• Clinical Research •

Effect of intravitreal conbercept treatment before vitrectomy in proliferative diabetic retinopathy

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Abstract

• AIM: To evaluate the safety and efficacy of intravitreal conbercept (IVC) injections as pretreatment for pars plana vitrectomy (PPV) in severe proliferative diabetic retinopathy (PDR).

• METHODS: This was a retrospective chart review of all patients who underwent PPV for PDR from January 2014 to October 2016. Patients who underwent IVC injection before PPV were assigned to the IVC group; the others were assigned to the control group. The IVC was performed 3-7d before surgery in the IVC group. All the eyes in the two groups were operated by the same doctor to complete the vitrectomy. Intraoperative complications and the changes in best-corrected visual acuity (BCVA) before and after surgery were compared between the two groups.

• RESULTS: A total of 68 eyes of 63 patients (22 eyes in the IVC group and 46 eyes in the control group) were examined. The risk of intraoperative bleeding was lower in the IVC group (2/22) than in the control group (25/46, *P*=0.000). Furthermore, the use of endodiathermy was significantly lower in the IVC group (1/22) than in the control group (12/46, *P*=0.047). The surgical time in the IVC group (112.64±34.52min) was significantly shorter than in the control group (132.85±40.04min, *P*<0.05). Compared to the BCVA before surgery, the mean BCVA was significantly improved after surgery for both groups (*P*<0.05).

• CONCLUSION: PPV is an effective treatment and can improve vision in patients with PDR. Preoperative intravitreal injection of conbercept could reduce the chances of intraoperative bleeding and the use of endodiathermy and shorten the operative time, which are beneficial in the management of PDR.

• KEYWORDS: conbercept; proliferative diabetic retinopathy; vitrectomy

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INTRODUCTION

Diabetic retinopathy (DR) has become one of the common causes of blindness in China. Neovascularization is the hallmark of proliferative diabetic retinopathy (PDR)[1], and the complications of proliferative fibrovascular membrane contraction are vitreous hemorrhage (VH) and traction retinal detachment (TRD), which may lead to blindness[2]. Vitrectomy is the main treatment for PDR. The surgical techniques include VH clearance, fibrovascular membrane removal, and retinal traction relief. However, the proliferative fibrovascular membrane in PDR patients is strongly adhered to the retina. Therefore, pulling or stripping the membrane during surgery can cause massive hemorrhaging, which is difficult to stanch, definitely influences the surgical field, and results in the extension of surgical time[3]. It also leads to the development of complications such as iatrogenic retinal damage and the frequent use of hemostatic procedures during surgery[4]. It has also been reported that intraoperative bleeding during pars plana vitrectomy (PPV) increases the risk of vitreous hemorrhage in the early postoperative period, which further emphasizes the necessity for careful hemostasis in surgery[5].

Several factors have been shown to be involved in the process of angiogenesis and the associating fibrous proliferation[6-9]. Vascular endothelial growth factor (VEGF) plays an important role in the formation of retinal neovascularization. Anti-VEGF agents have been reported to cause regression of pre-proliferative and proliferative DR and to hasten the resolution of diabetic VH[10-13]. Many studies have reported that intravitreal injection of anti-VEGF agents was used as a pretreatment for vitrectomy to minimize intraoperative complication, facilitate surgery, and contribute to a better outcome. Al-Kharashi *et al*[14] reported the tendency to reduce incidence of early post-vitrectomy hemorrhage in patients who

underwent pretreatment with intravitreal bevacizumab (IVB). Faisal *et al*[15] compared the rate of intraoperative bleeding in patients with diabetic VH undergoing PPV with, versus without, preoperative IVB injection. They found the numbers of intraoperative bleeding are also significantly lower in the IVB group than in the control group.

