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Effect of panretinal photocoagulation combined with intravitreal Conbercept in the treatment of proliferative diabetic retinopathy with different stages

Tian-Hui Shan[1,3], *Jia-Xuan Yu*[1,3], *Chun-Li Liu*[1,3], *Xiang Gao*[1,3], *Gong-Qiang Yuan*[1,2,3], *Xiao-Lei Sun*[1,2,3], *Jing-Jing Zhang*[1,2,3]

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[1]Eye Institute of Shandong First Medical University; Eye Hospital of Shandong First Medical University (Shandong Eye Hospital), Jinan 250021, Shandong Province, China; [2]State Key Laboratory Cultivation Base, Shandong Provincial Key Laboratory of Ophthalmology, Qingdao 266071, Shandong Province, China; [3]School of Ophthalmology, Shandong First Medical University, Jinan 250117, Shandong Province, China

Correspondence to: Jing-Jing Zhang. Eye Institute of Shandong First Medical University, Eye Hospital of Shandong First Medical University (Shandong Eye Hospital), Jinan 250021, Shandong Province, China; State Key Laboratory Cultivation Base, Shandong Provincial Key Laboratory of Ophthalmology, Qingdao 266071, Shandong Province, China; School of Ophthalmology, Shandong First Medical University, Jinan 250117, Shandong Province, China. zhangjingjing@sdfmu.edu.cn; Xiao-Lei Sun. Eye Institute of Shandong First Medical University, Eye Hospital of Shandong First Medical University (Shandong Eye Hospital), Jinan 250021, Shandong Province, China; State Key Laboratory Cultivation Base, Shandong Provincial Key Laboratory of Ophthalmology, Qingdao 266071, Shandong Province, China; School of Ophthalmology, Shandong First Medical University, Jinan 250117, Shandong Province, China. sxlsunxiaoleixl@sina.com

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玻璃体腔注射康柏西普联合全视网膜激光光凝治疗不同分期增殖性糖尿病视网膜病变

单田慧[1,3],俞嘉宣[1,3],刘春莉[1,3],高 翔[1,3],原公强[1,2,3],孙晓蕾[1,2,3],张静静[1,2,3]

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作者单位:[1](250021)中国山东省济南市,山东第一医科大学附属眼科研究所 山东第一医科大学附属眼科医院(山东省眼科医院);[2](266071)中国山东省青岛市,山东省眼科学重点实验室省部共建国家重点实验室培育基地;[3](250117)中国山东省济南市,山东第一医科大学眼科学院

作者简介:单田慧,毕业于潍坊医学院,硕士研究生,主治医师,研究方向:眼底病。

通讯作者:张静静,毕业于青岛大学,博士,主任医师,副教授,研究方向:眼底病.zhangjingjing@sdfmu.edu.cn;孙晓蕾,毕业于青岛大学,博士,副主任医师,讲师,研究方向:眼底病.sxlsunxiaoleixl@sina.com

摘要

目的:评价玻璃体腔注射康柏西普联合全视网膜激光光凝(PRP)治疗不同分期增殖性糖尿病视网膜病变(PDR)的疗效。

方法:回顾性病例研究。选取于 2018-01/2020-06 期间初次就诊于我院的 PDR 患者 100 例 100 眼,入选患者均行玻璃体腔注射康柏西普治疗,并在注药后 1mo 内进行 PRP 治疗。依据我国糖尿病视网膜病变临床诊疗指南,根据眼底荧光血管造影及眼底检查结果分为 3 组:A 组早期 PDR 组 34 眼;B 组高危 PDR 组 43 眼,C 组纤维增生早期 PDR 组 23 眼。观察 3 组患者基线情况以及联合治疗后 1、3、6mo 和末次随访时的最佳矫正视力(BCVA)、黄斑中心厚度(CMT)、玻切手术率,视网膜脱离率。

