· Original article ·

Effect of intravitreal bevacizumab injection before vitrectomy on proliferative diabetic retinopathy

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Received:2010-06-29 Accepted:2010-08-16

Abstract

• AIM: To evaluate the effect of intravitreal bevacizumab (IVB) injection 1 week before pars plana vitrectomy (PPV) in proliferative diabetic retinopathy (PDR) patients.

• METHODS: A retrospective research was done on 46 PDR patients who were divided into PPV group (n = 28) and IVB group (n = 18, PPV with preoperative IVB). Bevacizumab was injected 1 week before PPV. Main outcome measures were visual acuity, incidence of iatrogenic retinal breaks, intraoperative and postoperative bleeding.

• RESULTS: At 1 month after surgery, visual acuity in PPV (82.1%) and IVB group (88.9%) improved significantly (P < 0.01) and the difference between the two groups was not significant. Iatrogenic retinal breaks were reported in 18 cases (64.3%) in PPV group and 4 cases (22.2%) in IVB group (P < 0.05). Intraoperative bleeding was encountered in all cases in PPV group and 7 cases (39%) in IVB group (P < 0.01). Postoperative bleeding was reported in 9 cases (32.1%) in PPV group and none in IVB group (P<0.01).

• CONCLUSION: IVB injection before PPV is helpful in reducing iatrogenic retinal breaks, intraoperative and postoperative bleeding in PDR patients.

• KEYWORDS: bevacizumab; vascular endothelial growth factor; proliferative diabetic retinopathy; vitrectomy

DOI:10.3969/j.issn.1672-5123.2010.09.004

Li CR, Sun SG, Hong W. Effect of intravitreal bevacizumab injection before vitrectomy on proliferative diabetic retinopathy. *Int J Ophthalmol (Guoji Yanke Zazhi)* 2010;10(9):1654-1656

INTRODUCTION

Nonclearing vitreous haemorrhage, preretinal fibrovascular membrane and tractional retinal detachment are major causes of severe vision decrease in patients with proliferative diabetic retinopathy (PDR)[1]. Vitrectomy is generally used to remove vitreous haemorrhage and preretinal fibrovascular membranes and relief of vitreoretinal traction. Intraoperative bleeding and iatrogenic retinal breaks were the main complications during surgery of removing preretinal fibrovascular membrane in PDR[2]. Intraoperative bleeding interferes with fundus examination, detection of iatrogenic retinal breaks, performing laser therapy and leads to time-consuming surgery. Ghost cell glaucoma and postoperative bleeding are main consequences of this complication[3].

Bevacizumab (Avastin), a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF) was approved by the US Food and Drug Administration (FDA) for the treatment for metastatic colorectal cancer. Recent reports on the intravitreal bevacizumab (IVB) injection showed promise for targeting VEGF-implicated intraocular neovascularization seen in age-related macular degeneration and proliferative diabetic retinopathy (PDR)[4]. It has been recently shown to enhance the clearance of vitreous hemorrhage and induce involution of retinal neovascularization and anterior segment neovascularization with no reported complications and has been used in the treatment of proliferative diabetic retinopathy (PDR) and other retinal vascular diseases[4,5]. The purpose of this study is to evaluate the effect of intravitreal bevacizumab (IVB) injection before vitrectomy in PDR patients.

MATERIALS AND METHODS

Participants and Grouping Preoperative evaluation included blood hypertension, blood glucose, best-corrected visual acuity (BCVA), slit-lamp, gonioscopy, ultrasonography and fundus fluorescein angiography (FFA). The surgical indication included preretinal fibrovascular membrane involving or threatening the macula, unclearing vitreous hemorrhage of at least 1 month, vitreous hemorrhage with rubeosis iridis, massive preretinal bleeding covering the posterior pole and BCVA of 0.12 or worse. Patients with pregnancy, history of haemodialysis, history of IVB injection and vitrectomy, BCVA of 0.15 or better were excluded.

