Am J Transl Res 2022;14(2):1324-1331
www.ajtr.org /ISSN:1943-8141/AJTR0140559

Original Article

Pars plana vitrectomy assisted by intravitreal injection of conbercept enhances the therapeutic effect and quality of life in patients with severe proliferative diabetic retinopathy

Qin Wang[1*], Hui Cai[2*], Dahua Xu[3], Lin Cui[1], Yan Zhang[4], Mei Chen[1]

[1]Chongqing Aier Eye Hospital, Chongqing 400020, Chongqing, China; [2]Department of Oncology, Fengdu People's Hospital of Chongqing, Chongqing 408020, China; [3]College of Eye Sciences, Central South University, Changsha 410015, Hunan, China; [4]Department of Ophthalmology, Dazhou Central Hospital, Dazhou 635000, Sichuan, China. [*]Equal contributors.

Received November 15, 2021; Accepted January 5, 2022; Epub February 15, 2022; Published February 28, 2022

Abstract: Objective: To explore the application value of intravitreal injection of Conbercept (IVC)-assisted pars plana vitrectomy (PPV) in patients with severe proliferative diabetic retinopathy (PDR). Methods: Forty-eight patients with severe PDR who underwent surgical treatment in Chongqing Aier Eye Hospital between October 2019 and June 2021 were retrospectively enrolled, and their clinical data were analyzed. Of them, 22 patients receiving PPV alone were assigned to the PPV group, and the remaining 26 patients treated with IVC-assisted PPV were included in the PPV+IVC group. The intra-operative indicators, postoperative complication rate, visual acuity (VA) improvement, and postoperative quality of life (QoL) were compared between the two groups. The levels of vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and basic fibroblast growth factor (bFGF) in aqueous humor (AH) as well as serum contents of interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) were determined by Enzyme Linked Immunosorbent Assay (ELISA). Results: Compared to the PPV group, the operation time of the PPV+IVC group was significantly shorter, and the incidence of severe intraoperative blood loss (IBL), bipolar electrocoagulation hemostasis, iatrogenic retinal breaks (IRBs), postoperative silicone oil tamponade (SOT), and overall complications were significantly reduced. After surgery, the central macular thickness (CMT) was lower and the best corrected visual acuity (BCVA) assessed by the standard visual acuity chart and VA were significantly more improved in the PPV+IVC group versus the PPV group. After the use of Conbercept, the AH levels of VEGF, PlGF, and bFGF in the PPV+IVC group decreased and were significantly lower than those in the PPV group. The PPV+IVC group also showed lower serum levels of TNF-α, IL-6, and IL-1β than the PPV group. Conclusions: IVC-assisted PPV can effectively reduce the difficulty of surgical treatment for PDR, better improve the postoperative VA of patients, and reduce inflammation with fewer complications.

Keywords: Conbercept, pars plana vitrectomy, proliferative diabetic retinopathy, VEGF

Introduction

Diabetes is one of the most common metabolic diseases with an increasing incidence, posing a grave threat to human life and health [1]. In 2015, approximately 415 million people worldwide were reported to have diabetes, and the number is likely to exceed 640 million by 2040 [2]. Diabetic retinopathy (DR) is the most common type of diabetic microangiopathy and, if left untreated, can lead to progressive visual impairment and eventual blindness [3]. With the increasing number of patients with diabetes, the incidence of DR also continues to increase, affecting more than 130 million people worldwide [4]. DR can be divided into non-proliferative and proliferative types, among which proliferative diabetic retinopathy (PDR) is the one with greater harm and increased treatment difficulty [5]. Currently, pars plana vitrectomy (PPV) is the first choice for the treatment of PDR. It can remove the long-standing hematocele in the vitreous cavity, block the pathway of neovascularization, and restore the retina to

a stable intraocular structure [6]. However, the procedure will also cause some adverse complications, such as retinal detachment (RD), neovascular glaucoma and recurrent vitreous hemorrhage, which undoubtedly delay the visual recovery of patients and may increase surgical cost [7]. Therefore, it is necessary to find a way to reduce the negative effects of PPV.