结果:本研究平均随访 14.60±11.64mo(6-52mo)。患者平均年龄为 54.22±9.32 岁。治疗后行玻切手术患者 15 眼(15.0%),3 组玻璃体切除率分别为 2.9%(A 组)、13.9%(B 组)、34.7%(C 组)。治疗后无视网膜脱离情况发生。末次随访较基线水平,3 组患者治疗后 BCVA 和 CMT 值均有改善。

结论:玻璃体腔注射康柏西普联合 PRP 治疗不同分期 PDR 是安全有效的,可有效提高患者视力,减轻视网膜水肿。

关键词:增殖性糖尿病视网膜病变;玻璃体切除术;全视网膜光凝;康柏西普

Abstract

• AIM: To investigate the effectiveness of panretinal photocoagulation (PRP) combined with intravitreal conbercept (IVC) for patients with different stages of proliferative diabetic retinopathy (PDR).

• METHODS: Retrospective study. The medical records for 100 patients (100 eyes) with PDR treated with PRP combined with IVC from January 2018 to June 2020 were reviewed, including 34 eyes with early PDR (group A), 43 with high-risk PDR (group B), and 23 with fibrovascular PDR (group C). The baseline information, best corrected visual acuity (BCVA), central macular thickness (CMT), the rate of vitrectomy and retinal detachment of the patients in the three groups at 1, 3, 6mo and the last follow-up after combination treatment were observed.
• RESULTS: The patients were followed up for 14.60±11.64mo(6-52mo), with a mean age of 54.22±9.32 years. We found 15 eyes (15.0%) who underwent vitrectomy after the combination treatment. The vitrectomy rates of the three groups were 2.9% in group A, 13.9% in group B, and 34.7% in group C. We found no instances of retinal detachment after the treatments. Most patients demonstrated improved BCVA and CMT values with the treatments.
• CONCLUSION: PRP combined with IVC is safe and effective in patients with different PDR stages.
• KEYWORDS: proliferative diabetic retinopathy; pars plana vitrectomy; panretinal photocoagulation; Conbercept
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INTRODUCTION

Proliferative diabetic retinopathy (PDR) is the most common cause of severe visual loss in patients with diabetes mellitus[1]. Panretinal photocoagulation (PRP) has been the gold standard therapy for people with PDR since the 1970s, as it causes regression of retinal neovascularization (RNV) and reduces the risk of severe vision loss by destroying areas of peripheral retina that drive RNV formation, while preserving the central vision[2-3]. PRP has been shown to reduce the risk of severe vision loss by 50%-60%[4]. However, many patients need supplemental laser treatments, and nearly 5.3%, show disease progression that ultimately requires pars plana vitrectomy (PPV) after a seemingly adequate PRP procedure[5]. The PRP procedure is inherently destructive, it has associated side effects (*e.g.*, pain, transient visual disturbances, loss of peripheral or night vision, increased risk of macular edema, and central vision loss), and is not always effective[6].

Intravitreal anti-vascular endothelial growth factors (VEGF) agents have revolutionized the management of diabetic eye disease. VEGF have been shown to participate in the RNV and retinal vascular leakage related with PDR[7-8]. Ranibizumab, bevacizumab, and aflibercept are three different VEGF inhibitors that have demonstrated a positive effect on the regression of RNV[6,9-11]. Intravitreal anti-VEGF injections have become alternatives to PRP for PDR management[11]. However, the duration of their effect is short and treatment requires repeated intravitreal injections[12]. In addition, the cost of treatment and visits are important considerations for patients with PDR[11]. Combination treatment is thought to increase the rate of success of PRP, achieving RNV regression with visual acuity improvements and few side effects. However, some reports have suggested that combination treatment could cause retinal detachment, especially in patients with fibrovascular PDR. Arevalo JF *et al*[13] identified 11 eyes out of 211 (5.2%) with intravitreal bevacizumab (Avastin) injections that developed or had progression of tractional retinal detachment. We designed this study to assess whether combination treatment reduces the rate of PPV and the incidence of retinal detachment in patients with fibrovascular PDR.

