

## Original Article

# The effect and safety of intravitreal ranibizumab combined with vitrectomy for proliferative diabetic retinopathy

Hua Rong<sup>1,2\*</sup>, Yueli Xu<sup>3\*</sup>, Meiping Zhang<sup>3</sup>, Minyun Cai<sup>3</sup>, Hongping Cui<sup>3</sup>

<sup>1</sup>Tongji University School of Medicine, Shanghai 200092, China; <sup>2</sup>Department of Ophthalmology, Shanghai Construction Group Hospital, Shanghai 200083, China; <sup>3</sup>Department of Ophthalmology, East Hospital, Tongji University School of Medicine, Shanghai 200120, China. \*Equal contributors.

Received February 16, 2016; Accepted June 12, 2016; Epub April 15, 2017; Published April 30, 2017

**Abstract:** Objective: In this paper, we aimed to evaluate the effect and safety of intravitreal ranibizumab with vitrectomy for proliferative diabetic retinopathy (PDR) patients treatment. Methods: Total 26 PDR (29 eyes) patients admitted to our hospital between June 1, 2014 and January 1, 2015 were retrospectively analyzed. There were 13 cases (15 eyes) in vitrectomy (PPV) group and 13 cases in intravitreal ranibizumab with vitrectomy (IVR/PPV) group. The surgery duration, electrocoagulation utilization, BCVA and complications were evaluated in the two groups. Results: The mean surgery duration was significantly shorter in IVR/PPV group ( $80 \pm 15.08$  min) than PPV group ( $108.07 \pm 11.63$  min) ( $t=5.822$ ,  $P=0.0000$ ). The incidence of iatrogenic slit pore, vitreous hemorrhage, hyphema was significantly reduced in IVR/PPV group ( $P<0.05$ ). At 6 month after operation, the visual acuity of patients were improved in both two groups and visual acuity increase of patients in IVR/PPV group was higher than PPV group ( $P=0.015$ ). Conclusion: Intravitreal ranibizumab combined with vitrectomy for PDR patients treatment significantly reduced the surgery duration, the incidence of bleeding and complications. It may be a promising therapy for PDR patients.

**Keywords:** Intravitreal ranibizumab, vitrectomy, proliferative diabetic, retinopathy

## Introduction

Proliferative diabetic retinopathy (PDR) is a serious blinding disease, which is characterized by vitreous hemorrhage, neovascularization originating from the retina and tractive retinal detachment. Pars plana vitrectomy (PPV) is usually reserved for PDR treatment. However, the PPV shows difficulties in the operation process. Hemorrhage during operation increases the difficulties by extending the operation time and increasing the risk of bleeding post-operation [1]. Furthermore, the bleeding out of the control in surgery may result in operation failure.

Recently, advances have been achieved in exploring the mechanism of DR with the application of molecular biology and cell biology technique. Drugs targeting vitreous concentration of vascular endothelial growth factor

(VEGF) rises significantly [2] and provides novel perspective for PDR treatment. Ranibizumab (Lucentis) is a recombinant, humanized, monoclonal antibody Fab that can inhibit the vascular proliferation by targeting VEGF-A. Intravitreal ranibizumab was firstly used for the treatment of neovascular age-related macular degeneration. The efficacy and safety of intravitreal ranibizumab treatment have been widely validated. It is reported that ranibizumab shows promising ambient effect in the perioperative period of PDR, but the long-term safety remained to be evaluated. For the ambient effect, ranibizumab has been widely used in vitreous body related surgery in clinic.

In this paper, we retrospectively analyzed the 26 PDR patients (29 eyes) admitted to our hospital. The efficacy of vitrectomy combined with intravitreal ranibizumab for PDR patients was evaluated, compared with vitrectomy surgery.

# The effect and safety of intravitreal ranibizumab combined with vitrectomy for PDR

## Methods

### Patients

Total 26 cases (29 eyes) diagnosed with proliferative diabetic retinopathy (PDR) between June 1, 2014 and January 1, 2015 were retrospectively analyzed in our study. Patients with FBG (fasting blood-glucose)  $\leq 7.8$  mmol/L and diagnosed with Type II diabetes mellitus for more than 1 month were included in our work. The ultrasound B-mode scan showed that included patients presented with vitreous hemorrhage, exudative membrane and/or traction retinal detachment (TRD). For PDR patients without vitreous hemorrhage, hyperplasia and/or TRD were tested by fundus examination. Best corrected visual acuity (BCVA) for patients was measured at light sense to 0.2. All the subjects were given vitrectomy treatment.

