ORIGINAL ARTICLE

Aflibercept and Bevacizumab Injection Effects on Visual Acuity of Post Vitrectomy Diabetic Retinopathy

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ABSTRACT

Background: Diabetes Mellitus is a systemic disease that can lead to diabetic retinopathy. One of diabetic retinopathy management is vitrectomy. Intravitreal anti-vascular endothelial growth factor (VEGF) perioperative injections could reduce both during and post vitrectomy complications and improve visual acuity.
Aim: To compare the effect between pre-vitrectomy aflibercept and bevacizumab intravitreal injection on the visual acuity of post vitrectomy proliferative diabetic retinopathy patients.
Method: This study used randomized controlled trial design. A total of 24 subjects was divided into two groups: pre-vitrectomy aflibercept injection as a treatment group and bevacizumab injection as a control group. Each subject was injected 4-7 days before vitrectomy then visual acuity (logMAR) was evaluated one week and one month after vitrectomy.
Results: The mean of post vitrectomy visual acuity in aflibercept group was 1.63±1.56 while in bevacizumab group, it was 1.54±1.99. There was visual acuity improvement one month post vitrectomy in both groups but it had no significant difference (p=0.771). Vitreous hemorrhage during and post vitrectomy occurred less often on aflibercept group. Iatrogenic retinal tear occurred 17% on both groups. Neovascular glaucoma occurred on severe ischemic cases.
Conclusion: Both aflibercept and bevacizumab intravitreal injection had the same effects for improving post vitrectomy visual acuity and there was no significant difference between these groups.
Keywords: visual acuity, vitrectomy, bevacizumab, aflibercept

INTRODUCTION

Diabetes Mellitus (DM) is a systemic disease that can cause diabetic retinopathy (DR) complications. DR is one of the leading causes of blindness at the age of 20 years to 74 years in America[1]. The Household Health Survey of the Republic Indonesia Ministry of Health in 1995, DR has not been defined and still included in "other blindness" as much 28%[2].

Management of RD includes blood sugar control, laser photocoagulation, intra-vitreal anti-VEGF or steroids injection and vitrectomy surgery. Vitrectomy in diabetic proliferative retinopathy (DPR) aims to reduce the ischemic area, remove thick vitreous hemorrhage that contain growth factors, release vitreo-retinal traction and for endolaser therapy. In addition, vitrectomy could increase retinal oxygenation, which could improve the integrity of the inner blood retinal barrier[3].

Complications of vitrectomy are intraoperative bleeding, corneal edema, iatrogenic retinal tear, neovascular glaucoma, cataracts and etc, so may reduce post-vitrectomy visual acuity.[3] Administration of bevacizumab (anti vascular endothelial growth factor /VEGF) as an adjuvant before vitrectomy was reported to cause blood vessel contraction, increase pericyte ratio and TGF-beta in the fibrovascular membrane, thereby reducing the complications of intravitrectomy and post-vitrectomy hemorrhage. Ushida *et al.*[4] reported pre-vitrectomy intravitreal bevacizumab injection (VEGF) safety and improvement of vision between 20/200 to 20/70 in RDP.

Ranibizumab and bevacizumab could only bind to VEGF-A while Aflibercept (VEGF-trap) was a VEGF trap receptor and competes with VEGFR receptors, and can bind VEGF-A, VEGF-B and PIGF to have the ability to eliminate the effects of stronger proangiogenic substances. Aflibercept has a higher affinity than ranibizumab and bevacizumab. The half-life of aflibercept, ranibizumab, and bevacizumab is 4.7 days, 2.9 days and 4.3 days, respectively. Therefore, the duration of 2 mg Aflibercept effect was 48-83 days[5, 6].

This study compared the effect between pre-vitrectomy aflibercept and bevacizumab intravitreal injection on visual acuity of post vitrectomy proliferative diabetic retinopathy patients.

METHODS

This study used randomized controlled trial design. A total of 24 subjects was divided into two groups of pre-vitrectomy aflibercept injection as a treatment group and bevacizumab injection as a control group. This study was held in Dr Kariadi Hospital Semarang and Diponegoro National Hospital Semarang both outpatient and inpatient care from January 2015 January – July 2016 .

The subjects of the study were proliferative diabetic retinopathy patients recruited by a consecutive sampling. The visual acuity was checked using Snellen chart and then converted to the logMar scale. The retinopathy was examined by using slit lamp and +78 D condensing lens. The indication of vitrectomy was 2 months of vitreous hemorrhage and/ or tractional retinal detachment that affect or endanger the macula.