Conbercept (KH902; Chengdu Kanghong Biotechnology, Sichuan, China), a novel anti-VEGF agent, is a fusion protein anti-VEGF drug independently developed in China, which is formed by the second immunoglobulin (Ig)-like domain in VEGF receptor (VEGFR) 1 and the 3rd and 4th Ig-like domains in VEGFR2, and human IgG Fc fragments are fused, and were approved for the treatment of DME in May 2019, with lower dissociation rate, long half-life, prolonging its action time in the eye, and inhibiting neovascular growth by antagonizing VEGFR signaling. It has the advantages of long action time, high affinity and multiple targets[14]. Among the various clinical studies that have been conducted, the 12-month multi-center randomized double-blind parallel controlled Phase trial (SAILING) and the 12-month extended study provide evidence for the long-term efficacy and safety of conbercept in the treatment of DME[15]. However, few reports on the efficacy of conbercept for the treatment of patients with different PDR stages are available. Thus, the main purpose of this study was to monitor the effects of PRP combined with intravitreal conbercept (IVC) in patients with different PDR stages and to assess whether the combination treatment reduces the number of cases requiring PPV and the incidence of retinal detachment in patients with fibrovascular PDR.

SUBJECTS AND METHODS

Ethical Approval The Medical Ethics Committee of Shandong Eye Hospital approved this study (No. SDSYKYY201801-2). We conducted the study respecting the tenets of the Declaration of Helsinki. We conducted a retrospective analysis with records of patients admitted to Shandong Eye Hospital between January 2018 and June 2020. The treatment procedures and the risks and benefits of the intraocular injection therapy combined with PRP were explained to all patients before anti-VEGF treatment initiated. All patients voluntarily signed written treatment informed consent forms.

Patients Our analysis included records of patients over the age of 18 with a diagnosis of PDR in at least one eye who had received IVC. We obtained data from 100 eyes with a primary diagnosis of PDR at the Shandong Eye Hospital between January 2018 and June 2020 followed for at least 6mo. The follow-ups were extended for 1mo postoperatively for patients who ultimately underwent vitrectomy. All patients underwent fundus fluorescein angiography (HRA2, Heidelberg, Germany) to identify their PDR level. We carefully reviewed the medical records of the patients and applied the following exclusion criteria: 1) prior PRP or focal/grid photocoagulation; 2) a previous intraocular surgery; 3) any history of anti-VEGF treatment; 4) severe lens opacity precluding fundus examination; 5) intraocular pressure >21 mmHg; 6) other causes of RNV (such as retinal vein occlusion and radiation retinopathy).

Diagnosis and Classification of Proliferative Diabetic Retinopathy Physicians diagnosed and classified PDR following the China clinical diagnosis and treatment guidelines of PDR (2022)[16]. This classification is based on ETDRS classification criteria with subtle adjustments for the clinical conditions in the country. The patients in our records had PDR classified into periods IV or V as follows: 1) Period IV (early PDR): Presence of retinal neovascularization of the disk (NVD) or retinal neovascularization elsewhere (NVE). NVD values greater than 1/4 to 1/3 of the disc diameter (DD), NVEs greater than 1/2 DDs, or patients with preretinal or vitreous hemorrhage were classified as "high-risk" cases; 2) Period V (fibrovascular proliferation stage): Appearance of fibrovascular membranes that may be associated with preretinal or vitreous hemorrhage. In our study, patients with fibrovascular PDR presented few fibrovascular membranes that may have been accompanied by some retinal hemorrhage, but they were not eligible for vitrectomy. We divided data from patients into three groups: A: for those with an early PDR; B: for those at high risk of PDR; and C: for those with fibrovascular PDR.

Treatments and Follow-ups All patients received an IVC (0.5 mg/0.05 mL) injection 1wk before the first PRP session. All enrolled eyes were scheduled to undergo a scatter laser treatment using a 532-nm argon green laser (Vision one, LUMENIS, USA) at 3 to 4 time points in one month (one-week intervals). The laser treatment was administered in 400 to 500 spots per episode. Patients developing drug-related complications (such as intense vitreal hemorrhage or tractional retinal detachment) underwent PPV.