Vascular endothelial growth factor (VEGF) is a highly specific vascular endothelial cell (VEC) growth factor, that can regulate vascular permeability, extracellular matrix degeneration, VEC growth, and angiogenesis [8]. Earlier research has shown that the introduction of anti-VEGF drugs as adjuvant therapy before surgery can significantly reduce intraoperative blood loss (IBL) and shorten the operation time (OT), thus improving the surgical outcome [9]. Conbercept, a novel anti-VEGF drug, was approved by China Food and Drug Administration (CFDA) in 2013 to treat age-related macular degeneration [10]. Use of Conbercept in PDR patients after PPV is effective in accelerating the recovery of vision and reducing non-clearing vitreous hemorrhage (NCVH) [11]. However, there is still a lack of systematic reports on the application value and safety of preoperative use of Conbercept in patients with severe PDR undergoing PPV. At present, excessive inflammation is considered to be an important factor leading to PDR progression, in addition to angiogenesis [12].

The purpose of this study was to explore the application value of intravitreal injection of Conbercept (IVC)-assisted PPV in patients with severe PDR and its influence on serum inflammatory factors (IFs).

Materials and methods

Research participants

In this retrospective study, a total of 48 patients with severe PDR who underwent surgical treatment in Chongqing Aier Eye Hospital from October 2019 to June 2021 were selected as the research subjects. Among them, 22 patients receiving PPV alone were assigned to the PPV group, and the remaining 26 patients treated with IVC-assisted PPV were included in the PPV+IVC group. Inclusion criteria: Patients with PDR diagnosed by preoperative fundus examination, ophthalmologic auxiliary examination and intraoperative findings; Patients with clinical DR staging of V-VI [13]; Patients with monocular disease; Patients with provision of the signed informed consent by patients or their families. Exclusion criteria: Pregnant and lactating patients; Patients with contraindications to surgery and/or drugs used; Patients with heart, liver, lung and kidney dysfunction; Patients with previous history of intraocular surgery; Patients with glaucoma, corneal leukoplakia and other diseases that affect the observation results; Patients with myopia, amblyopia, strabismus and other diseases that affect the research results; Patients with poor blood glucose control; Patients with incomplete clinical data; Patients with prior use of anti-VEGF drugs. This study conformed to the *Declaration of Helsinki* and was approved by the Institutional Ethics Committee of Chongqing Aier Eye Hospital.

Treatment

IVC: Patients were treated with intraocular drops of antibiotics before surgery. In the supine position, the patient was routinely disinfected and covered with towels for intraocular surgery, and the conjunctival sac was irrigated with povidone iodine after surface anesthesia. The injection needle carried by Conbercept Ophthalmic Injection (manufactured by Chengdu Kanghong Pharmaceutical Group Co., Ltd., SFDA Approval No. S20130012) was inserted flatly into the flat part of the ciliary body, which was 3.5 mm behind the superior temporal corneal limbus, and 0.05 mL of the drug was injected into the vitreous body. Sterile cotton swabs were applied to press the puncture opening during injection to avoid drug overflow. Postoperative bleeding was observed, and antibiotic eye drops were used to prevent infection.

PPV: All patients in both groups completed preoperative ophthalmic examinations including visual acuity (VA), slit-lamp microscope, gonioscopy, ocular B-ultrasound, intraocular pressure (IOP), and fluorescein angiography, and their blood glucose was controlled to the normal range before surgery (fasting blood glucose <7 mmol/L, postprandial blood glucose <9.0 mmol/L). IVC was performed 3-5 days before surgery. Topicamide eye drops were used to dilate the pupil of the affected eye, and 20 g/L

lidocaine and bupivacaine were mixed equally for retrobulbar anesthesia. Cataract phacoemulsification and vitrectomy unit was used for the operation. The conjunctiva about 4.0 mm behind the corneal limbus was punctured obliquely with a 23 G puncture knife, and the trocar was placed into the flat part of the ciliary body to cut the vitreous body at the axis. The range of resection was the central area, the vitreous body at the base and the peripheral part. The cutting speed was controlled at 3,600-3,900 r/min and the negative pressure was 360-400 mmHg. During the operation, vitreous hemorrhage was removed and a small amount of triamcinolone acetonide was injected after vitreous detachment. If the patient's pre-retinal proliferative membrane was closely connected to the optic disc or retina, blunt separation of the adhesion between the two was performed to release the retinal traction and restore the retina. The 532 nm fundus laser photocoagulation was performed extensively in the retina, but not in the macular area and superior and inferior temporal vascular arches. After PPV, neovascularization hemorrhage or bleeding of the blood vessel wall stump was treated by spontaneous coagulation. In case of repeated bleeding, 23 G intraocular bipolar electrocoagulation was used for hemostasis. For severe retinal traction or retinal degeneration or tear, silicone oil tamponade (SOT) was performed after gas-liquid exchange. The incision was closed after the operation.