Patients conforming to exclusion criteria were excluded, such as (1) Patients with retinal artery occlusion, high myopia, pterygium, glaucoma, cornea disease and uveitis; (2) Phacocotasmus  $\geq$  IV stage; (3) History of Glucocorticoid treatment within 6 months; (4) Vitreous hemorrhage was not induced by PDR; (5) Patients with cardiovascular diseases (such as hypertension) and immune diseases (such as systematic lupus erythematosus, Behcet and Ankylosing Spondylitis).

### Groups

The 26 cases were divided into two groups including vitrectomy (PPV) treatment group (n=13/15 eyes) and intravitreal ranibizumab injection combined with vitrectomy (IVR/PPV) treatment group (n=13/14 eyes). There were 6 males (7 eyes) and 7 females (8 eyes) in PPV group. The mean age for the patients was  $56.54 \pm 14.29$  years ranging from 32 to 82 years. The diabetes duration for patients ranged from 5 to 30 years and the mean duration was  $13.31 \pm 7.57$  years. The preoperative BCVA (logMAR) in cases of PPV group was between 0.7 and 2.0 and the mean BCVA was logMAR ( $1.69 \pm 0.35$ ), mean intraocular pressure (IOP) =  $16.62 \pm 7.28$  mmHg (1 mmHg = 0.133 kPa).

Patients aging from 37 to 88 years (mean:  $59.08 \pm 14.17$  years) were included in IVR/PPV group, which comprised 6 males (7 eyes)

and 7 females (7 eyes). The baseline information for cases were mean diabetes duration =  $13.85 \pm 7.80$  (range, 5~30), mean pre-operative BCVA (logMAR) =  $1.59 \pm 0.50$  (range, 0.7~2.0), mean IOP pre-ranibizumab injection =  $14.23 \pm 3.51$  mmHg and the mean IOP pre-vitrectomy was  $13.69 \pm 2.42$  mmHg. There was no significant difference in gender ( $\chi^2=0$ ), age (t=0.41), duration of diabetes (t=0.15) and pre-operative BCVA (t=0.47) between two groups. In addition, no difference was observed between average IOP in PPV group and average IOP pre-ranibizumab injection and pre-vitrectomy (P>0.05).

### Ranibizumab intravitreal injection

The patients in IVR/PPV group were given the intravitreal injection of ranibizumab by one skilled physician at 3-7 d before vitrectomy surgery. Before treatment, tropicamide (10 ml: 50 mg, SANTEN OY, JAPAN) was administered to the eyes of patients. Surface anesthesia was performed for patients by Proxymetacaine hydrochloride (15 ml: 75 mg, s.a. ALCON-COUVREUR n.v., Belgium). Then, 5% povidone-iodine was applied for preoperative disinfection of the conjunctival sac (500 ml: 25 mg, Shanghai likang disinfection technology co., LTD, Shanghai, China) with an eye speculum. After the conjunctival sac was washed with normal saline solution, we used forceps to stabilize the eye and made a location 3.5 mm behind limbus. The intravitreal injections of 0.5 mg Ranibizumab (0.2 ml: 2 mg, Novartis Pharma Stein AG, Switzerland) were performed with a 4.5-gauge needle. The needle was visualized in wall of eyeball about 1 cm. After the needle was withdrawn, the needle mouth was pressed for a moment and dropped with 5% Povidone-iodine solution, followed by washing with normal saline. Finally, the ofloxacin (3.5 g: 10.5 mg, Shenyang xing qi pharmaceutical co., LTD, Shenyang, China) was instilled in eyes.

### Vitrectomy surgery

The vitrectomy surgery was performed by a single surgeon with the application of ALCON Accurus 800 vitreous cutting system and Novus Spectra high power 532 nm laser system. The patients in both two groups were subjected to 23G pars plana vitrectomy with standard three-port system. Patients complicated

# The effect and safety of intravitreal ranibizumab combined with vitrectomy for PDR

**Table 1.** The improvement of BCVA in two groups

Group	BCVA (logMAR) pre-operation	BCVA (logMAR) post-operation	t	p
IVR/PPV	1.59±0.50	0.87±0.50	4.77	0.000
PPV	1.69±0.35*	1.37±0.47#	2.564	0.023

\*P>0.05 compared with IVR/PPV group before operation; #P<0.05 compared with IVR/PPV after operation.