Follow-up visits were scheduled at 1, 3, and 6mo after the initial PRP session, and the patients who underwent vitrectomy were examined at last 1mo after the surgical procedure. Physicians calculated the PPV and retinal detachment rates, and conducted best corrected visual acuity (BCVA) and intraocular pressure measurements, slit lamp biomicroscopy, fundus examinations, optical coherence tomography (OCT) (Optovue, Fremont, California, USA) and fluorescein angiography (HRA2, Heidelberg, Germany) scans at all follow-up visits. In addition, all adverse events were also recorded. The study eyes were subjected to standard ophthalmological examinations at each visit. The decimal visual acuity was converted to the logarithm of the minimum angle of resolution units for the statistical analysis.

Outcome Measures The primary outcome measures in our study include the vitrectomy and retinal detachment rates after combination treatment. The secondary measures include the BCVA and central macular thickness (CMT) values before and after treatment. The systemic complications and serious adverse reactions were recorded for the evaluation of treatment safety.

Statistical Analysis The statistical package for social sciences (SPSS) (version 22.0 for Windows; SPSS, Chicago, IL, USA) software was used for the statistical analysis of the data. Continuous variables were expressed as means and standard deviations and categorical variables as distribution frequencies. Baseline values between groups were compared using the Mann-Whitney test and the changes in BCVA and CMT within or between groups by means of repeated measures ANOVA. The proportions of the patients with visual acuity and CMT changes between groups were assessed using Chi-square tests. In addition, a Cox regression model was generated to analyze the risk factors for PPV requirements and retinal detachment occurrence, and for changes in BCVA and CMT adjusted for sex, age, and follow-up times. The statistically analyses was conducted at a significance level of 5%.

RESULTS

Patient Characteristics at Baseline Between January 2018 and June 2020, 100 study eyes/participants randomly met the inclusion criteria and had completed the follow-up period. All patients were followed up for at least 6mo, with a mean follow-up time of 14.60±11.64mo (6-52mo). The three comparative subgroups were generally well balanced in baseline ocular characteristics. Table 1 lists the demographic details and baseline findings of patients in the three groups.

Vitrectomy Rate and Retinal Detachment Rate at the Last Follow-up At the last follow-up, 15 eyes (15%) had undergone vitrectomy (15 for vitreous hemorrhage and none for retinal detachment). The vitrectomy rates of the three groups were 2.9% for group A, 13.9% for group B, and 34.7% for group C (P<0.001; Table 2). The mean follow-up period was 16.8mo (ranging from 8 to 24mo). No retinal detachments occurred. Tables 3 and 4 list the BCVA and CMT changes before and after vitrectomy.

Best-corrected Visual Acuity and Central Macular Thickness Changes The mean baseline LogMAR BCVAs were similar at 0.34±0.24 in group A, 0.28±0.27 in group B, and 0.29±0.24 in group C with no significant differences. After treatment, the mean baseline BCVA (LogMAR) values had increased after 6mo in all groups (P<0.05; Table 5).

Table 1 Baseline characteristics of subjects

Variables	Group A (n=34)	Group B (n=43)	Group C (n=23)	P
Age ($\bar{x}\pm s$, years)	56.74±9.97	52.25±9.41	54.13±7.43	0.350[b]
Female (n, %)	13 (38.2%)	22 (51.1%)	9 (39.1%)	0.455[a]
Duration of diabetes ($\bar{x}\pm s$, a)	9.81±6.35	9.95±5.54	9.78±5.29	0.560[b]
Insulin treatment (n)	19	22	12	0.915[a]
Hypertension (n)	16	14	10	0.404[a]
DME (n)	21	16	11	0.101[a]
BCVA($\bar{x}\pm s$, LogMAR)	0.34±0.24	0.28±0.27	0.29±0.24	0.405[b]
CMT ($\bar{x}\pm s$, μm)	320.38±105.79	280.37±71.69	305.35±105.79	0.085[b]
Follow-up time ($\bar{x}\pm s$, mo)	12.26±9.36	15.90±13.37	15.61±11.64	0.357[b]

BCVA: Best-corrected visual acuity; DME: Diabetic macular edema; CMT: Central macular thickness. [a]Chi-square test; [b]analysis of variance.