Forty-six PDR patients undergoing pars plana vitrectomy (PPV) were divided into 2 groups; PPV group (28 patients, 28 eyes) undergoing PPV from Jan. 2006 to Jun. 2008 and IVB group (18 patients, 18 eyes) undergoing PPV with preoperative IVB injection from July 2008 to Jun. 2009. The age of the patients in PPV group ranged between 34 and 60 years with a mean of 43 ± 12 years; 12 patients (42.9%) were male and 16 (57.1%) were female. The age of the patients in IVB group ranged between 36 and 58 years with a mean of 42 ± 9 years; 10 patients (55.6%) were male and 8 (44.4%) were female. BCVA of all cases was less than 0.12. All cases had type 2 diabetes mellitus and had not previous panretinal photocoagulation (PRP) treatment.

This study was approved by the local research committee. All

patients signed a consent form before the study.

Surgical Interventions Bevacizumab was injected 7 days prior to surgery. 1.5mg(0.06mL) of bevacizumab(100mg/4mL; Genentech, South San Francisco, California) was injected into the vitreous cavity using a 26-gauge needle, 3.5-4mm posterior to the inferotemporal limbus after topical anaesthetic administration under sterile conditions.

Standard 3-port pars plana vitrectomy (PPV) using 20-G vitrectomy systems (Bausch & Lomb, USA). Preretinal fibrovascular membranes were removed using different techniques including membrane peeling, segmentation, delamination and en bloc dissection. PRP was done at the end of surgery. No internal limiting membrane peeling was done in any of the surgeries. The internal tamponade used was decided intraoperatively, either air or silicone oil (silicone oil was used if any multiple retinal break occurred during fibrovascular tissue dissection).

Patients were examined after 1 day, 1 week, and 1 month post-surgery.

Statistical Analysis Values were expressed as mean ± standard deviation. Software used was SPSS 10.0. $P<0.05$ was considered statistically significant.

RESULTS

PPV Group Best-corrected visual acuity of 1 month after surgery showed improvement in 23 cases (82.1%), stabilized in 1 cases (3.6%) and deteriorated in 4 eye (14.3%). The mean final visual acuity reached 0.12. Six cases (21.4%) reached 0.5 or better.

Intraoperative bleeding was encountered in all cases. Iatrogenic retinal breaks were reported in 18 cases (64.3%). Gas was used in 3 cases (10.7%) and silicone oil in 15 cases (53.6%). Postoperative bleeding was reported in 9 eyes (32.1%); 3 cases of them were during the first one postoperative week and 1 occurred 1 month after PPV. Seven cases cleared spontaneously within 1-3 weeks without treatment and 1 case was performed repeat surgery.

IVB Group Final visual acuity showed improvement in 16 cases (88.9%), no change in 2 cases (11.1%). The mean final visual acuity reached 0.15. Eight cases (44.4%) reached 0.5 or better. The difference in the mean visual acuity between the two groups was not statistically significant ($P>0.05$).

Intraocular bleeding was encountered in 7 cases (100% in PPV group and 39% in IVB group, $P<0.01$). Iatrogenic breaks occurred in 4 cases (64.3% in PPV group and 22.2% in IVB group, $P<0.05$). Silicone oil was used in these 4 cases (22.2%). Postoperative bleeding was reported none in IVB group (32.1% in PPV group and 0 in IVB group, $P<0.01$).

DISCUSSION

VEGF has been shown to contribute significantly to proliferative diabetic retinopathy. Retinal ischemia leads to an increased production of intravitreal VEGF by pigment epithelial cells, pericytes and endothelial cells. Inhibition of VEGF activity such as IVB and panretinal photocoagulation may decrease VEGF levels and inhibit retinal neovascularization. Bevacizumab can induce regression of retinal neovascularization in diabetic patients and AMD patients[6,7]. The effects of bevacizumab in patients with retinal neovascularization secondary to diabetic retinopathy have been evaluated in a number of studies. In a study by Averyl[8], fluorescein angiography revealed reduction of leakage from the foci of neovascularization within 1 week after IVB in 45 eyes with PDR. Moradian *et al*[9] reported regression of the neovascularization in eyes with active progressive PDR.

