·康弘征文论著·

Conbercept for late postoperative vitreous cavity haemorrhage in patients with proliferative diabetic retinopathy

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康柏西普治疗增殖性糖尿病视网膜病变患者玻璃体切除术后迟发性玻璃体出血

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摘要

目的:观察玻璃体腔注射康柏西普治疗增殖性糖尿病视网膜病变(PDR)患者玻璃体切除术后迟发性玻璃体出血(POVCH)的效果。

方法:回顾性分析。纳入PDR患者玻璃体术后发生POVCH患者56例57眼,其中康柏西普组28眼行玻璃体腔内注射0.05mL康柏西普,对照组29眼不进行玻璃体腔内注射康柏西普,观察或使用口服药物治疗。记录患者玻璃体切除前后、玻璃体腔注药前后、POVCH后1mo时及随访结束时最佳矫正视力(BCVA)、玻璃体积血分级、眼压、眼底情况及再次手术(玻璃体腔灌术)情况。并观察POVCH发生时患者血糖、血压及心理等全身情况。

结果:POVCH后1mo时,康柏西普组的BCVA优于对照组(1.26±0.13 *vs* 1.76±0.20; $P=0.04$),POVCH发生时及随访结束时两组BCVA无统计学差异($P=0.08$,0.24)。玻璃体积血混浊改善程度:康柏西普组显效13眼,有效9眼,无效6眼;对照组显效11眼,有效3眼,无效15眼,差异有统计学意义($P=0.03$)。康柏西普组POVCH眼再次手术率低于对照组(21% *vs* 51%, $P=0.045$)。康柏西普组平均玻璃体注药次数为2.24±1.16(1~5)次。随访12~24(平均16.47±3.34)mo。POVCH发生的28眼中,发现眼底纤维血管膜11眼(19%),视网膜新生血管11眼(19%),新生血管性青光眼10眼(18%),虹膜新生血管4眼(7%)。POVCH出血吸收后补充视网膜光凝44眼(77%)。POVCH发生时患者血糖和(或)糖化血红蛋白高、血压异常者43例(75%),情绪激动或劳累者6例(11%)。

结论:玻璃体腔内注射康柏西普可促进PDR患者POVCH积血吸收,提高视力,降低再次玻璃体切除手术的几率,同时也应注意严格控制PDR患者的血糖、血压、精神心理等全身因素。

关键词:康柏西普眼用注射液;玻璃体切除手术;玻璃体切除术后再积血;糖尿病视网膜病变

Abstract

• AIM: To observe the efficacy of intravitreal injection of conbercept in the treatment of late postoperative vitreous cavity haemorrhage (POVCH) in patients with proliferative diabetic retinopathy (PDR).

• METHODS: A total of 56 patients (57 eyes) with late POVCH after vitrectomy in patients with PDR were retrospectively analyzed. Among them, 28 eyes that received intravitreal injection of 0.05 mL conbercept were selected as the conbercept group, whereas 29 eyes that did not receive intravitreal injection of conbercept were selected as the control group. Best corrected visual acuity (BCVA), the degree of vitreous haemorrhage (VH), intraocular pressure and ocular fundus were recorded before and after vitrectomy and injection, at 1mo after late POVCH and at the end of follow-up, respectively. Moreover, the number of eyes that received the secondary surgery (vitreous lavage) was compared and the patients' general conditions such as blood glucose, blood pressure and mental health were observed.

• RESULTS: BCVA was better in the conbercept group than in the control group(1.26±0.13 *vs*.1.76±0.20; $P=0.04$) at 1mo after late POVCH.There was no difference in BCVA at POVCH onset and at the end of follow-up between the two groups ($P=0.08$, 0.24). In terms of VH opacity, there was significant improvement in 13 eyes, moderate improvement in 9 eyes and no improvement in 6 eyes in the conbercept group. However, in the control group, there was significant improvement in 11 eyes, moderate