Until recently, conbercept (KH902; Chengdu Kanghong Biotech Co., Ltd., Sichuan, China), a humanized, soluble VEGF receptor protein, used as an adjuvant to PDR vitrectomy, was rarely reported on. Conbercept is a new drug independently developed by China in recent years, but reports about the effectiveness of this drug on PDR have rarely been evaluated. Whether it can reduce intraocular hemorrhage, frequent electrocoagulation, or vitrectomy time requires a large sample for research and conclusions. To demonstrate the safety and efficacy of a preoperative intravitreal injection of conbercept, we compared the intraoperative and postoperative complications of PDR patients undergoing PPV with preoperative intravitreal conbercept injection and without it.

SUBJECTS AND METHODS

This study was a retrospective clinical trial conducted with patients with PDR at the Eye Hospital of Wenzhou Medical University, from January 2014 to October 2016. It followed the tenets of the Declaration of Helsinki. Local ethical approval was obtained from the Ethics Committee of the Affiliated Eye Hospital of Wenzhou Medical University, Zhejiang, China. Sixty-eight eyes of 63 patients with severe PDR, such as nonabsorbent VH and fibrocellular proliferation accompanied by TRD or not, were included in this study. All these patients had to undergo vitrectomy.

The inclusion criteria consisted of patients who had PPV because of PDR, patients who had intravitreal conbercept (IVC) injection 3-7d before surgery (rather than other anti-VEGF drugs), and patients who were followed up for at least 3mo.

Exclusion criteria consisted of previous vitreoretinal surgery, patients with IVC injection >1wk before the surgery, neovascular glaucoma, known coagulation abnormalities or current use of anticoagulant or antiplatelet therapy that had high bleeding risk, and additional vitreoretinal pathologies such as retinal detachment, uveitis, and retinal artery or vein occlusion.

According to whether an IVC injection had been administered 3-7d before surgery, patients were divided into the IVC group and the control group. In the IVC group, 2 eyes had pseudophakic intraocular lens (IOL) compared with 1 eye in the control group (Fisher exact test, P=0.243). In the IVC group, 2 eyes had PDR without TRD, and 20 eyes had PDR with TRD. In the control group, 6 eyes had PDR without TRD, and 40 eyes had PDR with TRD. Patients in the IVC group received ICV [0.05 mg/0.05 mL (Chengdu Kanghong Biotech, Inc. Chengdu, Sichuan, China)] in the superior temporal sector 3.5-4 mm from the sclerocorneal limbus with a sterile technique 3-7d (mean 4.95±1.33d) before PPV.

Table 1 Baseline characteristics of participants pre-operation

Characteristics	IVC group (n=22)	Control group (n=46)	P
Age, y	52.73±9.20	57.52±9.47	0.053
Gender, male (%)	13 (59.1)	21 (45.7)	0.300
Duration of diabetes, y	9.27±6.50	13.54±9.47	0.061
Lens status, n (%)			0.243
Pseudophakic	2 (9.1)	1 (2.2)	
Phakic	20 (90.9)	45 (97.8)	
Stage of PDR, n (%)			1.000
PDR without TRD	2 (9.1)	6 (13.0)	
PDR with TRD	20 (90.9)	40 (87.0)	
BCVA	1.85±0.57	1.66±0.47	0.154

IVC: Intravitreal conbercept; PDR: Proliferative diabetic retinopathy; TRD: Traction retinal detachment; BCVA: Best-corrected visual acuity.

All patients underwent a 3-port, 23-gauge PPV at the speed of 5000 cuts per minute. Phacoemulsification and IOL implantation were performed through a 2.0-mm clear corneal incision in patients who had mild to severe cataract and were older than 50. All injections and surgery were performed by the same experienced surgeon (Shen LJ). All proliferative membranes had to be removed as much as possible during the operation. Peeling the inner limiting membrane (ILM), releasing the retinal traction, closing the retinal hole, and endodiathermy were conducted if required during the surgery. Intraoperative pan-retinal endolaser photocoagulation was used during the surgery. An intraocular tamponade with long-acting gas or silicone oil (SO) was used if necessary at the end of the operation. Silicone oil was preferred in the case of intraoperative complications (*e.g.*, severe bleeding, iatrogenic retinal break), when a complete removal of the fibrovascular tissue was not possible, or when the surgery had been particularly long and complex. Patients in the control group received PPV directly. The following parameters were also recorded: intraoperative bleeding, frequency of required endodiathermy, need of SO tamponade, and duration of surgery. These parameters were used to evaluate whether conbercept could improve a PPV. Intraoperative bleeding was divided into mild and severe. It was defined as mild if it was stopped by increasing the infusion pressure, by pressing with a blunt instrument, or both, and severe if endodiathermy was required. The surgical time was recorded from the start of the operation to the end of closing the sclera. There was no significant difference at baseline between the 2 groups (Table 1).