**Table 2.** The outcomes after treatment in two groups

Groups	Electrocoagulation	Iatrogenic slit pore	Bleeding (≤6 month)	Bleeding (≥6 month)
IVR/PPV	1 (7.14)	1 (7.14)	2 (14.28)	0 (0)
PPV	7 (46.67)*	8 (53.33)*	9 (60)*	6 (40)*

\*P<0.05 compared with IVR/PPV group.

with cataract also underwent the ultrasonic emulsification. The surgical procedures included eliminating vitreous hemorrhage, stripping new tunica vasculosa lentis, releasing vitreous traction, returning the retina, a total gas-fluid exchange.

## Evaluation

The duration of operation and the use of electrocoagulation was recorded. The complications such as iatrogenic slit pore, bleeding in early period of postoperation (within 1 month), bleeding in the later period (more than 1 month). BCVA was tested at 6 month after operation.

## Statistical analysis

The statistical analysis was performed by SPSS18.0. All the data were expressed as mean ± SD. Difference between groups were analyzed by t test and Fisher exact test for measurement data and enumeration data, respectively. P≤0.05 was considered to be significant.

## Results

### Surgery duration

The mean surgery duration in IVR/PPV group was 80±15.08 min, ranging from 105 min to 60 min, while the mean surgery duration in PPV group was 108.07±11.63 min (rang, 93 min-130 min). There was significant difference in the surgery time between two groups (t=5.822, P=0.000).

### BCVA post-operation

In the follow-up period, the mean BCVA (logMAR) of IVR/PPV group was 0.87±0.50, ranging from 0.3 to 1.7. In PPV group, the BCVA (logMAR) of patients were between 0.7 and 2.0 with mean of 1.37±0.47. The mean BCVA in PPV group was significantly higher than IVR/PPV group (t=2.803, P=0.015) (**Table 1**).

### Outcomes

Total 10 patients (11 eyes) with cataract in IVR/PPV group were subjected to ultrasonic emulsification and 11 patients (12 eyes) in PPV group. The 8 eyes in IVR/PPV group were filled with silicone oil, while 15 eyes in PPV group was filled with silicone oil in the operation. In the IVR/PPV group, 1 eye was subjected to electrocoagulation for excessive bleeding and 7 eyes in PPV group. Iatrogenic slit pore was observed in 1 eye of IVR/PPV group and 8 eyes in PPV group. In the early postoperative period, 2 eyes in IVR/PPV group suffered recurrent bleeding and 9 eyes in PPV group. In the later period after operation, no recurrent bleeding was observed in IVR/PPV group and total 6 eyes suffered recurrent bleeding in PPV group. The incidence of iatrogenic slit pore, bleeding, recurrent bleeding was significantly lower in IVR/PPV group, compared with PPV group (P<0.05). The frequency of the use of electrocoagulation was significantly decreased in IVR/PPV group, compared with PPV group (P=0.035). Additionally, 3 eyes in PPV group suffered iris neovascular glaucoma within 6 month after operation. All the information was listed in **Table 2**.

## Discussion

PDR patients are usually accompanied with the destruction of retinal vessel, retina ischemia, appearance of retina and iris neovascularization that may result in vitreous hemorrhage and tractional retinal detachment. During the vitrectomy surgery, bleeding is an event attributed to retinal neovascularization and vitreous hemorrhage, which may result in ambiguous operation view and increase the difficulties in surgery. Previous studies showed that retinal neo-

vascularization is the main cause of hemorrhage during operation, which is mediated by the secretion of cytokines caused by retina ischemia. VEGF as the cytokine, plays a potent role in angiogenesis and tunica vasculosa lentis development [3]. It is reported that VEGF is over-expressed in the progression and development of DR and is the main pathogenic factor for DR.

The current drugs targeting VEGF mainly include Avastin, Lucentis and Macugen [4]. Lucentis is considered to be the most effect drug and has been approved to be the only drug targeting VEGF for treating the eye diseases by the USA FDA. The efficacy and safety of intravitreal ranibizumab have been proved in treating AMD by a large amount of studies [5].

In our work, 13 cases (14 eyes) in IVR/PPV group were pre-treated by intravitreal ranibizumab and then subjected to vitrectomy. The retina and iris neovascularization was regressed significantly, which obviously reduced the incidence of bleeding and iatrogenic slit pore, frequency of electrocoagulation utilization and surgery duration, compared with PPV group ( $P < 0.05$ ). Intravitreal ranibizumab significantly reduced the iatrogenic injury of retina and hemorrhage during operation and thus increased the probability of surgery success and reduced the incidence of recurrence.