improvement in 3 eyes and no improvement in 15 eyes (P= 0.03). Eyes in the conbercept group showed less possibility of reoperation than those in the control group (21% *vs.* 51%, P= 0.045). The mean times of injections in the conbercept group was 2.24±1.16 (range: 1-5). The follow-up period ranged from 12 to 24mo, with an average of 16.47±3.34mo. Among the 28 eyes with POVCH, 11 (19%) eyes had the fundus fibrous vascular membrane and 11 (19%) eyes had retinal neovessels. Neovascular glaucoma (NVG) and iris neovascularization were observed in 10 (18%) and 4 (7%) eyes, respectively. After the amelioration of haemorrhage of POVCH in 57 eyes, 44 (77%) eyes were supplemented with retinal photocoagulation. At POVCH onset, 43 (75%) patients exhibited abnormal blood glucose (glycosylated hemoglobin) and (or) blood pressure, and 6 (11%) patients were reported to felt tired or anger.

• CONCLUSION: Intravitreal injection of conbercept for late POVCH in patients with PDR can promote the amelioration of haemorrhage, improve visual acuity, and reduce the need for reoperation. Moreover, strict control of systemic factors such as blood pressure, blood glucose and psychological situation is crucial in patients with PDR for late POVCH.

• KEYWORDS: Conbercept; vitrectomy; postoperative vitreous cavity haemorrhage; diabetic retinopathy
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INTRODUCTION

Postoperative vitreous cavity hemorrhage (POVCH) is the major complication after vitrectomy in proliferative diabetic retinopathy (PDR), which leads to visual impairment and necessitates reoperation. POVCH has two main forms: early and late. Early POVCH is defined as haemorrhage occurring in the first few days after surgery or within 4wk of surgery, whereas late POVCH is defined as haemorrhage occurring more than 4wk after surgery, following a period during which the vitreous cavity was cleared[1]. Most cases of POVCH in exhibit spontaneous clearing, and non-clearing POVCH necessitates repeat vitrectomy in approximately one third to a half of cases[2].

Anti-vascular endothelial growth factor (VEGF) drugs can inhibit the signal transduction pathway of VEGF and its receptors, and these drugs have been widely used in the treatment of PDR and diabetic macular edema (DME). Many studies have reported that vitrectomy combined with anti-VEGF drugs in PDR can significantly reduce the incidence of intraoperative and early post-operative haemorrhage and improve the post-operative visual function[3-6]. However, the effect of pre-or intraoperative intravitreal bevacizumab on the incidence of late postoperative haemorrhage remains unknown. Conbercept is a recombinant fusion protein that can inhibit VEGF-A, VEGF-B and placental growth factor receptors. Numerous trials have demonstrated the long-term efficacy and safety of intravitreal conbercept injection[7-10]. A Meta-analysis revealed that intravitreal conbercept is more effective than intravitreal ranibizumab in terms of functional and anatomic outcomes for treating DME[11]. However, limited data are available on the effect of conbercept in late POVCH. This study investigates the role of conbercept in late POVCH in patients with PDR.

MATERIALS AND METHODS

Ethical Approval This study was approved by the Medical Ethics Committee of Hebei Eye Hospital (No.2021LW001). Informed consent was obtained from each patient in accordance with the Declaration of Helsinki.

Subjects This retrospective analysis was conducted at Diabetic Eye Disease Ward of Hebei Eye Hospital from January 1, 2016 to July 5, 2020. A total of 57 eyes that received vitrectomy without filling silicone oil for PDR were included in this study. The conbercept group comprised 27 patients (28 eyes) who received intravitreal injection of conbercept for late POVCH in PDR between July 1, 2018 and July 5, 2020. A total of 29 patients (29 eyes) who did not receive intravitreal injection of conbercept between January 1, 2016 and July 1, were selected as the control group. The degree of vitreous haemorrhage (VH) was graded according to the vitreous opacity classification standard as follows[12-13]: grade I: vitreous opacity does not affect fundus observation; grade II: clear red reflex and blurred visualization of the optic disc and blood vessels; grade III: red reflex but invisibility of retinal vessels; grade IV: no red reflex in the pupil area. The grading of VH was evaluated by one person using 90D indirect ophthalmoscope. The inclusion criteria were as follows: 1) Patients with a diagnosis in line with the late POVCH diagnostic criteria; 2) Higher degree of VH than grade II, with no obvious membrane leading to the retina, as confirmed by fundus examination, and with no retinal traction and detachment, as confirmed by B-ultrasound. The exclusion criteria were as follows: 1) Patients with neovascular glaucoma before primary vitrectomy; 2) Patients with ocular haemorrhage caused by external factors violence such as trauma; 3) Patients with coagulation disorders such as platelet abnormalities and long-term use of anticoagulant drugs; 4) Patients with severe cardiac or renal dysfunction.