Outcome measures

The primary outcome measures were surgical indicators, postoperative complications, best corrected visual acuity (BCVA) assessed by the standard visual acuity chart, central macular thickness (CMT) and VA improvement. All other indicators were secondary outcome measures. The specific evaluation criteria are as follows.

Surgical indicators and postoperative complications were recorded. The former mainly included OT, severe IBL, bipolar electrocoagulation hemostasis, iatrogenic retinal breaks (IRBs) and postoperative SOT, while the latter mainly covered high IOP, NCVH, RD, subconjunctival hemorrhage (SCH) and endophthalmitis (EO).

Before and 3 months after operation, the BCVA of patients was examined. The greater the value, the better the VA. OSE-5000OCT optical coherence tomography was used to perform linear horizontal and vertical scanning of the macular fovea. The images were saved and analyzed and measured with the built-in software, and the CMT was recorded.

The VA improvement of patients was re-examined 3 months after surgery: Improved: the postoperative VA improved by ≥2 lines compared with that before operation. For patients with manual VA before operation, the VA improved to counting fingers or above. Stable: the postoperative VA was relatively improved or decreased by <1 line. Declined: the postoperative VA decreased by >2 lines.

Patients' quality of life (QoL) was assessed at 3 months after treatment using the SF-36 scale, mainly from the aspects of cognitive, physical, role and emotional functioning. Out of 100 points for each dimension, a higher score indicated a better prognostic QoL.

From all patients, 0.5 mL aqueous humor (AH) samples were collected when they were admitted to the hospital for dilated fundus examination and when undergoing PPV. The samples were centrifuged (1,630×g, 4°C) for 10 min, and the supernatant was refrigerated at -70°C until analysis. Additionally, 3 mL peripheral venous blood was extracted from each patient at admission and one month after surgery, and centrifuged (1,000×g, 4°C) for 15 min. AH levels of VEGF, placental growth factor (PIGF), and basic fibroblast growth factor (bFGF), as well as serum contents of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) by Enzyme Linked Immunosorbent Assay (ELISA). VEGF, TNF-α, IL-6 and IL-1β ELISA kits were purchased from Wuhan Boster Biotech, and PIGF and bFGF ELISA kits were ordered from Sigma, USA.

Statistical processing

Data processing and image rendering were performed by SPSS 19.0 (Shanghai Yijun Information Technology) and GraphPad Prism 7, respectively. The comparison of the count data between two groups used the Chi-square test. For measured data, independent samples t-test was used for inter-group comparisons,

Table 1. Comparison of general data between the two groups

Group	PPV group (n=22)	PPV+IVC group (n=26)	χ^2/t	P
Age (Y)	55.95±11.11	55.08±9.72	0.295	0.770
Male/female (n)	13/9	16/10	0.030	0.863
Course of diabetes mellitus (year)	5.95±1.84	5.15±1.76	1.560	0.126
Intraocular pressure (mmHg)	16.05±2.78	15.27±2.38	1.127	0.266
Hypertension [n (%)]	8 (36.36)	11 (42.31)	0.176	0.675
BMI (kg/m^2)	24.49±1.58	24.70±1.57	0.475	0.637

Note: BMI, body mass index.

Table 2. Comparison of surgical indicators

Group	PPV group (n=22)	PPV+IVC group (n=26)	χ^2/t	P
Operation time (min)	72.23±10.18	55.81±9.81	5.821	<0.001
Severe intraoperative blood loss [n (%)]	10 (45.45)	4 (15.38)	5.215	0.022
Bipolar electrocoagulation hemostasis [n (%)]	9 (40.91)	3 (11.54)	5.483	0.019
Iatrogenic retinal breaks [n (%)]	5 (22.73)	1 (3.85)	3.884	0.049
Postoperative silicone oil tamponade [n (%)]	7 (31.82)	2 (7.69)	4.553	0.033