The inclusion criteria were as follows: age 40-60 years, and type II DM patients who had never undergone laser photocoagulation therapy, intra-vitreal anti-angiogenesis injection, vitrectomy surgery and other eye surgery. The exclusion criteria were as follow : (a) cloudy

refractive medium; (b) history of stroke; (c) history of heart disease and; (d) there was inflammation or intraocular infection.

Subjects who met the inclusion criteria were then randomized. The first group was given intravitreal aflibercept injection and the second group was given bevacizumab injection according to the standard of royal college ophthalmology 4-7 days before vitrectomy. Vitrectomy performed by one operator without knowing the type of injection.

Visual acuity was observed 1 week and 1 month post vitrectomy. The surgical complications were recorded and evaluated 1 month post vitrectomy. This study had obtained approval from Diponegoro University Health Research Ethics Committee / Dr Kariadi Hospital Semarang and Diponegoro National Hospital Semarang. All subjects had given written informed consent to participate in the study. Data analysis were performed using Mann-Whitney test at 0.05 of significance level.

RESULTS

As many as 24 subjects were included in this study. Twelve subjects were assigned to aflibercept recipient group and 12 subjects were assigned to bevacizumab recipient group. Baseline characteristics of subjects enrolled in this study are described in the table 1.

Table 1 shows the age differences between the two groups that were not statistically different (p=0.839). More Phakic lens status conditions were found in the bevacizumab group compared with the aflibercept group. There was no significant difference in lens status in both groups (p=0.546). HbA1C levels of bevacizumab group were 7.75% while the aflibercept group had 7.15% level of HbA1C. This showed that the mean blood sugar levels were almost similar between the two groups and were not statistically significant (p=0.729). Moreover, primary indications of vitrectomy in this study were permanent vitreous hemorrhage, tractional retinal detachment, and combination of both. Primary indications of vitrectomy of both groups were not statistically different (p=0.785).

As can be seen from table 2, increased visual acuity of post-vitrectomy was observed in both groups compared to pre-vitrectomy. However, the difference was not statistically significant (p=0.652). Bevacizumab group showed an increased of 0.42 while aflibercept group showed an increased of 0.22 on visual acuity (logMAR). The difference was also not statistically significant (p=0.728).

The number of subjects with increased or persistent visual acuity was larger in aflibercept group (9 subjects, 74%) compared to bevacizumab group (8 subjects, 66%). Subjects with decreased visual acuity were observed more in the bevacizumab group (34%) than in aflibercept group (Table 3).

Intraoperative hemorrhage was found more common in bevacizumab group (5 subjects, 42%) than the aflibercept group (4 subjects, 33%). Iatrogenic retina tears had occurred as much as 17% in both groups. Neovascular glaucoma in bevacizumab group was found in severe preoperative conditions with grade 4 of vitreous hemorrhage and tractional retinal detachment. Active hemorrhage occurred during the operation procedure. In Aflibercept group, neovascular glaucoma was observed in pre-vitrectomy conditions of severe tractional retinal detachment and grade 3 of vitreous haemorrhage (Table 4).

Table 1. Subject characteristics

Characteristic	IVT Aflibercept	IVT Bevacizmab	*P**
Age (year)			
Median SD	51 ± 12	53.50 ± 9	0.839
Range	38-66	40-59	
Lens Status			
Phakic	11 (92%)	10 (84%)	0.546
Pseudophakic	1 (8%)	2 (16%)	
Diabetes			0.729
HbA1C (%)	7.15 ± 3.9	7.75 ± 1.4	
Primary indication			
Vitreous hemorrhage	6	3	0.785
Tractional retinal detachment	4	6	
Combination of vitreous hemorrhage and tractional retinal detachment.	2	3	

*Mann-Whitney test *p<0.05 significant*

Table 2. Post vitrectomy visual acuity difference between groups

Parameter	Aflibercept Group	Bevacizumab Group	*P**
Pre-vitrectomy visual acuity median (LogMAR)	1.63 ± 1.18	2.48 ± 1.38	0.652
Post-vitrectomy visual acuity median	1.63 ± 1.56	1.54 ± 1.99	0.771
Visual acuity improvement post vitrectomy	0.22 ± 0.63	0.42 ± 1.18	0.728

*Mann-Whitney test (*p<0.05 significant)*

Table 3. Visual acuity change after vitrectomy

Groups	Visual acuity 1 month after vitrectomy		
	Improved	Equal	Weakened
Aflibercept	7 (58%)	2 (16%)	3 (26%)
Bevacizumab	8 (66%)	0	4 (34%)