Eyes in the conbercept group received intravitreal conbercept (0.5 mg/0.05 mL) in 3 to 5d for late POVCH. Repeated conbercept injection was administered when the degree of vitreous opacity was reduced but not completely resolved after 4wk of follow-up until the vitreous blood was completely absorbed. Vitreous lavage with or without filling silicone oil was performed if the VH was not reduced after 4wk. Vitreous lavage with or without filling silicone oil was performed for eyes in control group if the VH was not reduced after 4wk of non-surgical treatment or no-treatment or the treatment with oral medicines

Histopathological Examination Similar to the degree of VH, the best corrected visual acuity (BCVA), ocular fundus

of patients with late POVCH and intraocular pressure (IOP) before and after primary vitrectomy, POVCH onset and after POVCH treatment were recorded. The number of eyes with vitreous lavage and other general conditions of patients, including blood glucose and blood pressure, at the time of late POVCH were recorded. Diabetic health education was provided to patients with unstable general condition. Under the guidance of the internal medicine team at our hospital, the blood sugar and blood pressure of these patients were strictly controlled. In addition, we provided detailed information to patients about the treatment of POVCH, including the risks and attentions of intravitreal injection or vitreous lavage, possible complications after treatment, and the need for re-treatment. Fundus fluorescein angiography (FFA) was performed on the eyes when VH was resolved, and retinal photocoagulation was supplemented according to FFA. The number of injections was documented, and the complications, such as cardiovascular events, retinal detachment and endophthalmitis, were observed during the follow-up.

BCVA, the degree of VH and ocular fundus were observed and analyzed at 1mo before and after late POVCH. The number of eyes with reoperation (vitreous lavage) was compared between the two groups. The BCVA was converted into LogMAR visual acuity [LogMAR = Log (1/decimal vision)][14].The LogMAR value of counting fingers was 2.0 and that of hand motion was 3.0[15]. The effect of the amelioration of VH was evaluated according to the degree of VH opacity[13] as follows: 1) Significantly effective: decrease was found in vitreous opacity from grade IV to grade II, from grade III to grade I, and from grade II to clear fundus; 2) Moderate effective: decrease was found in vitreous opacity from grade IV to grade III and from grade III to grade II; 3) Ineffective: there was no change or aggravation of VH.

Statistical Analysis SPSS 22.0 software (IBM Corporation, Armonk, NY, USA) was used to analyze data. The measurement data are presented as the mean and standard error ($\bar{x} \pm s$). Depending on the differences in observation indices and data, two groups were compared using the independent samples t-test and χ^2 test. The data before and after treatment were compared using the paired-samples t-test. A value of $P<0.05$ was considered significant.

RESULTS

A retrospective analysis was performed on 57 eyes with late POVCH in patients with PDR. The conbercept group comprised of 14 male and 13 female patients (28 eyes), whereas the control group comprised of 16 male and 13 female patients (29 eyes). The patients' mean age of the conbercept, and control groups was 50.86±1.86 and 54.83±1.67 years old, respectively. The duration of diabetes in the conbercept and control groups was 10.70±1.15 years and 9.04±1.07 years, respectively. All patients had type II diabetes mellitus. In the conbercept group, 16 (57%) cases had other systemic diseases such as hypertension, and 12 (43%) cases did not exhibit any complication. In the control group, 19 (66%) cases had complications and 10 (34%) cases exhibited no complication. The time of POVCH onset ranged from 1 to 7 (2.99±0.22) mo. In the conbercept group, 21 (75%) eyes underwent vitrectomy combined with phacoemulsification, and 7 (25%) eyes underwent vitrectomy alone. In the control group, 16 (55%) eyes underwent vitrectomy combined with phacoemulsification, and 13 (45%) eyes underwent vitrectomy alone. Overall, 9 (32%) eyes accepted primary vitrectomy with only preoperative intravitreal anti-VEGF without preoperative pan-retinal photocoagulation (PRP). The conbercept group comprised 9 eyes (32%) with only preoperative PRP but with no preoperative intravitreal anti-VEGF, 4 eyes (14%) with both preoperative PRP and preoperative intravitreal anti-VEGF and 6 eyes (21%) with neither preoperative PRP nor preoperative intravitreal anti-VEGF. The control group comprised 11 eyes (38%) with only preoperative intravitreal anti-VEGF, 8 eyes (28%) with only preoperative PRP, 3 eyes (10%) with both and 7 eyes (10%) with neither preoperative PRP nor preoperative intravitreal anti-VEGF. However, no significant differences were observed in the basic characteristic of eyes between the two groups (Table 1).