Table 3. Comparison of complications

Group	PPV group (n=22)	PPV+IVC group (n=26)	χ^2	P
High intraocular pressure [n (%)]	3 (13.64)	3 (11.54)		
Non-clearing vitreous hemorrhage [n (%)]	5 (22.73)	2 (7.69)		
Retinal detachment [n (%)]	2 (9.09)	1 (3.85)		
Subconjunctival hemorrhage [n (%)]	3 (13.64)	2 (7.69)		
Endophthalmitis [n (%)]	2 (9.09)	0		
Total incidence (%)	15 (68.18)	8 (30.77)	6.684	0.010

and paired T test was used for intra-group comparisons before and after treatment. The comparison of measured data between multiple groups was performed by one-way analysis of variance, followed by post-hoc Tukey HSD test to verify the correctness of statistical values. A significance level of P<0.05 was used in all analyses.

Results

Comparison of general data

No significant difference was observed in general data such as age, gender, diabetes course, IOP, hypertension and body mass index (BMI) between the two groups (all P>0.05). See **Table 1**.

Comparison of surgical indicators

The operation was successfully completed in all the enrolled patients. Compared to the PPV group, the OT of the PPV+IVC group was significantly shorter, and the cases of severe IBL, bipolar electrocoagulation hemostasis, IRBs, and postoperative SOT were fewer (all P<0.05). See **Table 2**.

Comparison of complications

By recording the complications, it was found that there was no significant difference in the incidence of common complications such as high IOP, NCVH, RD, SCH and EO between the two groups (all P>0.05). However, the overall incidence of complications was significantly lower in the PPV+IVC group compared with the PPV group (P<0.05). See **Table 3**.

Comparison of BCVA and CMT

The BCVA and CMT were not significantly different between the two arms before surgery (all P>0.05). Postoperatively, BCVA increased and CMT decreased in both arms, with more signifi-

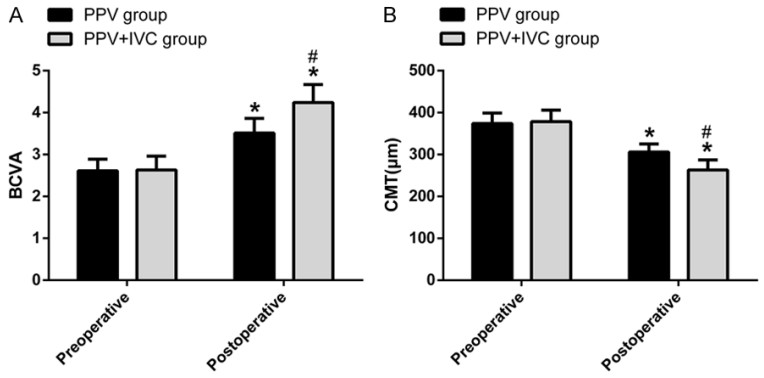

Figure 1. Comparison of best corrected visual acuity (BCVA) assessed by the standard visual acuity chart and central macular thickness (CMT). A: Comparison of BCVA between the two groups before and after surgery. B: Comparison of CMT between the two groups before and after surgery. Note: *P<0.05 *vs* before treatment within the group; #P<0.05 *vs* the PPV group.

Table 4. Improvement of vision acuity

Group	PPV group (n=22)	PPV+IVC group (n=26)	χ^2	P
Improved [n (%)]	10 (45.45)	20 (76.92)	5.035	0.025
Stable [n (%)]	11 (50.00)	6 (23.08)	3.776	0.052
Declined [n (%)]	1 (4.55)	0	1.207	0.272

Table 5. Comparison of postoperative quality of life between two groups

Group	PPV group (n=22)	PPV+IVC group (n=26)	t	P
Cognitive functioning	68.86±6.08	77.96±7.74	4.468	<0.001
Physical functioning	67.14±6.64	72.46±5.19	3.115	0.003
Role functioning	70.73±5.68	74.15±5.57	2.101	0.041
Emotional functioning	63.86±7.78	70.15±6.56	3.040	0.004

cant alterations in the PPV+IVC group (all P<0.05). See **Figure 1**.

VA improvement

Three months after operation, the VA improvement rate in the PPV+IVC group was 76.92%, which was significantly higher than that of 45.45% in the PPV group (P<0.05). See **Table 4**.

