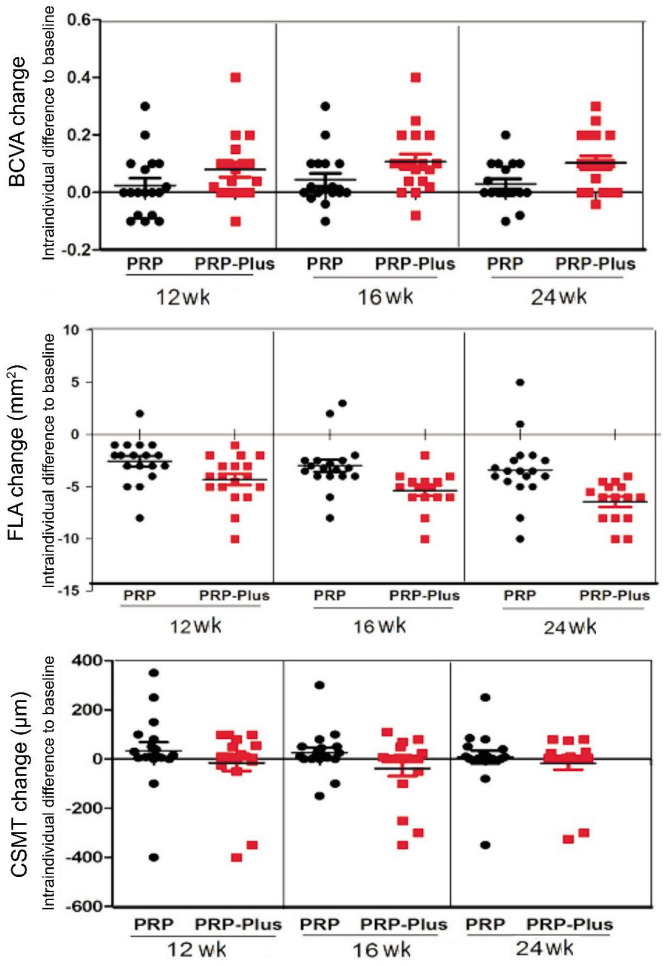

Figure 3 Distributions of the intraindividual differences A: The 12, 16 and 24wk after treatment-baseline of BCVA; B: FLA from active neovascularization; C: CSMT (μm) for PRP and PRP-Plus IVB. The horizontal line across the data is the mean±SD.

At baseline, the mean±SD CSMT was 251.5±51.3 μm in the PRP group and 317.3±62.2 μm in the PRP-Plus group (P=0.2433). A CSMT increase of approximately 10% was observed after treatment in the PRP group (P>0.05), while a trend towards significant decrease in CSMT was observed in the PRP-Plus group (P<0.05) at all study visits (Figure 3; Table 3).

DISCUSSION

PRP currently is the mainstay and gold standard well-known principal therapy for PDR since the Diabetic Retinopathy Study was published [14]. It is estimated that about 60% PDR patients respond to laser PRP with retinal NV regression within 3mo. Although PRP reduces the possibility of severe visual loss, it is a destructive procedure, and it has several side effects, such as macular edema, constricted visual field and laser-induced VH. Many diabetic patients need additional laser therapy and 4.5% of them eventually require vitrectomy surgery despite laser PRP[3]. Especially, additional laser therapy or surgical intervention has been necessary after PRP performance for high-risk PDR. Moreover, NV regression may take several weeks after completion of PRP, and NV continues to grow despite the first session of PRP in one-third of patients. Therefore, VH may lead to visual loss and preclude complete laser PRP in these patients. Recent reports have shown that VEGF plays a key role in NV of the eye, and that intravitreal anti-VEGF injection can lead to regression of NV in PDR, neovascular age-related macular degeneration, central retinal vein obstruction and iris NV[15-17]. It may play as a new therapeutic option or an adjuvant agent to PRP in some patients of PDR, such as when VH precludes

the visualization of fundus and prevents adequate laser PRP. The main shortcoming of bevacizumab is the short duration of its effect. Conversely, laser PRP has better durability. In the current study [4], combined anti-VEGF therapy and supplemental PRP accelerated the VH clear-up and NV regression. And IVB also had synergistic effects, when used in combination with PRP for the treatment of high-risk PDR with severe NVD.

Results of the present study suggest that both treatments (PRP and the combination of IVB with PRP) are associated with significant regression of actively leaking NV in patients with high-risk PDR. However, the use of IVB in addition to PRP was associated with a larger reduction in FLA than PRP alone. In the similar studies comparing PRP versus PRP plus IVB or ranibizumab for high-risk PDR, PRP-Plus therapy resulted in marked regression of NV compared with PRP alone[4,7,10].

Although both treatments are associated with significant regression of active NV, no significant BCVA change was observed after treatment in the PRP-Plus group, while slight visual acuity worsening was observed in partial patients treated only with PRP. Macular edema is the leading cause of visual loss in diabetic retinopathy patients [18]. The intravitreal anti-VEGF injection can reduce macular interstitial fluid or edema that, even when subclinical, might cause retinal functional impairment [19-21]. However, in the current study, It is stated that the early visual gains due to IVB were not maintained 5y after treatment [22]. In our study, no difference in average CSMT emerged between the groups throughout the 24-week follow-up period. Of note, our study included mainly patients without clinically significant macular edema, and in these patients, a trend towards CSMT decrease was observed in the PRP-Plus group, while a CSMT increase was observed in eyes treated with PRP alone. In the present study, in both groups, BCVA remained relatively stable and did not differ from baseline, of note, a significant improvement in BCVA was observed in the PRP-Plus group after intravitreal anti-VEGF treatment compared with PRP group. This difference may be explained by the clearing of pre-existing preretinal or VH and improvement in diabetic macular edema. It is assumed that the adjunctive use of bevacizumab with PRP would have the potential to prevent, at least in part, the development of macular edema in patients.

No difference in IOP and lens grading score between the two groups was observed throughout the study, and no significant change in IOP was observed at any study visit compared with baseline in either group. The results of our study are consistent with data from other studies regarding no apparent association between IVB injection and increase in IOP, cataract development/progression, or an increased rate of endophthalmitis and the study drug[23]. But systemic and local adverse events about IVB must be monitored for long term, because the current study suggest that multiple intravitreal injections could be associated with sustained IOP elevation[24]. And in the literature, a serious complication of branched retinal artery obstruction after IVB injection was observed in one patient with PDR, possibly due to the thromboembolic effects of bevacizumab[8].

There are also more comfort and less retinal functional loss for PRP-plus intravitreal anti-VEGF injection in comparison to PRP alone for high-risk PDR treatment [6,25-26]. In conclusion, bevacizumab appears to have a place in the treatment of PDR. The observed anatomic (by ophthalmic examination and FA) and visual acuity improvements after combined IVB injection and PRP demonstrated that it was a safe and useful alternative or adjunctive treatment for high-risk PDR. The limitations of this present study included the fact that it had relatively small number of patients (sufficient for statistical purposes) and short-term follow-up period. A long-term prospective study is needed to confirm the maintenance of therapeutic benefit suggested in this study and to determine the optimal dosing regimen. Evaluation of possible long-term ocular and systemic adverse effects is also essential. Further randomized studies will strengthen the current findings, giving evidence to guide treatment choices in the management of high-risk PDR.

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