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Changes of vascular endothelial growth factor after vitrectomy for macular edema secondary to retinal vein occlusion

H. NOMA[1], H. FUNATSU[1], T. MIMURA[2], S. HORI[3]

[1]Department of Ophthalmology, Yachiyo Medical Center, Tokyo Women's Medical University, Chiba
[2]Department of Ophthalmology, University of Tokyo Graduate School of Medicine, Tokyo
[3]Department of Ophthalmology, Tokyo Women's Medical University, Tokyo - Japan

PURPOSE. *To examine whether vitrectomy combined with retinal photocoagulation reduces the vitreous level of vascular endothelial growth factor (VEGF) in patients with macular edema associated with retinal vein occlusion (RVO).*
METHODS. *The authors measured VEGF levels in vitreous samples from four eyes of four patients with RVO during vitrectomy and fluid samples obtained during revitrectomy 3 to 9 months postoperatively for complications: an epiretinal membrane in two patients, macular holes in one patient, and vitreous hemorrhage in one patient. During vitrectomy, retinal photocoagulation was performed on the ischemic region of the retina in all cases (mean of 510 shots).*
RESULTS. *In four eyes with RVO, there was a difference in the vitreous VEGF levels between the vitreous samples obtained during vitrectomy (mean of 2692 pg/mL, range of 15.6–9040 pg/mL) and the fluid samples obtained at the time of revitrectomy (mean of 947 pg/mL, range of 15.6–3430 pg/mL).*
CONCLUSIONS. *The results suggest that the vitreous levels of VEGF may be reduced by vitrectomy combined with retinal photocoagulation for macular edema with RVO. It may be important to reduce the vitreous levels of VEGF by vitrectomy and retinal photocoagulation for ischemic retina in macular edema with RVO. (Eur J Ophthalmol 2008; 18: 1017-9)*

KEY WORDS. *Vascular endothelial growth factor, Macular edema, Retinal vein occlusion, Vitrectomy, Retinal photocoagulation*

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INTRODUCTION

It has been reported that vascular endothelial growth factor (VEGF), which increases vascular permeability, is a key mediator in retinal vein occlusion (RVO) (1, 2). Recently, Itakura et al reported high levels of VEGF in the vitreous cavity following vitrectomy for proliferative diabetic retinopathy (PDR) (3). On the other hand, Aiello et al (4) reported that the vitreous levels of VEGF were reduced after vitrectomy for PDR. However, the vitreous levels of VEGF after vitrectomy for macular edema with RVO are unknown. Therefore, in this study, we determined whether there is a difference in vitreous levels of VEGF before and after vitrectomy for macular edema with RVO. Additionally, we reported both cases of BRVO and CRVO because the number of cases was small, although there might be a difference in VEGF levels in cases of BRVO and CRVO.

Case reports

Undiluted vitreous specimens were obtained from a site as close to the preretinal area as possible in four eyes of four patients with macular edema secondary to RVO (2

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men and 2 women; mean age, 65.3±3.6 years). No eyes had undergone previous vitreous surgery or retinal photocoagulation. Samples of undiluted vitreous fluid (300–500 mL) obtained at the time of vitrectomy were collected into sterile tubes and rapidly frozen at –80°C. VEGF concentrations were measured by an enzyme-linked immunosorbent assay (ELISA) using human VEGF immunoassays (R&D Systems, Minneapolis, MN) (2). The assays were performed according to the manufacturer's instructions.

After sampling, a standard three-port pars plana vitrectomy with phacoemulsification cataract extractions and implantation of an intraocular lens was performed by one surgeon (H.N.). All patients without a detached posterior vitreous cortex underwent posterior vitreous detachment, but peeling of the internal limiting membrane was not performed. During vitrectomy, retinal photocoagulation was performed to the ischemic region of the retina in all cases (mean: 510 shots; range: 216–914 shots). The ischemic region of the retina was measured quantitatively using the public domain Scion Image program, the details of which have been reported previously (2). Macular edema improved in all patients after the first procedure vitrectomy. Three to 9 months later, we performed revitrectomy in the four RVO eyes without postoperative macular edema for complications: two eyes with an epiretinal membrane, one eye with a macular hole, and one eye with vitreous hemorrhage. We similarly collected fluid samples (300–500 mL from as close to the preretinal area as possible) using a sterile syringe at the time of revitrectomy and processed these samples in the same manner as the samples obtained at initial vitrectomy. The study was conducted according to the tenets of the Declaration of Helsinki. Institutional review board ethics committee approval was obtained. All patients provided informed consent. Clinical data, including the best-corrected visual acuity, were recorded at every visit.