QoL

The evaluation of postoperative QoL showed that the scores of cognitive, physical, role and emotional functioning in the PPV+IVC group were significantly higher than those of the PPV group (P<0.05). See **Table 5**.

Comparison of AH levels of VEGF, PIGF and bFGF

The AH levels of VEGF, PIGF, and bFGF, detected by ELISA, were not statistically different between the two arms before surgery (P>0.05). After surgery, the AH levels of VEGF, PIGF, and bFGF reduced significantly in the PPV+IVC group (all P<0.05) while they changed little in the PPV group (all P>0.05). In addition, the AH levels of VEGF, PIGF, and bFGF were markedly lower in the PPV+IVC group versus the PPV group (all P<0.05). See **Figure 2**.

Comparison of serum IFs

The serum levels of TNF-α, IL-6, and IL-1β, measured by ELISA, were not significantly different between the two arms before surgery (all P>0.05). Postoperatively, the serum levels of TNF-α, IL-6, and IL-1β reduced markedly in both arms (all P<0.05), with lower values in the PPV+IVC group compared to the PPV group (all P<0.05). See **Figure 3**.

Discussion

This study investigated the application value and safety of preoperative use of Conbercept in PDR patients undergoing PPV. The results indicated that preoperative IVC in PDR patients undergoing PPV could shorten the OT, and reduce the incidence of severe IBL, bipolar electrocoagulation hemostasis, IRBs, SOT, and overall complications. Moreover, it could promote visual recovery, reduce inflammation, and improve the QoL of patients.

Previous clinical experience showed that PPV was difficult due to intraoperative bleeding, possibly because: 1) Hemorrhage makes it difficult to stratify and divide fibrovascular tissue, which increases the risk of IRBs [14]; 2) Uncontrolled bleeding during surgery may lead

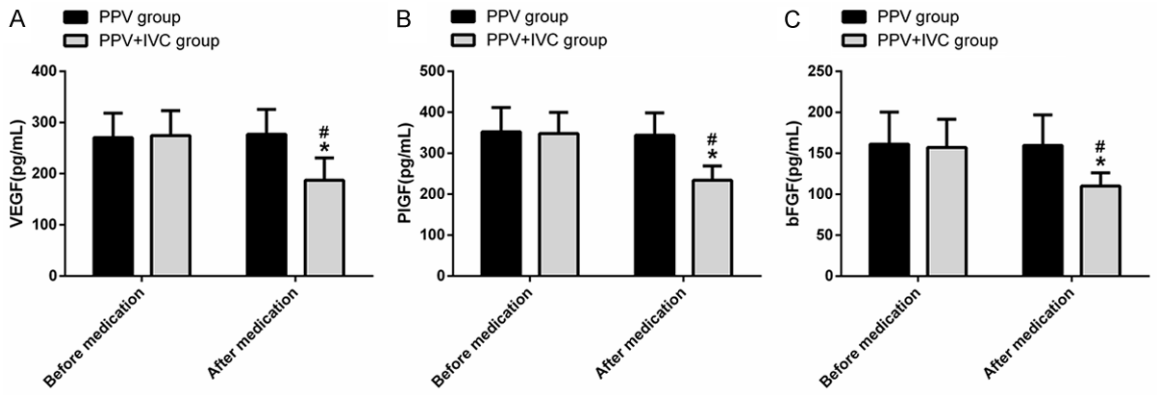

Figure 2. Comparison of vascular endothelial growth factor (VEGF), placental growth factor (PIGF), and basic fibroblast growth factor (bFGF) levels in aqueous humor. A: Comparison of VEGF levels in aqueous humor. B: Comparison of PIGF levels in room water. C: Comparison of bFGF levels in aqueous humor. Note: *P<0.05 *vs* before treatment within the group; #P<0.05 *vs* the PPV group.