Our data also showed that the incidence of bleeding pre- and post-operation was significantly reduced in IVR/PPV group compared with PPV group. We speculated that Ranibizumab played a key role in inhibiting the activation of VEGF-A by binding to VEGF-A1 and VEGF-A2 on the cell surface. Ranibizumab treatment reduced the proliferation of vascular endothelial cell, blood vessel leakage and neovascularization.

In addition, the visual acuity of patients in both two groups were improved significantly after treatment ( $P < 0.05$ ), which suggested that vitrectomy improved the restoration of retina, and facilitate visual acuity increase.

The visual acuity of patients in IVR/PPV group increased significantly compared with PPV group, which might be due to the decreased complications by intravitreal ranibizumab. Van Geest et al. [6] suggested that the treatment

with drug targeting VEGF was closely associated with the imbalance of connective tissue growth factor and VEGF. The clinical study indicated that bevacizumab aggravated the fibrosis and could promote the hyperplasia development. Tolentino [7] reported that ranibizumab injection reduced the inflammation response in eyes, but induced the bleeding and stroke. Sharma et al. [8] 10 reported that the inflammation response in eyes significantly inhibited by ranibizumab injection, compared with bevacizumab treatment. Although there were no serious complications in patients treated with ranibizumab, but ranibizumab injection increased the risk of thrombus of artery. In this paper, no adverse effect was observed in IVR/PPV group, which was consistent with the previous reports by Feiner et al. [9] and Bakri et al. [10]. Our study was limited by the small size of samples and short follow-up period. Further studies should be conducted to validate the safety of our intravitreal ranibizumab.

In conclusion, vitrectomy combined with intravitreal ranibizumab significantly improved the visual acuity and surgery success, and reduced the complications. However, the long-term safety and efficacy of intravitreal ranibizumab needed to be further validated.

### Acknowledgements

This study is supported by Pudong new area of health bureau of Shanghai, Health and family planning science and technology project (PW2013B-3).

### Disclosure of conflict of interest

None.

**Address correspondence to:** Hongping Cui, Department of Ophthalmology, East Hospital, Tongji University School of Medicine, Shanghai 200120, China. Tel: +86-021-61569781; Fax: +86-021-61569781; E-mail: hongpingcui1@126.com

### References

- [1] Oyakawa RT, Schachat AP, Michels RG, Rice TA. Complications of vitreous surgery for diabetic retinopathy: I. Intraoperative complications. *Ophthalmology* 1983; 90: 517-21.
- [2] Moradian S, Ahmadi H, Malihi M, Soheilian M, Dehghan MH, Azarmina M. Intravitreal bev-

## The effect and safety of intravitreal ranibizumab combined with vitrectomy for PDR

- acizumab in active progressive proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 2008; 246: 1699-705.
- [3] Penn J, Madan A, Caldwell R, Bartoli M, Caldwell R, Hartnett M. Vascular endothelial growth factor in eye disease. *Prog Retin Eye Res* 2008; 27: 331-71.
- [4] Wang H, Sun X, Liu K, Xu X. Intravitreal ranibizumab (lucentis) for the treatment of diabetic macular edema: a systematic review and meta-analysis of randomized clinical control trials. *Current Eye Res* 2012; 37: 661-70.
- [5] Pieramici DJ, Avery RL. Ranibizumab: treatment in patients with neovascular age-related macular degeneration. *Expert Opin Biol Ther* 2006; 6: 1237-45.
- [6] Van Geest RJ, Lesnik-Oberstein SY, Tan HS, Mura M, Goldschmeding R, Van Noorden CJ, Klaassen I, Schlingemann RO. A shift in the balance of vascular endothelial growth factor and connective tissue growth factor by bevacizumab causes the angiofibrotic switch in proliferative diabetic retinopathy. *Br J Ophthalmol* 2012; 96: 587-90.
- [7] Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol* 2011; 56: 95-113.
- [8] Sharma S, Johnson D, Abouammoh M, Hollands S, Brissette A. Rate of serious adverse effects in a series of bevacizumab and ranibizumab injections. *Can J Ophthalmol* 2012; 47: 275-9.
- [9] Feiner L, Barr EE, Shui YB, Holekamp NM, Brantley MA Jr. Safety of intravitreal injection of bevacizumab in rabbit eyes. *Retina* 2006; 26: 882-8.
- [10] Bakri SJ, Cameron JD, McCannel CA, Pulido JS, Marler RJ. Absence of histologic retinal toxicity of intravitreal bevacizumab in a rabbit model. *Am J Ophthalmol* 2006; 142: 162-4.