European Review for Medical and Pharmacological Sciences 2022; 26: 5939-5945

Study on the effects of ranibizumab as a pretreatment for vitrectomy in proliferative diabetic retinopathy: a retrospective cohort study

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Abstract. – OBJECTIVE: The effects of intravitreal ranibizumab (IVR) as a pretreatment for vitrectomy in proliferative diabetic retinopathy (PDR) need further study. The aim of this study is to further analyze this topic.

PATIENTS AND METHODS: The study group (n=26) was treated with IVR, while the control group (n=28) was not. The best corrected visual acuity (BCVA) at different time points within each group was compared. Operation time, intraoperative bleeding, silicone oil usage, iatrogenic retinal rupture and complications were compared between the groups.

RESULTS: BCVA at the 1st month after vitrectomy was significantly improved in the study group (t=2.081, p=0.047) but not in the control group (I=0.164, p=0.871). At the 1st month after vitrectomy, the BCVA of the study group was significantly higher than that of the control group (t=2.1467, p=0.0365). At the 6th month after vitrectomy, the BCVA of the study group was significantly higher than that of the control group (t=2.0424, p=0.0462). The operation time in the study group was significantly shorter than that in the control group (W=2.212, p<0.05). The rates of mild and severe intraoperative bleeding in the study group were significantly lower than those in the control group (p<0.05, respectively). There was no significant difference in complications between the two groups (p>0.05).

CONCLUSIONS: IVR before vitrectomy in patients with PDR can significantly improve BCVA in the early stage, improve BCVA at the 6th month after the operation, reduce the operation time and reduce intraoperative bleeding.

Key Words:
Proliferative diabetic retinopathy, Vitrectomy, Ranibizumab.

Introduction

Proliferative diabetic retinopathy (PDR) is a serious eye disease that can lead to permanent blindness. Vascular endothelial growth factor (VEGF) plays an important role in retinal microvascular complications of diabetic retinopathy. The VEGF expression level in diabetic retinas is approximately 3 times higher than that in nondiabetic retinas and this leads to the occurrence of neovascularization[1]. Vitrectomy is often applied when nonabsorbable vitreous hemorrhage, severe fibrovascular membrane hyperplasia, preretinal hemorrhage, refractory macular edema, retinal traction, retinal detachment, vitreous hemorrhage with cataract and vitreous hemorrhage with iris neovascularization occur as complications of PDR[2].

Ranibizumab, an ophthalmic anti-VEGF drug produced by Novartis, Switzerland, is a humanized mouse anti-VEGF monoclonal antibody derivative that can effectively eliminate neovascularization[3,4]. Kaivon et al[5] first reported the clinical effects of intravitreal ranibizumab (IVR) injected into the vitreous body before vitrectomy in PDR and concluded that both ranibizumab and bevacizumab could be used as adjuvant agents before vitrectomy, and their effects were similar. However, certain debates have lingered. For example, Chen et al[6] applied the PDR complexity score to allocate cases, studied the effect of IVR before vitrectomy in young PDR patients, and considered that the incidence of iatrogenic retinal rupture and the use of silicone oil were related to the complexity of the cases and were not affected by IVR. To further explore the clinical effects of IVR before PDR vitrectomy, 54 cases treated from January 2020 to June 2021 were retrospectively analyzed in this study.

Patients and Methods

This study was approved by the Ethics Committee of Lianshui People's Hospital affiliated

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with Nanjing Medical University (No.: 2021318-1). This study followed the tenets of the Declaration of Helsinki.

Diagnostic Criteria

The diagnosis and staging of PDR were performed by the staging method of the Ocular Fundus Disease Group of the Chinese Ophthalmological Society[2].

Inclusion Criteria

Those who met the criteria for diagnosis and staging were included.

Exclusion Criteria

(1) Tractional retinal detachment for more than 1 year or retinal detachment involving macular retinal detachment for more than 6 months; (2) Best corrected visual acuity (BCVA) was below finger counting; (3) History of panretinal photocoagulation (PRP), vitreoretinal surgery and other ophthalmic surgery except cataract; (4) The follow-up duration was less than 6 months or the patient underwent reoperation within 6 months; (5) Poor perioperative blood glucose (HbA1c > 90%); (6) Macular hole; (7) Iris neovascularization; (8) Anticoagulation, anti-platelet therapy and/or abnormal coagulation function.