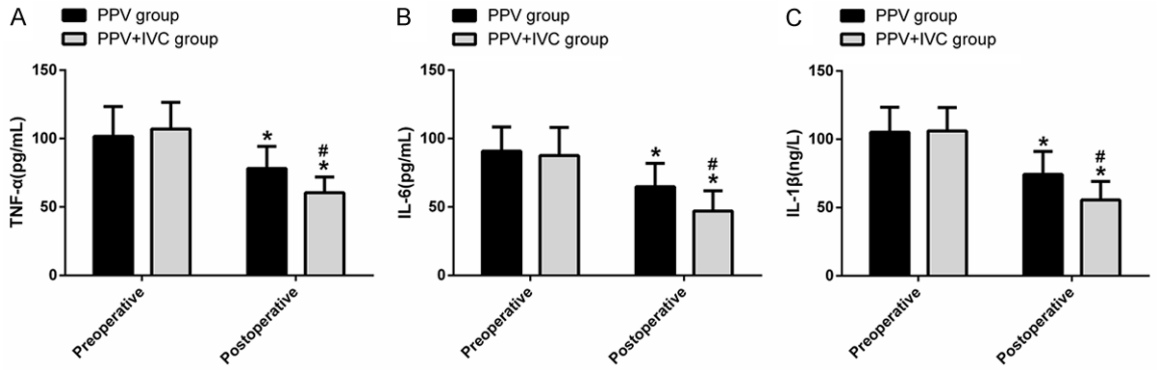

Figure 3. Comparison of serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). A: Comparison of TNF-α levels in serum. B: Comparison of IL-6 levels in serum. C: Comparison of IL-1β levels in serum. Note: *P<0.05 *vs* before treatment within the group; #P<0.05 *vs* the PPV group.

to loss of the surgical field and prolonged OT, thus increasing the probability of postoperative complications [15]. At present, many studies have shown that pre-use of anti-VEGF drugs can induce retinal neovascularization to subside and reduce intraoperative bleeding, thereby improving the maneuverability and visibility during surgery [16, 17]. As a new generation of anti-VEGF drugs, the affinity of Conbercept for VEGF is 50 times that of bevacizumab and 30 times that of Rezumab [18]. This study found that, compared to the PPV group, the OT of the PPV+IVC group was significantly shorter, with fewer patients suffering from severe IBL, bipolar electrocoagulation hemostasis, IRBs, and SOT. In addition, the overall incidence of complications was obviously lower in the PPV+IVC group. This shows that IVC can promote the smooth progress of PPV and reduce postoperative complications.

PLGF, a member of the VEGF family, can regulate endothelial cell activity, stimulate angiogenesis, and change vascular permeability [19]. BFGF is a growth factor with mitogen and antigenic activities that can accelerate endothelial cell proliferation and VEGF production [20]. The results of this study showed that, the PPV+IVC group had decreased intraoperative AH levels of VEGF, PIGF, and bFGF, reduced postoperative CMT, and improved postoperative BCVA and VA compared to the PPV group, with a significantly better QoL. This shows that IVC-assisted PPV can effectively improve the VA of patients, and is related to the reduction of VEGF, PIGF and bFGF, angiogenesis regression, and vascular permeability by Conbercept.

In addition to angiogenesis, inflammation is also considered as a key feature of PDR and interacts with angiogenesis in the pathogene-

sis of PDR [21]. TNF-α, IL-6 and IL-1β are three proinflammatory factors that are excessively elevated in PDR patients [22]. TNF-α can induce the connection between retinal pigment epithelial cells and VECs, destroy the blood-retinal barrier, and promote the transformation of the retina from a non-proliferative state to neovascularization, thus aggravating visual impairment [23]. IL-6 is a common pro-inflammatory cytokine that can increase vascular permeability and angiogenesis by inducing VEGF expression [24]. IL-1β can cause the infiltration and diffusion of serum proteins and red blood cells into the vitreous, as well as the migration of multinucleated cells and monocytes out of blood vessels, resulting in local exudation, edema, inflammation, widening of vascular endothelial gap, and destruction of blood-retinal barrier [25]. Previously, it is shown that intravitreal injection of ranibizumab (an anti-VEGF drug) can reduce the levels of various pro-inflammatory factors such as IL-1β, interferon-γ (IFN-γ), IFN-γ inducible protein 10 (IP-10), and TNF-α in the serum of patients with diabetic macular edema [26]. This study identified statistically reduced postoperative serum TNF-α, IL-6, and IL-1β levels in both arms, especially in the PPV+IVC group, indicating that the preoperative use of Conbercept in PDR patients undergoing PPV can effectively alleviate inflammation. The reason may be that the regression of retinal neovascularization induced by Conbercept and the interaction between angiogenesis and inflammation led to decreased levels of TNF-α, IL-6, IL-1β and other IFs.