Primary Outcomes BCVA was 1.26±0.13 in the conbercept group at 1mo after late POVCH, which was significantly higher than that in control group (1.76±0.20; $P=0.04$). However, no difference was observed in BCVA at POVCH onset and at the end of follow-up between the two groups ($P=0.08$ and 0.24, respectively; Table 2). According to the degree of VH opacity, the effect of the amelioration of VH at 1mo after late POVCH was evaluated. The VH opacity in the conbercept group was significantly improved (conbercept group *vs.* control group: significantly effective, 13 *vs.* 11 eyes; moderately effective, 9 *vs.* 3 eyes; ineffective, 6 *vs.* 15 eyes; $P=0.03$; Table 3). Finally, 6 eyes (21%) in the conbercept group and 15 eyes (52%) in the control group received vitreous lavage. The need for reoperation was reduced in the eyes that received intravitreal conbercept for late POVCH. ($P=0.045$; Table 4).

In the conbercept group, the average number of injections was 2.24±1.16 (range: 1-5), and the absorption time of POVCH in eyes with effects ranged from 5 to 83d, with an average of 45.54d. The follow-up period ranged from 12 to 24mo, with an average of 16.47mo. In the conbercept group, one eye POVCH occurred 5mo after the primary vitrectomy, which was resolved after one intravitreal conbercept injection. However, after 1a, VH recurred and was resolved after two intravitreal injections. In the control group, two eyes received the second vitreous lavage, as VH recurred after 5 and 7mo, after the first vitreous lavage operation for POVCH. We did not observe any serious ocular or systemic side-effects during the follow-up.

Secondary Outcomes After the amelioration of haemorrhage in POVCH in 57 eyes, 44 eyes (77%) were supplemented with retinal photocoagulation, 11 eyes (19%) exhibited the residual fibrous vascular membrane and 11 eyes (19%) exhibited

Table 1 Baseline characteristics of eyes between the two groups

Parameters	Conbercept group ($n=28$)	Control group ($n=29$)	P
Age ($\bar{x}\pm s$, years)	50.86±1.86	54.83±1.67	0.12
Duration of diabetes ($\bar{x}\pm s$, years)	10.70±1.15	9.04±1.07	0.41
Whether or not the merger with other systemic diseases			
with	16	19	0.59
without	12	10	
Sex			
M	14	16	0.80
F	13	13	
Primary vitrectomy			
Combined with phacoemulsification	21	16	0.12
Vitrectomy alone	7	13	
Primary vitrectomy preoperative			
PRP	9	8	
Anti-VEGF	9	11	0.93
Both PRP and VEGF	4	3	
Neither PRP nor VEGF	6	7	
The condition of the lens			
IOL eyes	21	16	
Len eyes	7	13	0.12
Aphakic eyes	0	0	
Time of POVCH onset ($\bar{x}\pm s$, months)	3.01±0.32	2.97±0.30	0.94
Baseline BCVA at POVCH onset ($\bar{x}\pm s$, LogMAR)	2.39±0.15	2.20±0.14	0.08
The degree of vitreous haemorrhage opacity at POVCH onset			
Grade I	0	0	
Grade II	3	4	0.89
Grade III	6	5	
Grade IV	19	20	
Follow-up period ($\bar{x}\pm s$, months)	16.32±0.69	16.62±0.68	0.76
Severe adverse events	0	0	-

Severe adverse events: retinal detachment, cardiovascular events, infections and so on. PRP: Pan-retinal photocoagulation; VEGF: Vascular endothelial growth factor; POVCH: Postoperative vitreous cavity hemorrhage.