Baseline of Both Groups

The PDR patients who underwent vitrectomy in Lianshui People's Hospital affiliated with Nanjing Medical University from January 2020 to June 2021 were retrospectively analyzed. The cases that received IVR before vitrectomy were allocated to the study group, and the cases that did not receive IVR were allocated to the control group. Finally, a total of 54 cases (54 eyes) were included, among which 28 cases (28 eyes) were in the control group and 26 cases (26 eyes) were in the study group. All of them signed informed consent forms.

Table I presents the demographics, preoperative systemic condition and ocular condition. The age of the study group was not normally distributed (Shapiro-Wilk test, p=0.035), but there was no significant difference between the two groups by a Wilcoxon rank sum test (w=0.611, p=0.541). There was no significant difference between sexes by Fisher's exact probability test (p=0.9999). There was no significant difference in BCVA between the two groups by two-sample t-tests (t=0.6116, p=0.5435), and there was no significant difference in the composition ratio of PDR grades IV, V and VI by Fisher's exact probability test (p=1, respectively). The control group had a nonnormal distribution of diabetes duration (Shapiro-Wilk test, p=0.039). There was no significant difference in the duration of diabetes (W=1.443, p=0.149) between the two groups according to the Wilcoxon rank-sum test. The preoperative intraocular pressure (IOP) of the study group was not normally distributed (Shapiro-Wilk test, p=0.046). There was no significant difference between the two groups according to the Wilcoxon rank-sum test (W=0.805, p=0.421).

Methods of Examination

BCVA was assessed using the international standard visual acuity chart, recorded in decimals and converted into the logarithm of minimum resolution angle (LogMAR). Slit lamp examination and IOP examination were performed before the operation. Detailed fundus examination, fundus fluorescein angiography (FFA) and macular optical coherence tomography (OCT) were performed if the refractive media was clear. When the refractive stroma was unclear, an ophthalmic B-ultrasound scan was used to check the condition of the vitreous body and retina. On the 1st day after the operation, when the refractive stroma was clear, BCVA, slit lamp examination and IOP examination were performed. The patients were followed up at the

Table I. Baseline characteristics of patients in the two groups.

	Control group	Study group	Statistic	p-value
Male (n)	14	13	-	0.9999
Female (n)	14	13	-	0.9999
Age (year)	45-70	51-64	W = 0.611	0.541
Diabetes duration (year)	5-21	13-19	W = 1.443	0.149
Preoperative IOP (mmHg)	11-21	12~20	W = 0.805	0.421
PDR grade IV (n)	9	8	-	1
PDR grade V (n)	2	2	-	1
PDR grade VI (n)	17	16	-	1

1st, 3rd and 6th months after surgery. BCVA, slit lamp, IOP and fundus examinations were performed at the follow-ups.

Therapeutic Method

In the study group, 3-5 days before vitrectomy, the eyes were treated with IVR, and 0.05 mg/0.05 ml Ranibizumab was injected into the vitreous body, while IVR was not used in the control group. A 27G vitrectomy machine (Alcon constellation) was used for vitrectomy. All patients underwent 27G vitrectomy by one doctor. The proliferative membrane was removed, and hemostasis was achieved by electrocoagulation or increased perfusion. The inner limiting membrane was removed or not, retinal photocoagulation was performed or not, and silicone oil filling was performed or not according to the pragmatic conditions. The stripping diameter of the internal limiting membrane was approximately 6 optic disc diameters. The PRP reached the retinal margin as near as possible with an exposure time of 0.2-0.3 mS and an energy of 120-360 mW. Indications for silicone oil injection included: (1) severe fibrovascular hyperplasia; (2) extensive vitreous detachment around the optic disc; (3) macular retinal detachment or combined traction; (4) rhegmatogenous retinal detachment; and (5) neovascularization extending to the peripheral part in more than 3 quadrants. If the lens needed to be removed, it was removed by phacoemulsification and an intraocular lens was implanted. The operation time was defined as the time from the first surgical incision to the final closure of the incision. When the postoperative IOP was higher than 25 mmHg, the IOP was reduced.