This study demonstrated multiple benefits of preoperative use of Compaxerib in PDR patients undergoing PPV, but some limitations remain. First, due to the small number of subjects included, it is inevitable that there will be selection bias or measurement bias that may weaken the relative reliability of our research results. Second, we did not obtain the AH samples of patients after operation due to their unwillingness, so we were unable to detect the changes in VEGF, PlGF, and bFGF levels in the AH after operation.

To sum up, preoperative use of Conbercept in PDR patients undergoing PPV contributes to smooth operation, reduced postoperative complications, accelerated visual recovery, and alleviated inflammation in patients, and is recommended for clinical application.

Acknowledgements

1. National Natural Science Foundation of China (81804149); 2. Sichuan Science and Technology Program (NO. 2018JY0388); 3. Chongqing Science and Health Technology Innovation and Application Development Project of traditional Chinese Medicine (2020-ZY024098).

Disclosure of conflict of interest

None.

Address correspondence to: Mei Chen, Chongqing Aier Eye Hospital, Chongqing 400020, China. Tel: +86-199-2313-2168; E-mail: cm-8988@163.com

References

[1] Pereira DM, Shah A, D'Souza M, Simon P, George T, D'Souza N, Suresh S and Baliga MS. Quality of life in people with diabetic retinopathy: Indian study. J Clin Diagn Res 2017; 11: NC01-NC06.

[2] Papatheodorou K, Banach M, Bekiari E, Rizzo M and Edmonds M. Complications of diabetes 2017. J Diabetes Res 2018; 2018: 3086167.

[3] Yang QH, Zhang Y, Zhang XM and Li XR. Prevalence of diabetic retinopathy, proliferative diabetic retinopathy and non-proliferative diabetic retinopathy in Asian T2DM patients: a systematic review and meta-analysis. Int J Ophthalmol 2019; 12: 302-311.

[4] Pang C, Jia L, Jiang S, Liu W, Hou X, Zuo Y, Gu H, Bao Y, Wu Q, Xiang K, Gao X and Jia W. Determination of diabetic retinopathy prevalence and associated risk factors in Chinese diabetic and pre-diabetic subjects: Shanghai diabetic complications study. Diabetes Metab Res Rev 2012; 28: 276-283.

[5] Boss JD, Singh PK, Pandya HK, Tosi J, Kim C, Tewari A, Juzych MS, Abrams GW and Kumar A. Assessment of neurotrophins and inflammatory mediators in vitreous of patients with diabetic retinopathy. Invest Ophthalmol Vis Sci 2017; 58: 5594-5603.

[6] Karimov M, Akhundova L and Aliyeva T. Pars plana vitrectomy for full-thickness macular holes in patients with proliferative diabetic retinopathy and active fibrovascular proliferation. Clin Ophthalmol 2020; 14: 4125-4133.

[7] Liao M, Wang X, Yu J, Meng X, Liu Y, Dong X, Li J, Brant R, Huang B and Yan H. Characteristics and outcomes of vitrectomy for proliferative