DISCUSSION

Although the vitreous level of VEGF may be low in the vitreous samples obtained by revitrectomy because there is difference between undiluted vitreous and fluid in specimens of primary vitrectomy and revitrectomy, this study demonstrated that there was a difference in the vitreous level of VEGF between the vitreous samples obtained during vitrectomy (mean of 2692 pg/mL, range of 15.6–9040 pg/mL) and the fluid samples obtained at the time of revitrectomy (mean of 947 pg/mL, range of 15.6–3430 pg/mL) in four eyes with RVO, in which VEGF levels in CRVO were higher than those in BRVO, suggesting that this reflects a clinical feature, differing from the results of Itakura et al (3) (Tab. I). It may be possible that the vitreous levels of VEGF were maintained at a high level after vitrectomy in their study because they did not perform panretinal photocoagulation (PRP) during vitrectomy, while the vitreous levels of VEGF were reduced by 75% in six eyes in the study by Aiello et al (4) because they performed PRP during vitrectomy. These findings suggest that, in RVO as well as PDR, the vitreous level of VEGF may be reduced by vitrectomy combined with retinal photocoagulation or by retinal photocoagulation alone. However, our sample size was small, so a multicenter, randomized larger prospective study is required to clarify

TABLE I - CLINICAL AND DEMOGRAPHIC DATA FOR THE PATIENTS WITH RETINAL VEIN OCCLUSION

Patient no.	Age (y), Gender	Clinical Phenomena	Duration of RVO (mo)	Extent of ischemia (disc areas)	PVD	Treatment	Comments before Vx	PC (shots)	Reason for Re-Vx	Duration between 1st and 2nd surgery (mo)	Visual Acuity Before Re-Vx	Visual Acuity After* Re-Vx	VEGF Level (pg/mL) Vx Sample	VEGF Level (pg/mL) Re-Vx Sample
1	70/ M	ME with BRVO	3	36	_	Vx, PEA+IOL	PC−, phakic	439	ERM	9	20/200	20/50	201	15.6
2	63/ F	ME with BRVO	3	14	+	Vx, PEA+IOL	PC−, phakic	216	MH	3	20/400	20/200	15.6	15.6
3	62/ M	ME with BRVO	3	43	_	Vx, PEA+IOL	PC−, phakic	470	ERM	4	20/40	20/30	1510	325
4	66 /F	ME with CRVO	4	92	+	Vx, PEA+IOL	PC−, phakic	914	VH	7	HM	20/800	9040	3430

*Best-corrected visual acuity at 6 months after revitrectomy.

BRVO = Branch retinal vein occlusion; CRVO = Central retinal vein occlusion; ME = Macular edema; PVD = Posterior vitreous detachment; ERM = Epiretinal membrane; MH = Macular hole; VH = Vitreous hemorrhage; Vx = Vitrectomy; PEA + IOL = Phacoemulsification and aspiration + intraocular lens implantation; PC = Photocoagulation; HM = Hand movements

whether vitrectomy combined with retinal photocoagulation reduces the vitreous level of VEGF in patients with macular edema associated with RVO in the future.

It has been reported that VEGF increases due to abnormalities of biochemical pathways, such as protein kinase C activation, the augmented polyol pathway, and non-enzymatic glycation (5). Itakura et al (3) suggested that VEGF is constantly secreted postoperatively in PDR. Therefore, VEGF may continue to increase due to an abnormality in carbohydrate metabolism even after vitrectomy in PDR. Also, VEGF may be secreted after the onset of BRVO, because we previously reported that the vitreous levels of VEGF were significantly elevated in patients with BRVO compared with control subjects, and the levels of VEGF were low in the control group without BRVO including hypertensive patients (2). Taken together, these data possibly suggest that the role of VEGF in RVO is different from that in PDR in the pathogenesis of retinopathy. Recently, it has been reported that the intravitreal injection of bevacizumab, which is a full-length humanized monoclonal antibody against VEGF, is beneficial for patients with macular edema in RVO (6). Accordingly, it may be important to reduce the vitreous levels of VEGF by retinal photocoagulation for ischemic retina in macular edema with RVO.

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Reprint requests to:
Hidetaka Noma, MD
Department of Ophthalmology
Yachiyo Medical Center
Tokyo Women's Medical University
477-96, Owada-shinden
Yachiyo, Chiba 276-8524, Japan
nomahide@tymc.twmu.ac.jp

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