Observational Items and Curative Effects Evaluation

Medical record information was collected, including age, sex, course of diabetes, IOP before the operation, PDR grade, BCVA before the operation, the operation time, the use of silicone oil during the operation, mild intraoperative hemorrhage (hemostasis was achieved by increasing perfusion or compression), iatrogenic retinal rupture, severe intraoperative hemorrhage (electrocoagulation was required) and BCVA.

Postoperative complications and adverse reactions were collected, including endophthalmitis, elevated IOP (>25 mmHg) on the 1st day after vitrectomy, early recurrent vitreous hemorrhage (within 4 weeks after the operation), late recurrent vitreous hemorrhage (4 weeks after the operation), iris neovascularization, neovascular glaucoma and retinal detachment.

Statistical Analysis

SAS 9.14 (SAS Institute Inc., Cary, NC, USA) software was used to analyze the data. The counting data were expressed as cases (n) and percentages (%), and Fisher's exact probability test was used. The Shapiro-Wilk test was used to determine whether the measurement data were normally distributed. The normally distributed data were expressed as $\bar{x} \pm s$. The independent sample *t*-tests were used to compare the preoperative baseline data and the intraoperative data between the two groups. For the data with a non-normal distribution, the Wilcoxon rank-sum test was used to compare the preoperative baseline data and the intraoperative data between the two groups. There was a significant difference when $p<0.05$. For BCVA (LogMAR), the measurement data were normally distributed and were expressed as $\bar{x} \pm s$. Repeated measures analysis of variance was performed for comparisons between the groups at different time points. The data with differences between groups were further analyzed for the differences between groups at different time points, and the independent sample *t*-test was used. The data with time differences were compared at different time points in the same group, and a paired *t*-test was performed.

Results

BCVA

There was a significant difference in BCVA between the two groups before and after treatment ($F_{group}=0.0035$, $p_{group}= 0.047$). There were significant differences in the time and interaction between the groups ($F_{time}=0.0974$, $p_{time}=0.039$; $F_{Group \times Time}=0.0697$, $p_{Group \times Time}=0.024$). A paired *t*-test was used for intragroup comparisons before and after treatment, and an independent sample *t*-test was used for intergroup comparisons. Table II presents the BCVA of the two groups.

At the 1st month after the operation, there was no significant difference between postoperative BCVA and preoperative BCVA ($t=0.164$, $p=0.871$) in the control group. At the 3rd month after the operation, the postoperative BCVA in the control group was significantly higher than the preoperative BCVA ($t=2.191$, $p=0.037$). At the 6th month after the operation, the postoperative

Table II. BCVA of two groups.

	Control (n = 28)	Study (n = 26)	Statistic	*p*-value
Preoperative	1.35 ± 0.42	1.38 ± 0.39	$t = 0.6116$	0.5435
1st month after operation	1.01 ± 0.34	0.74 ± 0.21[a]	$t = 2.1467$	0.0365[b]
3rd month after operation	0.51 ± 0.27[a]	0.49 ± 0.33[a]	$t = 1.1999$	0.2356
6th month after operation	0.41 ± 0.35[a]	0.36 ± 0.42[a]	$t = 2.0424$	0.0462[b]

qRT-PCR, quantitative Reverse-Transcription Polymerase Chain Reaction.

BCVA in the control group was significantly higher than the preoperative BCVA (t=2.463, p=0.020). At the 1st month after the operation, the postoperative BCVA in the study group was significantly higher than the preoperative BCVA (t=2.081, p=0.048). At the 3rd month after the operation, the postoperative BCVA in the study group was significantly higher than the preoperative BCVA (t=2.220, p=0.036). At the 6th month after the operation, the postoperative BCVA in the study group was significantly higher than the preoperative BCVA (t=2.356, p=0.027). At the 1st month after the operation, the BCVA of the study group was significantly higher than that of the control (t=2.1467, p=0.0365), and at the 6th month after the operation, the BCVA of the study group was significantly higher than that of the control (t=2.0424, p=0.0462).

Intraoperative Situations of the Two Groups

Table III presents the intraoperative conditions of the two groups. The operation time of the control group was not normally distributed (Shapiro-Wilk test, p=0.034), and the operation time of the control group was significantly longer than that of the study group according to the Wilcoxon rank-sum test (W=2.212, p=0.027). The incidence of mild intraoperative bleeding in the study group was significantly lower than that in the control group (p=0.0412), and the incidence of severe intraoperative bleeding in the study group was significantly lower than that in the control group (p=0.0032). There was no significant difference between the two groups in the incidence of iatrogenic retinal rupture (p=0.1029) or silicone oil use rate (p=0.1235).