Table 2 Number of patients with pars plana vitrectomy at final follow-up

	Group A	Group B	Group C	P
Number of patients with PPV (n, %)	1 (2.9)	6 (13.9)	8 (34.7)	0.000[a]

[a]Chi-square test; PPV: Pars plana vitrectomy.

Table 3 Follow-up of subjects performed pars plana vitrectomy

Patients	Baseline BCVA (LogMAR)	Baseline CMT (μm)	retinal detachment or not (B-scan)	intraoperative tamponade	postoperative BCVA (LogMAR)	postoperative CMT (μm)
A28	0.22	236	no	air	0.52	230
B14	0.30	242	no	silicone oil	0.82	270
B24	0.30	235	no	silicone oil	0.30	276
B30	0.30	220	no	air	0.10	228
B36	0.15	230	no	air	0.70	225
B38	0.10	480	no	silicone oil	0.52	300
B42	0.40	252	no	air	0.30	268
C1	0.00	297	no	air	0.10	291
C2	0.15	275	no	air	0.30	253
C3	0.52	200	no	air	0.40	200
C4	0.10	300	no	air	0.00	245
C6	0.22	356	no	silicone oil	0.22	264
C9	0.00	266	no	air	0.15	311
C22	0.22	540	no	air	0.22	250
C23	0.10	310	no	air	0.40	265

BCVA: Best-corrected visual acuity; CMT: Central macular thickness.

Table 4 Changes in best-corrected visual acuity and central macular thickness

Parameters	Baseline	Postoperative	P
BCVA ($\bar{x}\pm s$, LogMAR)	0.17±0.14	0.30±0.22	0.051[a]
CMT($\bar{x}\pm s$, μm)	290.22±89.21	256.44±28.61	0.141[a]

[a]analysis of variance; BCVA: Best-corrected visual acuity; CMT: Central macular thickness.

Table 5 Changes in best-corrected visual acuity of three groups

($\bar{x}\pm s$, LogMAR)

Groups	Baseline	Final	P
Group A	0.34±0.24	0.22±0.19	0.027[a]
Group B	0.28±0.27	0.15±0.17	0.016[a]
Group C	0.29±0.24	0.16±0.17	0.039[a]
Total subjects	0.30±0.25	0.17±0.18	0.000[a]

[a]analysis of variance.

The mean baseline retinal thicknesses in the central subfield were 320.38±105.79 μm in group A, 280.37±71.69 μm in group B, and 305.35±105.79 μm in group C. The mean baseline CMT values of three groups were similar. The mean baseline CMT decreased significantly in all groups after 6 months of treatment (P<0.05; Table 6).

The CMT values in patients with diabetic macular edema (DME) were similar in the three groups at 362.62±114.92 μm in group A, 339.14 ±71.90 μm in group B, and 362.73±127.52 μm in group C at baseline (P>0.05; Table 7). We found similar CMT values in the patients with DME and without DME after treatment in all the groups (P>0.05; Table 8).

We generated a Cox regression model to analyze the risk factors for PPV requirement and retinal detachment occurrence,

Table 6 Changes in central macular thickness of three groups ($\bar{x}\pm s$, μm)

Group	Baseline	Final	*P*
Group A	320.38±105.79	266.92±47.81	0.009[a]
Group B	280.37±71.69	253.05±46.03	0.038[a]
Group C	305.35±105.79	254.85±40.16	0.038[a]
Total subjects	299.71±93.32	258.13±45.46	0.000[a]

[a]analysis of variance.

Table 7 Baseline central macular thickness in patients with diabetic macular edema in three groups ($\bar{x}\pm s$, μm)

	Group A	Group B	Group C	*P*	*F*
CMT	362.62±114.92	339.14±71.90	362.73±127.52	0.792[a]	0.234[a]

[a]one way analysis of variance; CMT: Central macular thickness.

