Optic Atrophy after Anti-vascular Endothelial Growth Factor Injection in Diabetic Patients with Proliferative Diabetic Retinopathy

Apichart Singalavanija MD*, Kornwipa Hemarat MD*,
Napang Kedkovid MD*, Jutalai Tanterdtham MD*, Chakrapong Namatra MD*,
Adisak Trinavarat MD*, Nattawut Rodanant MD*, Somanus Thoongsuwan MD*

** Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Objective: *To study the prevalence of optic atrophy in patients with proliferative diabetic retinopathy (PDR) who underwent intravitreal bevacizumab injection and risk factors associated with optic atrophy.*
Material and Method: *A retrospective case control study enrolled 269 cases (394 eyes) of patients with PDR, in which 166 cases (219 eyes) received intravitreal bevacizumab injection. Associated factors such as type of DM, hemoglobin A1c level, hypertension, hypercholesterolemia, chronic kidney disease, previous intravitreal surgery, retinal detachment, and vitreous hemorrhage were recorded. Criteria for diagnosis of optic atrophy were decreased visual acuity, pale optic disc and decreased nerve fiber layer thickness, which was measured by Stratus optical coherence tomography (OCT). The association between intravitreal bevacizumab injection and optic atrophy was analyzed by multiple logistic regression.*
Results: *Two hundred sixty nine patients with PDR, consisting of 166 patients with intravitreal bevacizumab injection and 103 cases without bevacizumab injection. Optic atrophy was found in 11.4% (25/219 eyes) and 8% (14/175 eyes) respectively. There was no evidence that intravitreal bevacizumab injection and associated systemic diseases were related to optic atrophy. The risk factor that was related to optic atrophy was previous intravitreal surgery (adjusted odds ratio (OR), 2.57 [95% CI, 1.13, 5.84], p = 0.024).*
Conclusion: *Anti-VEGF (bevacizumab) does not increase the risk of optic atrophy. The ophthalmologists should be aware of subsequent optic atrophy development in patients with PDR who undergo surgical intervention.*

Keywords: *Optic atrophy, Anti-vascular endothelial growth factor, Proliferative diabetic retinopathy*

J Med Assoc Thai 2013; 96 (3): 318-23
Full text. e-Journal: *http://jmat.mat.or.th*

Diabetic retinopathy is one of the leading causes of blindness among the population. Currently the number of people with diabetes increased due to an aging population and improvements of the health care system. Patients with diabetes have multiple-organs involvement, including the eye. The common causes of blindness and visual disability are proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME)[1-3].

In PDR, capillaries non-perfusion area in the retina develop and the vascular endothelial growth factor (VEGF) can be found in the vitreous in response to ischemia. VEGF stimulates the formation of neovascularization at the retina and optic disc[4]. VEGF has many isoforms. In humans, it is a major stimulus for angiogenesis and increased vascular permeability. In animal studies, showed that VEGF-A is involved in the adaptive response to retinal ischemia and reduce retinal neuron apoptosis[5]. VEGF also has a neuroprotective effect. This appears to result from indirect consequences of increased angiogenesis and the direct stimulation of neuronal function[6].

Bevacizumab (Avastin®; Genetec, San Francisco, California, USA) is an anti VEGF and a cost-effectiveness drug. This drug is used worldwide to inhibit VEGF for treatment of macular edema, obliterating new vessels in diabetic retinopathy, and other retinal vascular diseases[7]. Although the drug shows safety use, there are reports that show adverse effects of intravitreal bevacizumab injection such as ischemic optic neuropathy[8,9], foveal atrophy[10] and optic atrophy[11]. All of these effects may be associated with many factors such as disturbance of retinal and choroidal circulation, imbalance of VEGF, and anti-VEGF in the ocular tissue, etc.

Correspondence to:
Singalavanija A, Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: 0-2411-2006, Fax: 0-2411-1906
E-mail apichart.sin@mahidol.ac.th

The aim of the present study was to find the prevalence of optic atrophy in patients with PDR who underwent intravitreal bevacizumab (Avastin®) injection and to analyze factors associated with optic atrophy.