Our current study revealed the efficacy of IVB in reducing the rate of iatrogenic breaks, intraocular and postoperative bleeding after vitrectomy in PDR patients. In this study, we found that IVB was helpful in quieting down the fibrovascular proliferation before vitrectomy, making surgery easier. In PPV group, 18 cases of iatrogenic breaks and 10 cases of multiple breaks were reported. It was often observed the presence of strong adhesion between the fibrovascular membranes and the retina. This leads to higher incidence of retinal iatrogenic breaks due to difficulty in peeling the clotted blood that adhered tightly to the retina. It was also difficult to completely remove the vitreous cortex around the breaks when the iatrogenic breaks occurred. The residual vitreous cortex in the iatrogenic break area may exert strong tractional force to the retina causing the retinal breaks to enlarge into bigger hole after vitrectomy. Only 4 cases in which iatrogenic breaks occurred in IVB group may reveal that IVB quiets down the fibrovascular proliferation and makes membrane-peeling easier. Hence, IVB reduced the rate of iatrogenic break and repeat surgery. Our result was supported by findings from Ishikawa *et al*[2] who reported IVB 7 days before PPV reduced the risk of increasing tissue traction due to excessive fibrosis in patients with severe PDR and tractional retinal detachment. It also demonstrated that there were decreased surgical time and less intraoperative bleeding in patients who received IVB 5 to 7 days before vitrectomy[10].

Intraoperative bleeding is one of the main complications associated with PPV in PDR[11]. We determined intraocular bleeding by direct observation during surgery. Intraoperative bleeding was observed in all cases of PPV group. Intraoperative bleeding interferes with fundus examination and detection of iatrogenic breaks. The removal of bleeding not only may create iatrogenic breaks, but also may extent the breaks and create much more bleeding. Often, surgery will not continue due to excessive intraoperative bleeding and there is a need to do the repeat surgery. Intraoperative bleeding also increases the risk of postoperative haemorrhage and should be avoided whenever possible. It is suggested that IVB is a good alternative to avoid haemorrhage. Intraocular bleeding was encountered in 7 cases of IVB group where there was minimum bleeding observed during surgical dissection of fibrovascular membranes and tissues. The use of IVB reduced intraoperative bleeding and iatrogenic breaks compare to the control group in our study. The use of IVB prior to PPV induced regression of new vessels, reduced intraoperative bleeding and made the surgery technically easier[8,12].

Postoperative bleeding was reported in 9 eyes (32.1%) and a

repeat surgery in 1 case in PPV group. The sources of hemorrhage are often difficult to determine in the early postoperative period. In our findings, the postoperative bleeding was often from severed fibrovascular membranes that may induce a repeat surgery. No postoperative bleeding was reported in all the IVB-treated cases in our study. IVB may provide complete VEGF blockade and prevent recurrence of bleeding in the early postoperative period. A single dose of bevacizumab could provide complete pharmacological blockage of VEGF for a minimum of 4 weeks[13]. Although some studies showed better visual results in the cases treated by IVB, there was no significant difference in our study.

In conclusion, preoperative IVB was helpful in reducing intraoperative and postoperative complication, with increase in safety of surgery. The combination of therapies offers the potential to revolutionize the approach to the complications of diabetic eye disease. It is necessary for our future study to increase the number of participants and observe the IVB-related complication.

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玻璃体腔内注射贝伐单抗对增生性糖尿病视网膜病变玻璃体手术的影响

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摘要

目的:评估术前1wk玻璃体腔内注射贝伐单抗对增生性糖尿病视网膜病变(PDR)玻璃体手术(PPV)的效果。

方法:对46例PDR患者进行回顾性研究,46例患者随机分为玻璃体手术(PPV)组($n=28$)和IVB组($n=18$, PPV术前注射贝伐单抗)。玻璃体术前1wk注射贝伐单抗,比较两组间视力,医源性视网膜裂孔发生率,术中和术后出血情况。

结果:术后1mo,PPV组和IVB组视力都明显提高(82.1%对88.9%)($P<0.01$),两组间并无明显差异。医源性视网膜裂孔发生率PPV组18例,IVB组4例(64.3%对22.2%)($P<0.05$)。术中出血PPV组28例,IVB组7例(100%对39%)($P<0.01$),术后出血PPV组9例,IVB组0例(32.1%对0)($P<0.01$)。

结论:术前注射贝伐单抗可以减少增生性糖尿病视网膜病变玻璃体手术中医源性视网膜裂孔、术中出血和术后出血发生率。

关键词:贝伐单抗;血管内皮细胞生长因子;增生性糖尿病视网膜病变;玻璃体切除手术