Table 8 Final central macular thickness in patients with or without diabetic macular edema in three groups ($\bar{x}\pm s$, μm)

Groups	with DME	without DME	*P*
Group A	285.52±50.08	236.69±22.87	
Group B	285.64±57.09	231.65±16.75	0.152[a]
Group C	269.27±45.61	241.66±30.59	

[a]Chi-square test. DME: Diabetic macular edema.

and BCVA and CMT value changes adjusted for sex, age, and follow-up times. The retinal detachment rate was zero. Sex, age, and follow-up times were not risk factors for PPV requirement, or BCVA and CMT changes. We found the PDR grading to be a risk factor for PPV requirement. Patients in group C were at higher risk of eventually requiring vitrectomy, followed by those in group B, and patients in group A had the lowest risk (Figure 1).

Systemic and Ocular Adverse Events During the study period, we found no evidence of serious systemic or ocular complications, or serious adverse drug reactions.

DISCUSSION

In the past few decades, with the development of society and economy and the change of people's life style, the prevalence of diabetes worldwide has increased year by year[17-19]. According to the 2021 IDF statistics, there are currently 537 million people aged 20-79 with diabetes worldwide, and this number is expected to grow to 783 million by 2045[20]. The number of adults with DR worldwide in 2020 is estimated to be 103.1 million. By 2045, this number is expected to increase to 160.5 million[21]. In China, the prevalence of diabetes increased from less than 1% in the 80s of the 20th century to nearly 11% in 2013 [22-26]. In 2018, the prevalence of Chinese mainland diabetes reached 12.4%, with pre-diabetic patients accounting for 38.1% of the total population[27]. The number of patients with diabetes mellitus in China is the largest in the world with more than 140 million patients[19]. DR is a retinal complication of diabetes and is

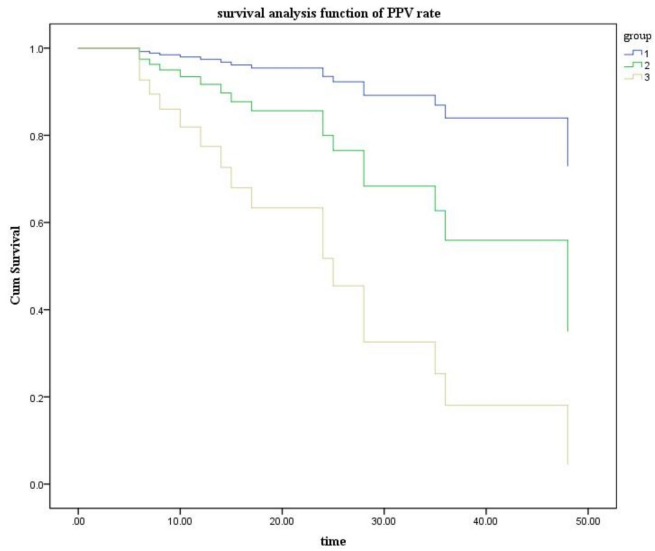

Figure 1 Survival analysis function of pars plana vitrectomy rate. PPV: Pars plana vitrectomy.

due to long-term retinal microvascular damage due to hyperglycemia, which also merges with the retina glial network lesions; A chronic, progressive blinding eye disease[28-29]. Glycemic level control and treatment of urine diseases and related complications is urgent. Retinal detachment and vitreous hemorrhages are major complications that can lead to severe visual loss or blindness in patients with PDR. Without interventions, nearly half of eyes with PDR experience severe visual loss within 5 years[2,30].

Reports regarding the effects of anti-VEGF drugs on PDR have stated that preoperative intravitreal anti-VEGF injections may facilitate vitrectomy in severe PDR cases. Increasing evidence from clinical trials has demonstrated the safety and efficacy of anti-VEGF injections for the treatment of PDR[31]. This has been demonstrated for bevacizumab, ranibizumab, and aflibercept[9], but other intravitreal anti-VEGF agents effective against RNV such as conbercept have not been sufficiently studied. Treatment with anti-VEGF injection and PRP has been shown to be effective in patients with PDR, according to the PROTEUS[6], Protocol S[31], and CLARITY[9] studies. Some researchers have investigated the efficacy of IVC combined with PRP in the treatment of high-risk PDR[32]. However, few reports on the efficacy of the combination treatment for patients of all PDR stages exist.