Material and Method

A retrospective chart review of 320 diabetic patients with PDR who attended the Department of Ophthalmology, Siriraj Hospital, Mahidol University, Bangkok between January 2010 and January 2012 was conducted. The list of patients with PDR were chosen from the database of the hospital (ICD-10-TM, code H 36.02: PDR, +E 11.3: diabetic patients with ophthalmic complications). The present study was approved by Siriraj Institutional Review Board.

The inclusion criteria were diabetic patients with PDR (new vessel at disc and/or new vessel elsewhere) who received conventional treatment such as laser photocoagulation, vitrectomy, or intravitreal bevacizumab injection. All patients had a follow-up period of at least 6 months.

The exclusion criteria included patients with previous eye injuries, previous glaucoma or neovascular glaucoma, posterior uveitis, retinal vascular occlusion, and optic nerve diseases such as optic neuritis or hereditary optic neuropathy.

Type and duration of diabetes mellitus and systemic diseases such as hypertension, hypercholesterolemia, chronic kidney disease, cardiovascular diseases, and other associated diseases were recorded.

Eye examinations included visual acuity, ocular tonometry, slit lamp biomicroscopy, and funduscopy. They were recorded. Patients who were diagnosed as having optic atrophy underwent fundus photography and retinal nerve fiber layer (RNFL) thickness measurement by optical coherence tomography (Stratus OCT, Carl Zeiss Meditec).

The criteria for diagnosis of optic atrophy were 1) decreased visual acuity 2) pale optic disc 3) average RNFL thickness by Stratus OCT less than the fifteenth percentile of normal value.

Optical coherence tomography: the fast RNFL thickness scan mode of Stratus OCT was used. A centered circular ring around the optic disc and a signal strength >6 was accepted for evaluation.

Hypertension was defined as a systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or higher or patients who received anti-hypertensive medications. Hypercholesterolemia was defined as cholesterol level higher than 200 mg/dl or patients taking anti-cholesterol medications. Chronic kidney disease was defined as kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for three months or more. Kidney damage could be assessed by the presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens

Laboratory investigations of fasting blood glucose and glycosylated hemoglobin (HbA1c), serum creatinine, cholesterol and urine analysis were recorded.

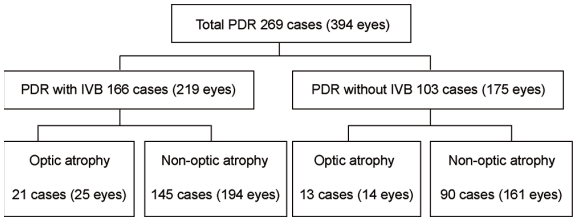
Intravitreal bevacizumab injection

Intravitreal anti-VEGF (bevacizumab) injection was indicated as follows: diabetic patients with new vessel at disc or retina elsewhere, and/or vitreous hemorrhage, patients with retinal fibrovascular proliferation indicated for vitrectomy. After lid scrubbing with 10% povidone iodine and 5% povidone iodine eye irrigation, 1.25 mg bevacizumab (0.05 ml) in a tuberculin syringe, with a 30-guage needle, was injected via pars plana. After injection, indirect ophthalmoscopic examination was performed to assess optic disc perfusion and topical antibiotics was prescribed four times daily for three days.

The patients with PDR were divided into PDR with intravitreal bevacizumab injection group and PDR without bevacizumab injection group. Both groups were divided into optic atrophy and non-optic atrophy subgroups (Fig. 1).