Ten cases of silicone oil use occurred in grade VI PDR in the control group, and 3 cases of silicone oil use occurred in grade VI PDR in the study group. In grade VI PDR cases, the usage of silicone oil in the study group was significantly lower than that in the control (p=0.0324). There was no significant difference in iatrogenic retinal rupture between the two groups. Nine cases of iatrogenic retinal rupture occurred in grade VI PDR in the control group, and 2 cases of iatrogenic retinal rupture occurred in grade VI PDR in the study group. Fisher's exact probability test showed that the incidence of iatrogenic retinal rupture in the study group was significantly lower than that in the control group (p=0.0255).

Postoperative Complications and Adverse Reactions

Relevant complications and adverse reactions included endophthalmitis, elevated IOP (>25 mmHg) on the 1st day after vitrectomy, early recurrent vitreous hemorrhage, late recurrent vitreous hemorrhage, new neovascular glaucoma and retinal detachment.

There was no endophthalmitis in either group. On the 1st day after the operation, there were 3 cases of elevated IOP in the control group and 2 cases in the study group. After treatment, they all recovered to normal within 1 week. There was no significant difference in the incidence of elevated IOP between the two groups (p=1). One case of

Table III. Intraoperative conditions of the two groups.

	Control	Study	Statistic	*p*-value
Operation time (min)	49 (41-56)	40 (35-45)	$W = 2.212$	0.027
Mild intraoperative bleeding (n)	9	2	-	0.0412
Severe intraoperative bleeding (n)	14	3	-	0.0032
Intraoperative silicone oil use (n)	10	4	-	0.1235
Iatrogenic retinal rupture (n)	9	3	-	0.1029

early recurrent vitreous hemorrhage occurred in both groups. There was no significant difference in the incidence of early recurrent vitreous hemorrhage between the two groups (p=1). There was 1 case of late recurrent vitreous hemorrhage in the control group and 0 cases of late recurrent vitreous hemorrhage in the study group. There was no significant difference in the incidence of late recurrent vitreous hemorrhage between the two groups (p=1). There was 1 case of iris neovascularization in the control group and 0 cases of iris neovascularization in the study group. There was no significant difference in the incidence of iris neovascularization between the two groups (p=1). There was 1 case of recurrent retinal detachment in the control group and no recurrent retinal detachment in the study group. There was no significant difference in the incidence of recurrent retinal detachment between the two groups (p=1).

Discussion

Proliferation and neovascularization in the vitreous body and retina in patients with PDR are serious and can cause tractional and rhegmatogenous retinal detachment. Vitrectomy is often used to treat PDR. This procedure is challenging due to vitreous hemorrhage, blurred surgical vision, difficult removal of the fibrovascular proliferative membrane and retinal rupture. Thus, researchers have focused on studying methods that can reduce the PDR-related bleeding, operation time and operation difficulty.

In the pathophysiology course of diabetic retinopathy, long-term hyperglycemia leads to a variety of biochemical and retinal vascular changes. Peritubular cell loss and endothelial cell damage lead to impaired blood-retinal barrier function and increased vascular permeability, while retinal artery basement membrane thickening eventually leads to vascular occlusion and a loss of perfusion[7]. The upregulation of VEGF expression plays the most important role in the pathological process of vascular permeability, ischemia and hypoxia[8]. Therefore, the application of anti-VEGF agents before vitrectomy is a very meaningful research hotspot.

It was previously reported[6] that iatrogenic retinal rupture and silicone oil use were related to the complexity scores of cases. Therefore, we further analyzed the differences in the incidence of iatrogenic retinal rupture and silicone oil use among different grades in PDR cases between the two groups. The incidence of iatrogenic retinal rupture and the usage of silicone oil in the study group were significantly lower than those in the control group.