Table 2 Comparison of best corrected visual acuity between the two groups ($\bar{x}\pm s$, LogMAR)

Group	POVCH onset	1mo after late POVCH	At the end of follow-up
Conbercept group	2.39±0.15	1.26±0.13	0.68±0.05
Control group	2.20±0.14	1.76±0.20	0.80±0.08
P	0.08	0.04	0.24

POVCH: Postoperative vitreous cavity hemorrhage.

Table 3 Comparison of changes of vitreous haemorrhage opacity between the two groups

Group	Eyes	Significantly Effective	Moderate Effective	Ineffective	P
Conbercept group	28	13	9	6	0.03
Control group	29	11	3	15	

Table 4 Comparison of the number of eyes requiring reoperation (vitreous lavage)

Group	Eyes	No vitreous lavage	vitreous lavage	P
Conbercept group	28	22	6	0.045
Control group	29	14	15	

retinal neovessels. Neovascular glaucoma (NVG) and iris neovascularization were observed in 10 (18%) and 4 (7%) eyes, respectively. A total of 44 eyes (71%) were supplemented with retinal photocoagulation after hemorrhage absorption of POVCH. DME was observed in 7 eyes (12%) after the first vitrectomy. The causes of POVCH in the two groups are shown in Table 5. The mean IOP at POVCH onset, after primary vitrectomy, and after treatment of POVCH was

Table 5 Causes of postoperative vitreous cavity hemorrhage in the two groups

Causes	Conbercept group ($n=28$)	Control group ($n=29$)	P
Residual fibrous vascular membrane	5	6	0.79
Retinal neovessels	5	6	0.79
Neovascular glaucoma	5	5	0.95
Iris neovascularization	2	2	1.00
Inadequate PRP	20	24	0.31
Abnormal blood glucose and/or blood pressure	21	22	0.94
Combined with DME	4	3	0.71
Tiredness or anger before POVCH	3	3	1.00

PRP: Pan-retinal photocoagulation; DME: Diabetic macular edema; POVCH: Postoperative vitreous cavity hemorrhage.

19.80±7.89mmHg, 15.90±2.66mmHg and 16.00±2.63 mmHg, respectively. IOP at POVCH onset was higher than that after primary vitrectomy ($P=0.008$) and after treatment of POVCH ($P=0.009$). IOPs before and after primary vitrectomy were equivalent ($P=0.139$). IOPs after treatment of POVCH and after primary vitrectomy were also equivalent ($P=0.858$; Table 6).

At POVCH onset, there were 43 (75%) cases with abnormal blood glucose (glycosylated hemoglobin) and/or blood pressure (Table 8), and 6 (11%) cases reported tiredness or anger before POVCH (Table 5). A total of 5 eyes were neither supplemented with retinal photocoagulation nor exhibited neovascularization and fibrous vascular membrane after POVCH resolution; However, 4 of these cases exhibited blood glucose or blood pressure abnormalities, and 1 case exhibited no systemic and psychological abnormalities.