Patients underwent a complete ophthalmological examination, including intraocular pressure (IOP), BCVA, and color fundus photography at baseline, 1, and 3mo after surgery. The BCVA was analyzed on a logarithm of minimal angle of resolution (logMAR) scale. Light perception was defined as 2.6 logMAR,

hand movement was defined as 2.3 logMAR, and counting-fingers vision was defined as 1.85 logMAR[16].

All the patients' baseline characteristics were collected and analyzed using SPSS version 22 (IBM Corp., Armonk, NY, USA). A *t*-test was used for pair-wise comparisons between the 2 groups, such as age, duration of diabetes, BCVA, and mean surgical time. Results were presented as mean and standard deviation. Sex, intraoperative bleeding, and SO endotamponade were analyzed using the Chi-square test. Lens status, stage of PDR, and endodiathermy analyses were performed using the Fisher exact test. The BCVA between the follow-up and baseline were evaluated by one-way analysis of variance (ANOVA). Value of $P<0.05$ was set for statistical significance.

RESULTS

The baseline characteristic data was described in Table 1. There were no statistically significant differences in sex, age, duration of diabetes, lens status, the severity of PDR (with or without JRD), or BCVA between the 2 groups. Phacoemulsification and IOL implantation were performed in 59.1% of eyes (13/22) in the IVC group, compared with 71.7% (33/46) in the control group. Phacoemulsification was performed in 13.6% (3/22) in the IVC group and 2.2% (1/46) in the control group. Six eyes (6/22) underwent only PPV in the IVC group, 12 (12/46) eyes in the control group (Fisher's exact test, $P=0.140$).

BCVA levels were analyzed at each follow-up period. However, there was no statistically significant difference at baseline, 1, and 3mo after surgery between the 2 groups ($t=1.441$, 0.424, 0.796, respectively; $P=0.154$, 0.673, 0.429, respectively). After 1mo, the postoperative BCVA (1.07±0.55) was significantly different from the baseline (1.85±0.57) in the IVC group ($P=0.000$, ANOVA). The postoperative BCVA (1.14±0.63) was also improved compared to the baseline (1.66±0.47) in the control group ($P=0.000$, ANOVA). After 3mo, the postoperative BCVA (0.85±0.64) was improved compared to the baseline (1.85±0.57) in the IVC group ($P=0.000$, ANOVA). The postoperative BCVA (0.99±0.67) was also improved compared to the baseline (1.66±0.47) in the control group ($P=0.000$, ANOVA). However, the BCVA between the 1-month follow-up and the 3-month follow-up showed no significant difference in the 2 groups (ANOVA, $P=0.230$ in the IVC group; $P=0.251$ in the control group; Table 2, Figure 1).

In the IVC group, the use of endodiathermy was necessary in 1 eye (4.5%). However, intraoperative bleeding occurred in 25 eyes (54.3%) in the control group, and 12 eyes (26.1%) required endodiathermy. The indication for using endodiathermy was that the bleeding could not be stopped by the increase of infusion bottle height. The difference in the severity of intraoperative bleeding was statistically