diabetic retinopathy in young versus senior patients. BMC Ophthalmol 2020; 20: 416.
[8] Yang Y, Liu Y, Li Y, Chen Z, Xiong Y, Zhou T, Tao W, Xu F, Yang H, Yla-Herttuala S, Chaurasia SS, Adam WC and Yang K. MicroRNA-15b targets VEGF and inhibits angiogenesis in proliferative diabetic retinopathy. J Clin Endocrinol Metab 2020; 105: 3404-3415.
[9] Smith JM and Steel DH. Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy. Cochrane Database Syst Rev 2011; CD008214.
[10] Zhou J, Liu Z, Chen M, Luo ZH, Li YQ, Qi GY and Liu T. Concentrations of VEGF and PlGF decrease in eyes after intravitreal conbercept injection. Diabetes Ther 2018; 9: 2393-2398.
[11] Ren X, Bu S, Zhang X, Jiang Y, Tan L, Zhang H and Li X. Safety and efficacy of intravitreal conbercept injection after vitrectomy for the treatment of proliferative diabetic retinopathy. Eye (Lond) 2019; 33: 1177-1183.
[12] Song S, Yu X, Zhang P and Dai H. Increased levels of cytokines in the aqueous humor correlate with the severity of diabetic retinopathy. J Diabetes Complications 2020; 34: 107641.
[13] Heng LZ, Comyn O, Peto T, Tadros C, Ng E, Sivaprasad S and Hykin PG. Diabetic retinopathy: pathogenesis, clinical grading, management and future developments. Diabet Med 2013; 30: 640-650.
[14] Hernández-Da Mota SE and Nuñez-Solorio SM. Experience with intravitreal bevacizumab as a preoperative adjunct in 23-G vitrectomy for advanced proliferative diabetic retinopathy. Eur J Ophthalmol 2010; 20: 1047-1052.
[15] Schachat AP, Oyakawa RT, Michels RG and Rice TA. Complications of vitreous surgery for diabetic retinopathy. II. Postoperative complications. Ophthalmology 1983; 90: 522-530.
[16] Guan J, Cai N, Liu LM, Zhao N and Liu NN. Ranibizumab pretreatment in vitrectomy with internal limiting membrane peeling on diabetic macular edema in severe proliferative diabetic retinopathy. Diabetes Ther 2020; 11: 1397-1406.
[17] Chen GH, Tzekov R, Mao SH, Tong YH, Jiang FZ and Li WS. Intravitreal conbercept as an adjuvant in vitrectomy for proliferative diabetic retinopathy: a meta-analysis of randomised controlled trials. Eye (Lond) 2021; [Epub ahead of print].
[18] Sun X, Zhang J, Tian J, Chen S, Zeng F and Yuan G. Comparison of the efficacy and safety of intravitreal conbercept with intravitreal ranibizumab for treatment of diabetic macular edema: a meta-analysis. J Ophthalmol 2020; 2020: 5809081.
[19] Al Kahtani E, Xu Z, Al Rashaed S, Wu L, Mahale A, Tian J, Abboud EB, Ghazi NG, Kozak I, Gupta V, Arevalo JF and Duh EJ. Vitreous levels of placental growth factor correlate with activity of proliferative diabetic retinopathy and are not influenced by bevacizumab treatment. Eye (Lond) 2017; 31: 529-536.
[20] Kaštelan S, Orešković I, Bišćan F, Kaštelan H and Gverović Antunica A. Inflammatory and angiogenic biomarkers in diabetic retinopathy. Biochem Med (Zagreb) 2020; 30: 030502.
[21] Wu G, Liu B, Wu Q, Tang C, Du Z, Fang Y, Hu Y and Yu H. Correlations between different angiogenic and inflammatory factors in vitreous fluid of eyes with proliferative diabetic retinopathy. Front Med (Lausanne) 2021; 8: 727407.
[22] Feng S, Yu H, Yu Y, Geng Y, Li D, Yang C, Lv Q, Lu L, Liu T, Li G and Yuan L. Levels of inflammatory cytokines IL-1beta, IL-6, IL-8, IL-17A, and TNF-alpha in aqueous humour of patients with diabetic retinopathy. J Diabetes Res 2018; 2018: 8546423.
[23] Khaloo P, Qahremani R, Rabizadeh S, Omidi M, Rajab A, Heidari F, Farahmand G, Bitaraf M, Mirmiranpour H, Esteghamati A and Nakhjavani M. Nitric oxide and TNF-alpha are correlates of diabetic retinopathy independent of hs-CRP and HbA1c. Endocrine 2020; 69: 536-541.
[24] Wu J, Zhong Y, Yue S, Yang K, Zhang G, Chen L and Liu L. Aqueous humor mediator and cytokine aberrations in diabetic retinopathy and diabetic macular edema: a systematic review and meta-analysis. Dis Markers 2019; 2019: 6928524.
[25] Zhu X, Xie M, Wang K, Zhang K, Gao Y, Zhu L and Zhou F. The effect of puerarin against IL-1beta-mediated leukostasis and apoptosis in retinal capillary endothelial cells (TR-iBRB2). Mol Vis 2014; 20: 1815-1823.
[26] Gnanasekaran S, Bandala-Sanchez E, Kolic M, Churilov L, Rogers SL, McAuley AK, Sandhu SS, Qureshi S, Lim LL and Wickremasinghe SS. The association between intravitreal ranibizumab therapy and serum cytokine concentrations in patients with diabetic macular edema. Mol Vis 2020; 26: 246-256.