DISCUSSION

The major vision-threatening complication associated with vitrectomy in PDR is recurrent vitreous haemorrhage (RVH). The incidence of POVCH in PDR has been reported to be 13% to 40%[16-19]. POVCH has two main forms: early and late. Early POVCH occurs within the first few days of vitrectomy and causes reduction in vision, whereas late POVCH occurs after a post-operative period during which the vitreous cavity is cleared, commonly at 2-6mo after vitrectomy[1]. Most authors have defined late POVCH as RVH occurring more than 4wk, and early POVCH as RVH occurring within 4wk after surgery[20-21]. Early POVCH commonly results from oozing of the remnants of new vessels or injured vessels, haemorrhage arising directly from the scleral incision used to perform surgery, and leaching of red blood cells from retained old haemorrhage. The causes of late POVCH often include recurrent or residual retinal neovascular membrane, iris or angle neovascularization and fibrovascular ingrowth at the sclerotomy sites, *etc.*[7-9]. Because of the differences in patient groups and surgical techniques, studies have reported inconsistent results regarding the incidence of POVCH and etiologies. For example, Hershberger *et al*[22], Yan *et al*[23] and Shi and Huang[16] reported that POVCH in 86%, 28%, and only 4% of eyes, respectively, was caused by fibrovascular ingrowth at the sclerotomy sites, indicating that retinal neovascularization was up to 47%. Fibrovascular tissue proliferation and neovascularization are the common causes of POVCH. In this study, iris neovascularization, retinal neovascularization, and fibrovascular membrane were observed in POVCH cases, and most patients accepted supplementation of laser photocoagulation. We excluded the eyes in which primary vitrectomy was performed by filling silicone oil. The metabolism of anti-VEGF drugs in the eyes filled with silicone oil is not precisely understood. Thus, primary vitrectomy cases and the severe PDR cases with combined traction retinal tears and rhegmatogenous retinal detachment were excluded. The eyes with POVCH were confirmed to have no retinal traction and detachment through B-ultrasound. Thus, the main causes of POVCH in this study were iris neovascularization, retinal neovascularization, and fibrous vascular membrane stump haemorrhage.

Many cases of POVCH haemorrhage can undergo spontaneous resolution. After vitrectomy, the gel structure of the vitreous is removed, so the red blood cells can circulate more freely from the vitreous cavity to the anterior chamber and were cleared by the trabecular meshwork pathways. Non-clearing POVCH may be associated with persistent haemorrhage, which is caused by high levels of VEGF, inflammatory cytokines and chemokines. Studies have reported that the persistent high-VEGF levels after vitrectomy in patients with PDR were associated with VH and NVG after surgery[24-25]. After vitrectomy, balanced salt solution replaces the vitreous gel, and eventually, the balanced salt solution is replaced by aqueous humor, thereby leading to less viscosity of the liquid in the vitreous cavity and improved transport of cytokines. VEGF stimulates iris or retinal neovascularization or fibrovascular proliferation, which may eventually lead to VH[26]. Anti-VEGF drugs can stop the active haemorrhage by causing relative vasoconstriction and regression of neovascularization. These drugs are also known to inhibit retinal neovascularization or fibrovascular tissue progression, which leads to POVCH.

In this study, the BCVA and reduction in the degree of VH in eyes that received intravitreal injection of conbercept for late POVCH in PDR were observed to be better than those in the eyes that did not receive intravitreal injection of conbercept at 1mo after POVCH onset. BCVA was similar between the two groups at the end of follow-up. The number of eyes that received vitreous cavity lavage was significantly less in the conbercept group, indicating that intravitreal conbercept administration for late POVCH can promote the resolution of