Statistical analysis

The data were prepared and analyzed using PASW statistics 18.0 (SPSS Inc., Chicago, Illinois, USA). Mann-Whitney U test was used for comparing continuous variables. Yates' continuity correction or Fisher's exact test was used for categorical variables. The association between risk factors and optic atrophy were examined by Chi-square test or Fisher's exact



IVB = intravitreal bevacizumab injection

Fig. 1 Flowchart illustrating diabetic patients with PDR and subsequent optic atrophy after intravitreal bevacizumab injection and a control group.

test. Multiple logistic regression was used to adjust for confounding factors and evaluate the factors that influence optic atrophy. The strength of association was measured using Odds ratio and its 95% confidence interval. A 2-tailed p-value <0.05 was considered statistically significant.

Results

Of 320 diabetic patients with PDR who attended the Department of Ophthalmology, 53 patients were excluded due to glaucoma, previous optic neuropathy, retinal vascular diseases, and incomplete information. Only 269 cases were recruited for the present study. Patients were 104 males and 165 females, aged 53.2±14.6 years, 21 cases were DM type1 while 248 cases were DM type2. Vitrectomy was performed in 104 cases (150 eyes).

Patients were divided into two groups. Group 1, patients with non-optic atrophy, 235 cases (355 eyes) and group 2, patients with optic atrophy 34 cases (39 eyes). The demographic data of patients is shown in Table 1. Optic atrophy was found after bevacizumab injection ranged from three weeks to fifty-two months. Upon analysis of the correlation between optic atrophy and risk factors, previous eye surgery (vitrectomy) and retinal detachment showed correlations with optic atrophy (Table 2). Multivariate analysis of risk factors demonstrated only previous eye surgery correlated with optic atrophy, adjusted OR 2.57; 95% CI 1.13, 5.84), p value = 0.024 (Table 3).

Discussion

The present study included 269 cases diabetic patients with PDR, optic atrophy was found in 34 cases (12.7%). In patients with PDR who underwent intravitreal bevacizumab injection, optic atrophy developed 21 cases in 166 cases (25/219 eyes; 11.4%) while in patients without bevacizumab

Table 1. Demographic data of patients with proliferative diabetic retinopathy

Factor	Total (cases) (n = 269)	Non-optic atrophy (n = 235)	Optic atrophy (n = 34)	p-value
Age (years)				0.838
Mean±SD	53.2±14.6	53.3±14.9	52.8±12.2	
Gender				0.319
Male	104 (38.7%)	94 (40.0%)	10 (29.4%)	
Female	165 (61.3%)	141 (60.0%)	24 (70.6%)	
DM				0.736
Type I	21 (7.8%)	18 (7.7%)	3 (8.8%)	
Type II	248 (92.2%)	217 (92.3%)	31 (91.2%)	
Underlying disease				
Hypertension	197 (73.2%)	172 (73.2%)	25 (73.5%)	1.000
Hypercholesterolemia	122 (45.4%)	107 (45.5%)	15 (44.1%)	1.000
Chronic kidney disease	91 (33.8%)	78 (33.2%)	13 (38.2%)	0.699
HbA1c	n = 183	n = 163	n = 20	0.635
Mean±SD	8.7±2.2	8.7±2.3	8.6±1.3	
Systolic blood pressure	n = 255	n = 224	n = 31	0.860
Mean±SD	143.6±22.8	143.6±23.2	144.3±20.7	
Diastolic blood pressure	n = 255	n = 224	n = 31	0.725
Mean±SD	81.3±14.5	81.4±14.1	80.1±17.6	

Table 2. The association of optic atrophy and risk factors

Factor	Non-optic atrophy (eyes) (n = 355)	Optic atrophy (eyes) (n = 39)	p-value[a]
Intravitreal bevacizumab injection	194 (54.6%)	25 (64.1%)	0.338
Previous eye surgery	126 (35.5%)	24 (61.5%)	0.003
Vitreous hemorrhage	156 (43.9%)	15 (38.5%)	0.627
Retinal detachment	94 (26.5%)	18 (46.2%)	0.016