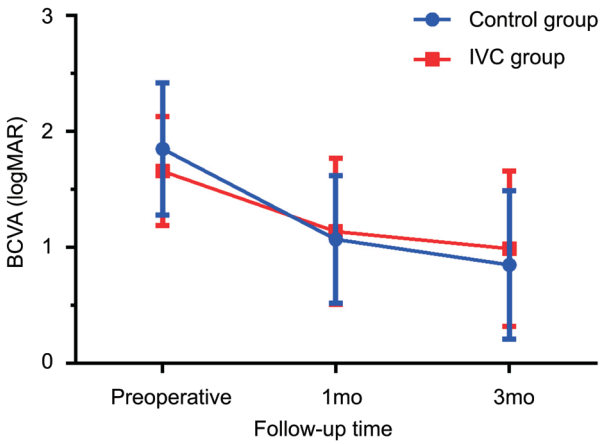

Figure 1 Visual outcome There was no statistically significant difference at baseline ($t=1.441$, $P=0.154$), 1mo ($t=0.424$, $P=0.673$) and 3mo ($t=0.796$, $P=0.429$) after surgery between the 2 groups. IVC: Intravitreal conbercept; BCVA: Best-corrected visual acuity.

Table 2 The change in BCVA between baseline and post-operation

mean±SD

BCVA (logMAR)	IVC group (*n*=22 eyes)	Control group (*n*=46 eyes)	*P*
Preoperative	1.85±0.57	1.66±0.47	0.154
1mo follow-up	1.07±0.55	1.14±0.63	0.673
3mo follow-up	0.85±0.64	0.99±0.67	0.429
F	17.266	15.699	
P	*P*<0.05	*P*<0.05	

BCVA: Best-corrected visual acuity; IVC: Intravitreal conbercept.

Table 3 Intraoperative and postoperative findings *n* (%)

Parameters	IVC group (*n*=22)	Control group (*n*=46)	*P*
Method of surgery			0.140
Phaco+IOL+PPV	13 (59.1)	33 (71.7)	
Phaco+PPV	3 (13.6)	1 (2.2)	
PPV	6 (27.3)	12 (26.1)	
Intraoperative bleeding	2 (9.1)	25 (54.3)	0.000
Endodiathermy	1 (4.5)	12 (26.1)	0.047
SO tamponade	7 (31.8)	21 (45.7)	0.278
Surgical time, min	112.64±34.52	132.85±40.04	0.046
High IOP	4 (18.2)	5 (10.9)	0.705

Phaco: Phacoemulsification; IOL: Intraocular lens implantation; PPV: Pars plana vitrectomy; SO: Silicone oil; IOP: Intraocular pressure.

significant ($\chi^2=12.732$, $P<0.001$), and a statistically significant difference was also found in the use of endodiathermy between the 2 groups ($P=0.047$, Fisher's exact test). In addition, an endotamponade with SO was performed in 7 eyes (31.8%) in the IVC group, compared to 21 eyes (45.7%) in the control group ($\chi^2=1.176$, $P=0.278$). The mean total surgical time was shorter in the IVC group (112.64±34.52min) than in the control group (132.85±40.04min; $t=2.032$, $P=0.046$; Table 3).

After the PPV, high IOP occurred in 4 eyes (18.2%) in the IVC group and 5 eyes (10.9%) in the control group. There

was no statistical difference between the 2 groups (P=0.456, Fisher's exact test). All the patients in the IVC group could tolerate the injection. No endophthalmitis, recurrent VH, or TRD progression were observed during the follow-up period in all the cases. No serious systemic adverse events, such as cardiovascular accident or allergic reaction, occurred in any cases.

DISCUSSION

Conbercept is composed of the second Ig domain of VEGFR1 and the third and fourth Ig domain of VEGFR2 to the constant region of human IgG1[17]. Gao *et al*[18] concluded that conbercept has excellent inhibitory effects on tumor angiogenesis both *in vitro* and *in vivo*. Therefore, it could be used as an effective antiangiogenic agent. The effect and safety of conbercept had been evaluated in patients with neovascular, age-related degeneration[19]. It could help improve BCVA at 3mo, and all the patients could tolerate the injections without side effects. In 2016, Sun *et al*[20] assessed the efficacy and safety of IVC injections in patients with macular edema secondary to retinal vein occlusion. They found that three monthly injections of conbercept may be appropriate for the initial management of branch retinal vein occlusion.