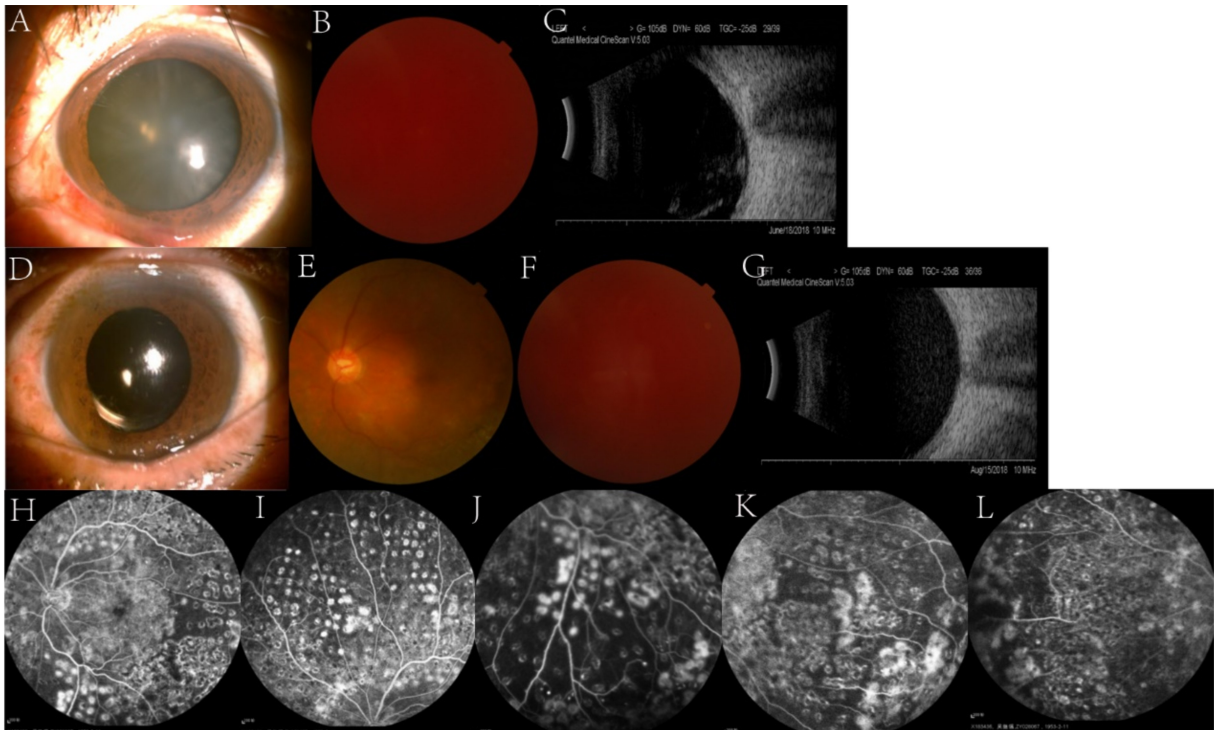

Figure 1 Images of the eye of a male patient with proliferative diabetic retinopathy (aged 65 years old), in whom vitreous haemorrhage occurred 2mo after vitrectomy. The patient received two injections of conbercept, and the recurrent vitreous haemorrhage was completely resolved. A-C: the anterior segment, fundus and B-ultrasound pictures before vitrectomy combined with phacoemulsification; D and E: the anterior segment and fundus pictures after vitrectomy, and the visual acuity was 0.2 (based on the normal visual acuity chart of international); F and G: the fundus and B-ultrasound pictures at postoperative vitreous cavity hemorrhage onset (the visual acuity was hand motion); H-L: fundus fluorescein angiography (FFA) pictures after complete resolution of recurrent vitreous haemorrhage. The visual acuity was 0.2 and retinal photocoagulation was supplemented according to FFA.

Table 6 Comparison of intraocular pressure before and after primary vitrectomy, POVCH onset, and after POVCH treatment

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

Before Primary vitrectomy	After Primary vitrectomy	After Primary vitrectomy	POVCH onset	POVCH onset	after treatment of POVCH	After Primary vitrectomy	after treatment of POVCH
15.10±2.41	15.90±2.66	15.90±2.66	19.80±7.89	19.80±7.89	16.00±2.63	15.90±2.66	16.00±2.63
$P=0.139$		$P=0.008$		$P=0.009$		$P=0.858$	

POVCH: Postoperative vitreous cavity hemorrhage.

Table 7 Details of systemic diseases in the conbercept and control groups

Systemic diseases	Conbercept group ($n=28$)	Control group ($n=29$)	P
None (only diabetes mellitus)	12	10	
Hypertension	9	14	
Diabetic nephropathy	1	0	
History of cerebral infarction	2	1	0.54
Hypertension + diabetic nephropathy	4	2	
Hypertension + history of cerebral infarction	0	1	
Hypertension + coronary atherosclerotic heart disease	0	1	

Table 8 The state of blood glucose level and blood pressure in the two groups

States	Conbercept group ($n=28$)	Control group ($n=29$)	P
Abnormal blood glucose and normal blood pressure	10	13	
Abnormal blood pressure and normal blood glucose	5	4	0.90
Abnormal blood glucose and abnormal blood pressure	6	5	
Normal blood glucose and normal blood pressure	7	7	

Abnormal blood glucose: glycated hemoglobin >7%; abnormal blood pressure; blood pressure >140/90 mmHg.

haemorrhage, improve visual acuity and reduce the need for reoperation. No serious ocular or systemic side-effect was observed during follow-up. The number of severe adverse events has been reported to be low in other studies. Intravitreal injection of conbercept may be a safe treatment for POVCH. However, the pathogenesis of PDR is complicated, and cross-talks between different angiogenesis and inflammation pathways are involved in POVCH pathogenesis[27-28]. In our study, conbercept was ineffective in some patients, suggesting that non-VEGF pathways might be involved in the pathogenesis of those patients with POVCH, and such patients can be treated with surgery to remove haemorrhage, so as to treat any underlying cause that may have been unidentified.