[a] Fisher's exact test or Yates' continuity correction test

Table 3. Univariate and multivariate analyses of risk factors for optic atrophy

Factor	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Intravitreal bevacizumab injection	1.48 (0.75, 2.94)	0.262	1.01 (0.46, 2.26)	0.972
Previous eye surgery	2.91 (1.47, 5.74)	0.002**	2.57 (1.13, 5.84)	0.024*
Vitreous hemorrhage	0.80 (0.41, 1.57)	0.513	0.57 (0.28, 1.19)	0.135
Retinal detachment	2.38 (1.22, 4.66)	0.011	1.66 (0.74, 3.71)	0.219

OR = odds ratio
*,** Significant at 0.05, 0.01 level respectively

injection, optic atrophy developed 13 cases in 103 cases (14/175 eyes; 8%). The results of statistical analysis of the study did not show that bevacizumab injection had an association with optic atrophy.

In the present study, optic atrophy was diagnosed by decreased visual acuity, a pale optic disc, and decreased RNFL thickness. In optic atrophy, there is loss of ganglion cells and thinning of nerve fiber layer. Decreased in RNFL thickness indicated axonal loss, which can be measured by OCT[12,13].

In the normal eye, there are variations of RNFL thickness in each quadrant. In diffuse RNFL atrophy, the OCT showed that RNFL thickness was related to the severity of RNFL damage[14]. There are studies showing the normal value of RNFL thickness in Asian subjects measured by Stratus OCT. The measurement showed an average thickness of 100.44±1.30 mm[15], 104.4±1.30 mm[14] and 105.8±9.2 mm[16], respectively. The present study revealed RNFL thickness average of 75.2±12.5 mm in patients with optic atrophy.

VEGF is a glycoprotein, an angiogenic, and vasopermeable factor. In the eye, VEGF is found in ganglion cell, Müller cell, and the retinal pigment epithelium. VEGF is essential for normal angiogenesis and is believed to have a neuroprotective effect and decrease cell apoptosis[5]. VEGF production increased in ischemic conditions, when the level of VEGF suddenly decreased, a closure of normal capillaries occurred[17].

The anti VEGF used in the present study was bevacizumab (Avastin®). Bevacizumab is a monoclonal antibody. The drug can penetrate through the retina to the choroid[18]. In a clinical study in PDR, intravitreal bevacizumab injections in a dose of 6.2 µg to 1.25 mg had a systemic inhibitory concentration for VEGF, the drug also affected new vessels in the fellow uninjected eye[19]. In animal experiments, bevacizumab has some effects on the choroid. It showed choriocapillaris disturbance and reduction of choriocapillaris endothelial cell fenestration[20]. When bevacizumab was injected in patients with PDR, the level of VEGF in the vitreous and plasma decreased. The effect lasted as long as one month after injection[21]. Patients with PDR have disturbance in retinal circulation, usually associated with hypertension, hypercholesterolemia, and chronic kidney disease. The authors think that bevacizumab may disturb the circulation of retina, choroid, and circulation around the optic nerve in some degree or there may be some effect to ganglion cells. Further studies should be performed. However, the results of the present study did not show statistical correlation between bevacizumab and optic atrophy.

The limitation of the present study is a retrospective review; some information was not completely recorded. There was some limitation of Stratus OCT in RNFL thickness measurements in patient who had fibrovascular membranes at the retina. If the membrane was at the posterior pole and thick, it may interfere with measurement. The value of RNFL thickness was higher than normal and had to be discarded.

In conclusion, the patients with proliferative diabetic retinopathy who need anti VEGF injection, the ophthalmologist should be aware of systemic organ involvement especially the changes in microcirculation. It may disturb the circulation of retina, choroid, vessels around optic nerve, and the neuroprotective mechanism of the body. However, the drug still can be beneficial for the treatment of new vessels in patients with PDR.

Acknowledgement

The authors wish to thank Dr. Sasima Tongsai for the statistical analysis and the advice of the statistical method.

Potential conflicts of interest

None.