The use of preoperative IVC for patients undergoing PPV for PDR was recently suggested. Du *et al*[21]observed the total VEGF level in hyperglycemic mouse eyes, which shows that the concentration of conbercept in the treated eyes increased immediately after injection and remained at high levels for 4d, but its concentrations in both the treated and fellow eyes decreased from day 7 after intravitreal injection[21]. These indicated that the half-life of conbercept tended to be shorter than of other anti-VEGF agents. Thus, injection is preferred to be performed 3-7d before the surgery. According to Sun *et al*[20], intravitreal injection of conbercept one week before PPV could shorten the surgical time, with fewer intraoperative complications in patients with PDR. However, lack of a large sample was a limitation.

In the current study, we selected patients with severe PDR to examine the effect of conbercept pretreatment on diabetic vitrectomy. The first index was the change of BCVA. The second indexes were the complications during the surgery and post-operation. It has been reported that VEGF played an important role in causing retinal angiotelectasis, basement membrane thickness, and Evans blue dye permeability in diabetes[22]. Therefore, conbercept, a strong anti-VEGF agent used as a pretreatment, surely facilitated the reduction of the rate of intraoperative complications due to the regression of neovascularization and fibrovascular membranes. Actually, we found that the complications that occurred during surgery in the IVC group were statistically less severe than in the control group.

Our research showed that conbercept could reduce intraoperative bleeding, which might cause blurred retinal visualization. The incidence rate of intraoperative bleeding and endodiathermy in the IVC group was obviously lower than in the control group. We speculated that after the use of conbercept, the surgical field and surgical plane were not obscured by a fresh blood clot. Retinal vessels were less likely to be damaged during delamination. The use of conbercept could reduce the possibility of intraoperative bleeding and iatrogenic retinal damage. SO tamponade was preferred in the cases of a long and complex surgery. SO tamponade was performed in 7 eyes (31.8%) in the IVC group and 21 eyes (45.7%) in the control group.

In our study, the mean surgical time in the IVC group was shorter than in the control group (112.64min *vs* 132.85min), which showed that conbercept had an effect by reducing the surgical time that was similar to other anti-VEGF agents that had been reported in many previous studies. However, our method of recording the surgical time was different from others. We chose the beginning of operation to the end as the total surgical time, and the severity of PDR in our patients was more complex. Peeling the ILM was performed in patients if necessary, which led to longer surgical time in our study than in other research. Moradian *et al*[13] reported that surgical time was shorter in the groups of patients treated with preoperative intravitreal Avastin injection than in the control group (57min *vs* 83min). Su *et al*[23] also found that preoperative IVC injection could minimize operation time, compared with the control group (43min *vs* 53min).

The following reasons result in the reduction of surgical time. First, after application of anti-VEGF agents, reduction in VEGF was thought to cause retraction and shrinkage of fibrovascular proliferative membranes, thereby improving ease of manipulative techniques and visualization at the time of surgery[24]. Second, in IVC patients, the need for tool exchange was reduced because we could manage most membrane dissection without endodiathermy and blood aspiration.

The BCVA at 1 and 3mo after surgery had improved compared to pre-operation in both the groups, which indicated that vitrectomy played an important role in PDR. Vitrectomy can directly remove VH, reattach the retina, relax the traction of the retina, and reduce the degree of macular edema, facilitating the recovery of visual function. However, there was no significant difference in BCVA between the 2 groups 1 and 3mo after surgery, perhaps because washing constantly with the irritating solutions can accelerate the metabolism of conbercept. Therefore, the postoperative effect from remnant conbercept might be negligible. In addition, lack of a large sample and long-term follow-up might affect the result.

All the patients tolerated the injections. No case was reported of endophthalmitis, TRD progression, or other systemically serious adverse events. The main limitations of our study are

retrospective study, the small sample size, and limited follow-up. We look forward to larger sample studies to assess the efficacy and safety of IVC pretreatment before vitrectomy in PDR in the longer term.

Our study confirmed that conbercept, as a new type of anti-VEGF agent, was likely effective as adjunctive therapy prior to vitrectomy for severe PDR.

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