Various trials have demonstrated the efficacy of intraoperative or postoperative intravitreal bevacizumab administration in reducing the risk of early POVCH, but the effect on late POVCH remains unknown[1,20-21]. With vitrectomy, any anti-VEGF drug injected before surgery in the vitreous cavity is completely washed out. Aqueous half-life is 9.82d after 1.5 mg intravitreal bevacizumab injection in humans with vitrectomized eyes[29]. Anti-VEGF drugs can maintain the VEGF level below the lower limit of monitoring level for up to 4wk in vitrectomized eyes[30-32]; Thus, repeat injection was given if no obvious resolution was observed 4wk after late POVCH. In this study, after an average of 2.24±1.16 injections, the VH was absorbed. Second vitrectomy was considered in case VH was not reduced after 2 intravitreal injections of conbercept. Under this condition, there may be the anti-VEGF native eye or no-neovascular factors caused POVCH. However, for eyes with combined neovascular glaucoma and macular edema, more intravitreal injections are needed to suppress neovascularization or maintain vision. Iris neovascularization or NVG was observed in 7 cases. After administering 4-5 injections, neovascularization regressed, recurrent HV resolved, and IOP returned to a stable state.

We also observed that for the eyes with POVCH combined with iridial neovascularization or a trial angle neovascularization, the risk of RVH was high after re-operations. In such cases, administering intravitreal anti-VEGF drugs may be more suitable than performing vitrectomy by filling or not filling the vitreous space with silicone oil. However, clinical studies with a larger sample size are needed to validate this finding.

Retinal photocoagulation insufficiency during the surgery often results from retinal edema and viscous subretinal fluid or haemorrhage. Despite full PRP, in approximately one third of cases, retinal new vessels either continue to grow or do not regress leading to RVH[33]. A study reported that intravitreal conbercept combined with PRP treatment could maintain good BCVA in patients with diabetic retinopathy[34]. Intravitreal conbercept administration in patients with POVCH can provide conditions to supplement retinal photocoagulation postoperatively, and it might be helpful to BCVA.

In addition, in this study, we observed that the IOP of patients with POVCH was higher than that after vitrectomy, which may be attributed to the blood cells blocking the trabecular meshwork and neovascular glaucoma appearing in some cases. After intravitreal conbercept injection, recurrent haemorrhage resolved, iris neovascularization regressed, and IOP decreased to the level similar to that after vitrectomy.

VH in patients with diabetes is a complicated pathological process. In patients with a long clinical history of diabetes mellitus, poor blood glucose control and hypertension are the risk factors for POVCH. In this study, we observed 43 (75%) POVCH cases with blood glucose and blood pressure abnormalities, and 6 (11%) POVCH cases reported tiredness or anger before POVCH. Dysfunction of vascular endothelial system in patients with diabetes can easily cause VH, especially under stressful condition. Therefore, like ocular factors, the blood glucose, blood pressure and systemic factors should be carefully considered while treating POVCH in patients with PDR.

In conclusion, the administration of intravitreal conbercept injection for treating late POVCH can promote resolution of haemorrhage, improve visual acuity, and avoid the need for reoperation. In addition, systemic factors such as blood pressure, blood glucose, and psychological situation in patients with diabetes mellitus should be strictly controlled. This study has some limitations as it is a retrospective study which has a small sample size. Thus, studies with a larger sample size are warranted to analyze the confounding factors. Prospective studies are necessary to confirm the effect of conbercept on late POVCH, and long-term follow-up studies are needed to better understand its complications and long-term effects on the prognosis. Finally, studying the cytokine levels may help in understanding the underlying molecular mechanism.

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