The typical characteristics of PDR include plasma leakage, retinal neovascularization, hemorrhage and fibrovascular proliferation at the vitreoretinal interface, which can develop into vitreous hemorrhage and tractional retinal detachment. It was reported that the expression level of VEGF in the vitreous body and fibrovascular tissues of PDR patients was significantly increased[9]. In PDR treated with anti-VEGF agents, the vascular components in the fibrovascular complex subside, which can further loosen the adhesion between the fibroproliferative membrane and the lower retina, making the fibroproliferative membrane easier to separate and peel off[10]. The possibility of intraoperative retinal hemorrhage and neovascularization can also be reduced. The reduction of intraoperative bleeding can also make the operative field of vitrectomy clearer, make the relevant operation easier while reducing the operation time. Therefore, IVR before PDR vitrectomy can reduce iatrogenic injury, reduce the absorption time of hemorrhage after vitrectomy, reduce the incidence of recurrent vitreous hemorrhage, and improve BCVA earlier.

Although long-term postoperative visual acuity is affected by lens transparency, macular edema and the retinal condition, IVR can still significantly reduce the central retinal thickness and improve BCVA at the 12th month after injection[11]. Zhu et al[12] reported that the half-life of bevacizumab in the vitreous body was 6.7 days, and its concentration could be maintained for 78 days above the effective concentration (EC50) values. Bevacizumab can be detected in the retina 14 days after vitreous injection. Although most of the vitreous body is removed during vitrectomy, Bevacizumab retained in the retina may still be effective[10]. The half-life of ranibizumab in the vitreous body was estimated to be 9 days[13]. Similarly, after vitrectomy, residual ranibizumab in the retina may still be effective. Thus, the BCVA of the study group was significantly higher than that of the control at the 6th month after treatment.

The results of this study have new findings compared with previous reports. Both ranibizumab and bevacizumab are anti-VEGF agents. A meta-analysis published in 2021[14] showed that the application of bevacizumab before PDR vitrectomy could reduce the operation time, reduce iatrogenic retinal rupture, increase visual acuity at the last follow-up, reduce vitreous hemorrhage and

reduce the rate of reoperation. These results were consistent with our results. However, our results are not completely the same as Hu et al study[15] in terms of visual acuity at the 6th month after the operation. Hu et al[15] believe that there was no significant difference in BCVA among the three groups (the vitrectomy group, the application of ranibizumab before vitrectomy, the application of ranibizumab before vitrectomy plus the application of triamcinolone acetonide after vitrectomy) at the 6th month after vitrectomy. This may be related to the numerous factors influencing long-term visual acuity. Through further study of different grades of PDR cases, we found that in grade VI PDR cases, IVR before vitrectomy can reduce the incidence of iatrogenic retinal rupture and the usage of silicone oil.

The mechanism is speculated to be related to IVR reducing the concentration of VEGF in the vitreous body before PDR vitrectomy, but the mechanism has not been fully clarified. The possible reasons include a reduction in retinal thickness after IVR, an increase in retinal mechanical strength, and an improvement in the retinal reattachment rate due to a lower degree of operation difficulty.

Most of the adverse reactions of IVR are related to the injection itself[16]. IVR is widely used in the treatment of diabetic retinopathy, macular edema caused by retinal vein occlusion, age-related macular degeneration and other diseases. This study found that the application of Ranibizumab before PDR vitrectomy improved BCVA at the 1st month after operation and improved BCVA at the last follow-up. It was found that in grade VI PDR cases, the usage of silicone oil and the incidence of iatrogenic retinal rupture in the study group were significantly reduced.

Our study has potential limitations as a retrospective cohort study. The sample size of this study is limited, and further large sample randomized controlled studies are required. The confounding factors include the degree of lens opacity, optic nerve condition, retinal condition, the influence of other cytokines[17], etc.

Conclusions

In brief, IVR before vitrectomy in patients with PDR can significantly improve BCVA in the early stage, improve BCVA at the 6th month after the operation, reduce the operation time and reduce intraoperative bleeding.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

This study was approved by the ethics committee of Lianshui People's Hospital (No.: 2021318-1). This study followed the tenets of the Declaration of Helsinki.

Informed Consent

Informed consent was obtained from all of patients and/or their legal guardian(s).

Funding

This research received no special fund.

Authors' Contribution

All authors contributed equally to the conception and design of this review, collection and interpretation of data from literature, manuscript editing. All authors gave their approval to submit.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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