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การเกิดขั้วประสาทตาฝ่อภายหลังการฉีด anti-vascular endothelial growth factor เข้าวุ้นตาในผู้ป่วยเบาหวานที่มีจอตาเปลี่ยนแปลงชนิด proliferative diabetic retinopathy

อภิชาติ สิงคาลวณิช, กรวิภา เหมะรัต, นภางค์ เกษโกวิท, จุฑาไล ตันฑเทอดธรรม, จักรพงศ์ นะมาตร์, อดิศักดิ์ ตรีนวรัตน์, ณัฐวุฒิ รอดอนันต์, โสมนัส ถุงสุวรรณ

วัตถุประสงค์: *เพื่อหาอุบัติการณ์ของการเกิดขั้วประสาทตาฝ่อในผู้ป่วย proliferative diabetic retinopathy (PDR) ที่ได้รับการรักษาโดยการฉีดยา bevacizumab (Avastin®) เข้าวุ้นตา และปัจจัยที่มีความสัมพันธ์กับการเกิดขั้วประสาทตาฝ่อ*

วัสดุและวิธีการ: *เป็นการศึกษาชนิด retrospective case control study ในผู้ป่วย PDR 269 ราย (394 ตา) ผู้ป่วย 166 ราย (219 ตา) รับการฉีดยา bevacizumab เข้าวุ้นตา ผู้ป่วยได้รับการบันทึกปัจจัยที่เกี่ยวข้อง เช่น ชนิดของเบาหวาน ระดับฮีโมโกลบิน เอ วัน ซี โรคทางกายที่เกิดร่วม ได้แก่ โรคความดันโลหิตสูง โรคไขมันในเลือดสูง โรคทางหลอดเลือดและหัวใจ โรคไตเรื้อรัง การรักษาโดยการผ่าตัด การเกิดจอตาลอก การมีเลือดออกในวุ้นตา การวินิจฉัยขั้วประสาทตาฝ่อโดยดูระดับสายตาลดลง ขั้วประสาทตามีสีซีด และความหนาของชั้น nerve fiber layer ต่ำกว่าค่าปกติ ทำการวิเคราะห์หาความสัมพันธ์ระหว่างการฉีดยา anti-VEGF เข้าวุ้นตาและการเกิดขั้วประสาทตาฝ่อและปัจจัยที่เกี่ยวข้อง*

ผลการศึกษา: *ผู้ป่วยเบาหวานที่รวบรวมทั้งหมด 269 ราย เป็นชาย 104 ราย หญิง 165 ราย กลุ่มผู้ป่วยที่ได้รับการฉีดยา bevacizumab เข้าวุ้นตา พบมีขั้วประสาทตาฝ่อร้อยละ 11.4 (25/219 ตา) ขณะที่กลุ่มผู้ป่วยที่ไม่ได้รับการฉีดยามีขั้วประสาทตาฝ่อร้อยละ 8 (14/175 ตา) ผู้ป่วยส่วนใหญ่ได้รับการฉีด bevacizumab ก่อนผ่าตัดวุ้นตา 1-2 สัปดาห์ จากการวิเคราะห์ไม่พบว่าการฉีดยาและโรคต่าง ๆ ที่พบร่วมมีความเกี่ยวข้องกับการเกิดขั้วประสาทตาฝ่อ แต่ปัจจัยที่มีผลต่อการเกิดขั้วประสาทตาฝ่อคือการได้รับการผ่าตัดวุ้นตา (adjusted odds ratio (OR), 2.57 [95% confidence interval (CI), 1.13, 5.84], p = 0.024)*

สรุป: *การนำยา anti-VEGF มาใช้รักษาผู้ป่วยเบาหวานระยะ proliferative diabetic retinopathy เพื่อทำลายหลอดเลือดใหม่ที่ผิดปกติ มิได้เพิ่มความเสี่ยงในการเกิดขั้วประสาทตาฝ่อ แต่การผ่าตัดวุ้นตาในผู้ป่วยกลุ่มนี้พึงต้องระวังการเกิดขั้วประสาทตาฝ่อซึ่งเป็นสาเหตุของสายตาพิการได้*