We designed this study to assess the efficacy of combination treatment (IVC with PRP) for patients with different PDR classifications (including early PDR, high risk PDR, and fibrovascular PDR). The staging method we used is based on the diabetic retinopathy staging in China from 1985 with modifications from the international classification of 2003. DRSS can be used in clinical studies to determine the severity of DR[33-35]. Our group A patients had an early PDR stage, corresponding to the international mild PDR 61B and moderate PDR 65B and 65C stages; group B patients had a high-risk PDR stage, corresponding to the 65A in moderate

PDR and 71D in high-risk PDR in the international staging; and patients in group C had PDR with early hyperplasia, corresponding to the 81-hyperplastic advanced DR without macular detachment international stage. We excluded patients with vitreous hemorrhages and those with stages 71A-C and 75 in the high-risk PDR international stages. After treatment, most enrolled eyes experienced higher BCVA and lower CMT values than those at baseline, and no retinal detachments occurred. We found a lower retinal detachment rate (0%) than that reported by Arevalo *et al*[13] at 5.2%. Preoperative retinal detachments were diagnosed on the basis of B-ultrasound results at the last follow-up before surgery. Several patients in the vitrectomy group received silicone oil tamponade due to the tight adhesion of their proliferative membranes to the retina or the difficulty in separating the posterior vitreous during the operation, resulting in local traction retinal detachment. We found no serious adverse reactions during the study, indicating the safety and efficacy of the combined treatment. In our study, 15 patients (15 eyes) out of 100 developed vitreous hemorrhages and received vitrectomy after the combination treatment (vitrectomy rate, 15.0%). However, the BCVA and CMT values were not worse than those at baseline at least 1mo after the vitrectomy. The patients with fibrovascular PDR were more likely to develop vitreous hemorrhages and need vitrectomy than the others. Compared with Flynn's vitrectomy rate of 5.3%, our vitrectomy rate at 15% is relatively high, possibly due to different patient classifications in the two studies. The patients enrolled in Flynn's study had non-proliferative PDR or early PDR, while we included patients with more severe stages including patients with early, high-risk, and fibrovascular PDR. Moreover, the vitrectomy rate in our early PDR group was only 2.9%, a rate lower than that in Flynn's study.

IVC with PRP provides enough time for the neovascularization in patients with PDR to regress and prevents severe vision losses. In addition, different PDR classifications result in accurate prognoses allowing patients to have reasonable psychological expectations and high satisfaction during the treatments. Moreover, in patients with fibrovascular PDR, IVC with PRP treatment can reduce the risk for vitrectomy requirements, reduce costs, and motivate patients to get treatments and attend follow-ups. Overall, we found that the combination therapy is safe and effective for the treatment of different PDR stages. Figures 2-4 are some pictures of typical cases of three groups. The two therapies complement each other and can improve the patient's vision by achieving neovascularization and macular edema regression, while improving retinal ischemic and hypoxic conditions, and preventing the occurrence of recurrent vitreous hemorrhages and traction retinal detachment caused by fibrovascular membranes. The combination therapy can also effectively reduce the incidence of retinal detachment in patients with PDR and evidence of some fibrovascular membrane formation. Even the few patients requiring additional vitrectomy after the combination treatment do not risk losing any visual acuity after the surgical procedure.