Table 4. Vitrectomy complication

Group	During vitrectomy	Total	Post vitrectomy	Total
Aflibercept	Vitreous hemorrhage	4 (33%)	Vitreous hemorrhage	0
	Iatrogenik retinal tear	2 (17%)	NV	2 (16%)
Bevacizumab	Vitreous hemorrhage	5 (42%)	Vitreous hemorrhage	3 (25%)
	Iatrogenik retinal tear	2 (17%)	NVG	1 (8%)
			TRD	0

NVG : Neovaskular glaucoma, TRD : tractional retinal detachment

DISCUSSION

The mean HbA1c level of bevacizumab group was 7.75%. It was lower in aflibercept group (7.15%), however the difference was not statistically significant (p=0.729). Glycosylated hemoglobin is a class of advanced glycation final product that can cause microvascular complications in diabetic retinopathy. HbA1c has been used as an incidence and the development predictor of diabetic retinopathy. Early Treatment Diabetic Retinopathy Study had identified HbA1c as the most important risk factor from the development of diabetic retinopathy to high-risk proliferative diabetic retinopathy. Diabetic patients having HbA1c levels greater than 8% would have visual threatening diabetic retinopathy, including severe NPDR, PDR or CSME.[7,8]

Vitrectomy in proliferative diabetic retinopathy in this study was performed with indication of vitreous hemorrhage persisting for 2 months, a tractional retinal detachment involving or threatening macula and a combination of both. The result showed that preoperative conditions of both groups were relatively similar and not different significantly. Visual acuity of post-vitrectomy condition may vary according to pre-vitrectomy condition, during surgery and post vitrectomy. The findings showed an increased of visual acuity after 1-month of post-vitrectomy in both groups. Mean visual acuity of post-vitrectomy was higher in bevacizumab group than the aflibercept group, nevertheless it was not statistically significant. Furthermore, the difference of visual acuity on pre-vitrectomy with post-vitrectomy condition was 0.42 in bevacizumab group and 0.22 in afflibercept group with no statistically significant difference.

Guthrie *et al*.[9] reported visual acuity of 6-month post-vitrectomy in proliferative diabetic retinopathy patients was 0.52 and average difference on visual acuity of pre-vitrectomy and post-vitrectomy was 1.27. The outcome was better than the results obtained in this study possibly because of longer observation time (6 months) and better visual acuity average of pre-vitrectomy conditions (logMAR).

Six-months observation allowed vitreous hemorrhage to be absorbed, resulting in an increased visual acuity. In this study, three subjects of bevacizumab group undergone 1 month observation were suffered vitreous post-vitrectomy hemorrhage that may reduce in six months. A better visual acuity of pre-vitrectomy suggests a better retinal function which will adversely affect the visual acuity of post-vitrectomy.

Sakamoto *et al.*[10] reported that 81% of patients had increased visual acuity, however 47% of them experienced decline in visual acuity during the 6-months observation. Eleven percent of patients had persistent visual acuity while 8% of patients suffered decreased visual acuity. In this study, in the treatment group of aflibercept, 16% subjects had persistent visual acuity 1 month after vitrectomy. Ozone *et al.* described 71% of subjects experienced improvement in visual acuity, 25% of subjects persisted, and 4% of subjects experienced decline in visual acuity.[11] The results are better than this study probably due to better visual acuity of pre-vitrectomy (1.39 LogMAR).

Factors that have shown to contribute on visual acuity after vitrectomy are systemic and ocular factors. Influential ocular factors include tractional retinal detachment, especially those involving macula and optic disc, macular abnormalities (non-perfusion capillaries, hard exudates, sclerotic blood vessels and macular thinning/atrophy) and neovascular glaucoma. The conditions indicate severe ischemic state. Tractional retinal detachment may lead to retinal detachment and retinal blood vessels damage, causing decrease in retinal function even with successful vitrectomy surgery. The damage persisted and would affect post-vitrectomy retinal function. Systemic factors that may cause decrease in visual acuity after vitrectomy include hemoglobin and triglyceride levels.[9,11]

The result found that intraoperative hemorrhage occurred more common in bevacizumab group than in aflibercept group. This suggests a better tendency for occlusion of neovascularization in aflibercept group. Cuirui *et al.*[12] stated the incidence of postvitrectomy vitreous hemorrhage as 32.1% in the group that was not given IVB injections compared to 0 in the group that was given IVB injection 7-days to previtrectomy ($p<0.05$).