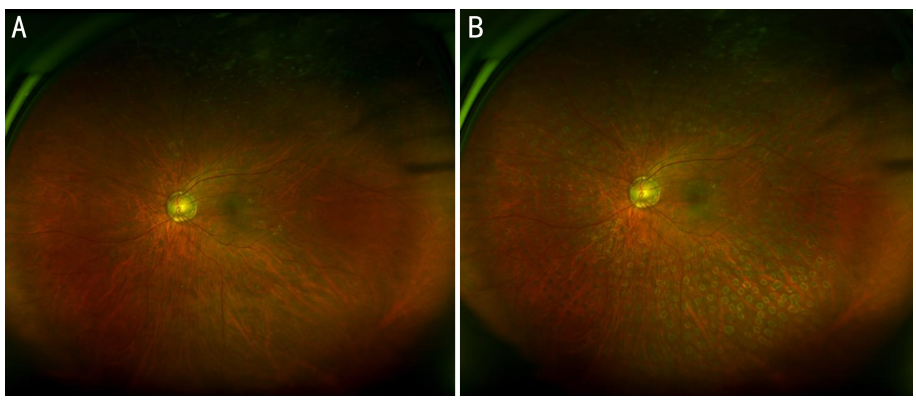

Figure 2 Case 1 in group A. A: Fundus photograph of baseline; B: Fundus photograph at last follow-up.

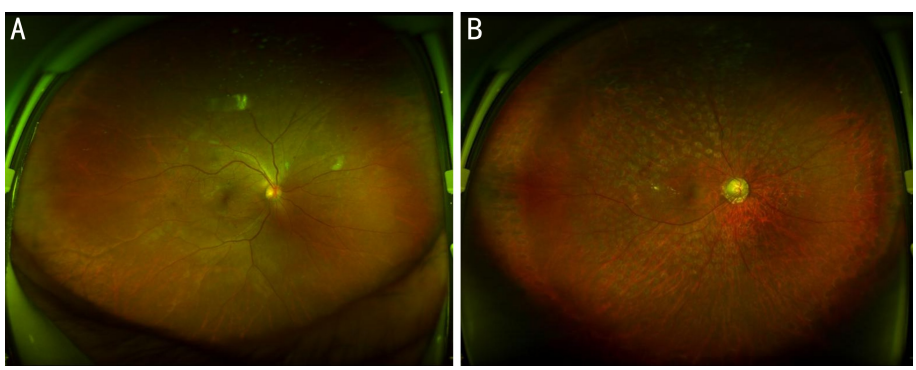

Figure 3 Case 2 in group B. A: Fundus photograph of baseline; B: Fundus photograph at last follow-up.

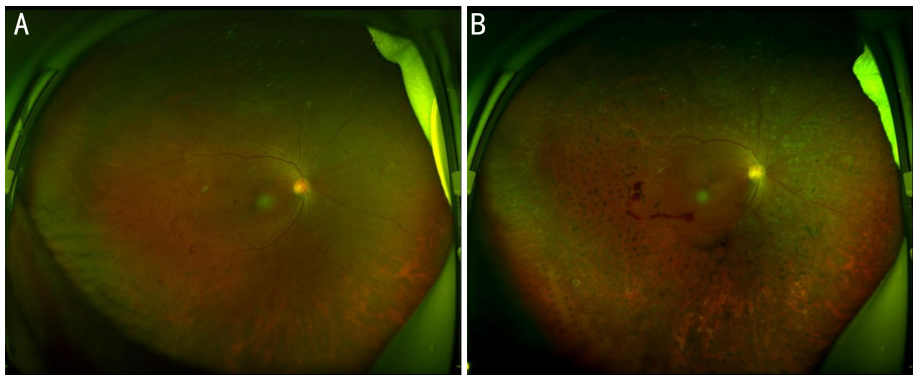

Figure 4 Case 17 in group C. A: Fundus photograph of baseline; B: Fundus photograph at last follow-up.

Its short follow-up time and small sample size are limitations of this study. A larger study with longer follow-up times would be ideal for validating and confirming our results, while also determining the benefits of the combination therapy (PRP plus IVC) for patients with different PDR stages.

CONCLUSIONS

PRP combined with IVC is safe and effective for patients with different PDR stages. Combination therapy can effectively reduce the PPV rate and the incidence of retinal detachment in patients with PDR who present some fibrovascular membrane formation. Even in the few patients requiring additional vitrectomy after the combined treatment, their visual acuity after surgery is not worse than the baseline value.

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