Iatrogenic retinal tears occurred as much as 17% in both groups. The effects of preoperative anti-VEGF include thinning of the fibrovascular membrane, hence it would be easier to release to reduce the risk of retinal tears.[11] Ozone *et al*. reported 11% incidence of iatrogenic retinal tears while Oshima *et al*. reported 19% case of iatrogenic retinal tear. Both of the former studies used trocar 25G which was smaller in size than the one used in this study (23G), making it easier to remove the membrane.[11]

Neovascular glaucoma occurred in severe preoperative conditions in both study groups. Bevacizumab group showed neovascular glaucoma of subjects with grade 4 of vitreous hemorrhage and tractional retinal detachment, while having an active hemorrhage during surgery. Three subjects who suffered recurrent vitreous hemorrhage had not experienced complication during surgery, however post-vitrectomy hemorrhage might be caused by active neovascularization. Endolasers and pre-vitrectomy intravitreal bevacizumab were not sufficient to make neovascularization regress. Neovascular glaucoma was observed in the aflibercept group on previtrectomy conditions of severe tractional retinal detachment and grade 3 of vitreous hemorrhage. Persistent tractional retinal detachment in subjects with decreased post-vitrectomy

visual acuity of aflibercept groups occurred in severe detachments conditions and ischemic retina. Ozone *et al.* reported that neovascular glaucoma occurred in 7% of cases where pre-vitrectomy was severe.[11]

Anti VEGF may be given on pre-vitrectomy, intra-vitrectomy and post-vitrectomy state. The effects of anti VEGF pre-vitrectomy may lead to neovascularization occlusion thus decrease the incidence of intra-vitrectomy hemorrhage and dilute fibrovascular tissue. Intraoperative hemorrhage leads to longer operating time and more increased complications i.e. iatrogenic retinal tears. Perioperative ranibizumab showed significant results in reducing intraoperative hemorrhage, facilitating the release of fibrovascular tissue and optimizing retinal photocoagulation lasers. In addition, post-vitrectomy hemorrhage and fibrovascular tissue development also decreased.[3,7,13]

Aflibercept is a soluble decoy receptor that has the stronger ability to bind VEGF-A than the original receptors, thereby inhibiting angiogenesis processes. This causes regression of neovascularization and facilitates removal of fibrovascular tissue adhesion. Aflibercept inhibits VEGF-A as well as PlGF which plays a role in the formation of neovascularization. Aflibercept has a higher affinity for VEGF-A and PlGF than bevacizumab[14,15].

Leonard *et al*.[16] at the annual scientific meeting reported an increase in 12 patient's visual acuity of 1-month post-vitrectomy as 64 letters ETDRS compared with 34 letters ETDRS of RDP patients given each 2 times and 1 time injection. The second injection was done at the end of surgery. Greatly reduced vitreous hemorrhage was reported. The study showed the good results due to visual acuity of pre-vitrectomy is still very good i.e 15 letters ETDRS (equivalent to 0.62 (logMAR)) while the study showed average visual acuity of 1.87 (logMAR).

This study presented no difference in visual acuity after vitrectomy in both groups. This was probably due to the condition of severe pre-vitrectomy conditions and the presence of other factors i.e systemic factors. Hence, even if the retinal traction had been repaired and the vitreous hemorrhage had been removed successfully, due to the damaged photoreceptor cell by long-term ischemia, the visual acuity of post-vitrectomy would still be deprived.

The result showed a tendency of decreasing hemorrhage during and post-vitrectomy in the aflibercept group compared to the bevacizumab group. This is likely due to better neovascularization occlusion in the aflibercept group. Higher secondary glaucoma in the aflibercept group may be caused by very short observation time. There was a possible administration of anti-glaucoma drug to control intra-ocular pressure, which is relatively lower than in bevacizmab group. Moreover, researcher who played a role as the operator subjectively felt the difference during surgery in terms of treating hemorrhage and the ease of removing fibrovascular tissue adhesion where aflibercept was better than the bevacizumab and control group.

There were some limitations of this study. First, some of the subjects had severe pre-operative retinal conditions (including duration of tractional retinal detachment, macular ischemic and atrophy). Second, the inability to considering systemic factors that may reduce post-vitrectomy visual acuity (i.e hemoglobin and triglyceride) and duration of operation, as well as only one time injection and the less number of subjects.

This study could be continued with longer observation time (6 months). Selection of more targeted subjects with relatively better visual acuity and larger number of subjects would describe the benefits of each treatment group better. The possibility of more than once intravitreal injections also needed to be taken into consideration in order to provide a better effect on the occlusion and dilution of fibrovascular tissue.

CONCLUSIONS

Both aflibercept and bevacizumab intravitreal injection had the same effect for improving post vitrectomy visual acuity and there was no significant difference between these groups. Further longitudinal studies are needed to strengthen our findings.

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