· Original article ·

Effects of single dose intravitreal bevacizumab injection on visual acuity, central macular thickness and ocular blood flow in patients with diabetic macular edema

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玻璃体内注射贝伐单抗对 DME 患者视力、黄斑中心厚度和眼血流的影响

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摘要

目的:探讨玻璃体内注射贝伐单抗对伴有黄斑水肿的糖尿病患者眼血流参数的影响。

方法:患者 21 例 21 眼,伴有弥漫性糖尿病性黄斑水肿(diabetic macular edema, DME),黄斑中心厚度(central macular thickness, CMT)> 320μm,无缺血性黄斑水肿或其他血管性视网膜疾病。患者术前以及注射 1.25mg/0.05mL 贝伐单抗 1d, 4wk 后接受三种眼科检查:视力(visual acuity, VA)检测、光学相干断层扫描(optical coherence tomography, OCT)测量 CMT 以及采用超声成像测量眼动脉(ophthalmic artery, OA)、视网膜中央动脉(central retinal artery, CRA)、鼻侧睫状后动脉(nasal posterior ciliary artery, NPCA)以及颞侧睫状后动脉(temporal posterior ciliary artery, TPCA)中的收缩期峰值血流速度(peak systolic velocities, PSV)和舒张末期血流速度(end-diastolic velocities, EDV)。阻力指数(resistive indices, RI)由软件自动计算,注射前与注射后 1d 的血流速度进行了比较。患者术前和注射后 4wk 的 VA 和 CMT 值进行了比较。

结果:注射前平均最佳矫正视力(best-corrected visual acuity, BCVA)为 0.88±0.21logMAR,注射后为 0.54±0.19logMAR (P<0.01)。平均 CMT 由注射前 440.57±54.58μm 下降至 250.33±31.12μm(-190.24±36.00μm)。PSV、EDV 和 RI 的变化并不显著。

结论:贝伐单抗注射后视力显着改善,CMT 降低,而 PSV、EDV 和 RI 在 OA、CRA、TPCA 和 NPCA 中没有显著变化。玻璃体内注射贝伐单抗注射液能改善 VA 和 CMT,但对于糖尿病患者的 OA、CRA、TPCA 和 NPCA 的血流速度没有影响。

关键词:糖尿病性黄斑水肿;玻璃体内注射贝伐单抗;眼部血液流量;光学相干断层扫描

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Abstract

• AIM: To investigate effects of intravitreal bevacizumab on ocular blood flow parameters in diabetic patients with macular edema.

• METHODS: This study included 21 eyes of 21 patients. Patients who had diffuse diabetic macular edema (DME), central macular thickness (CMT) > 320μm and have no ischemic macular edema or other vascular retinal disease included to this study. All patients underwent three ophthalmologic examinations before and at one day and at 4 weeks after bevacizumab 1.25mg/0.05 mL injection. Examinations including visual acuity (VA), measurement CMT by optical coherence tomography (OCT), peak systolic velocities (PSV) and end-diastolic velocities (EDV) of blood flows were measured by ultrasound imaging in the ophthalmic artery (OA), in the central retinal artery (CRA), in the nasal posterior ciliary artery (NPCA) and temporal posterior ciliary artery (TPCA). Resistive indices (RI) were automatically calculated by software of device. The velocities of blood flow before and one day after injections were compared. The values of patients before and 4 weeks after injections were compared for VA and CMT.

• RESULTS: Mean best-corrected visual acuity (BCVA) was 0.88±0.21 logarithm of the minimum angle of resolution (logMAR) before and after injection was 0.54±0.19 logMAR units (P<0.01). Mean CMT decreased from 440.57±54.58 μm to 250.33±31.12 (-190.24±36.00) μm. There were changes in the PSV, EDV and RI but this changes were not significant.

• CONCLUSION: There was a significant improvement in VA and a decrease in CMT after bevacizumab injection. Regarding the PSV, EDV and RI, no observed significant changes in the OA, CRA, TPCA and NPCA after bevacizumab injection. Intravitreal bevacizumab injection improved VA and the CMT. However, it didn't affect blood flow velocities in diabetic patients on the OA, CRA, TPCA and NPCA.

• KEYWORDS: diabetic macular edema; intravitreal bevacizumab; ocular blood flow; optical coherence tomography

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INTRODUCTION

Diabetic retinopathy is the leading cause of blindness in working aged-adults in westernised countries. Diabetic macular edema (DME) is a manifestation of diabetic retinopathy and is the leading cause of visual impairment that occurs with diabetic retinopathy[1]. Good visual acuity is associated with good vascular supplies and suitable thickness in the macula patients with diabetes mellitus[2]. Bevacizumab therapies are currently used for the treatment of patients with wet-age releated macular degeneration (AMD) and diabetic macular edema,rubeosis,proliferative diabetic retinopathy[3-7]. Bevacizumab (Avastin®; Genetech/Roche, South San Francisco, CA) is a humanized monoclonal antibody that binds all VEGF-A isoforms. The CRA supplies blood to the retina, and the PCA supplies blood the optic nerve head and choriodal layer. Therfore measurment of the blood flow velocities in the PCA and CRA may be good indicators of capillary blood flow of optic nerve head, retina and choroidal layer. Intravitreal bevacizumab frequently have been used in therapy of diabetic macular edema, choroidal neovascularization. In this study, we aimed to evaluate the effects of intravitreal bevacizumab therapy on retrobulbar blood flow parameters in patients with diabetic macular edema.

SUBJECTS AND METHODS

Subjects Twenty-one eyes of 21 patients (12 females and 9 men;age range 50-90 years; average age 65.47±12.06 years) with diffuse DME treated with 1.25mg bevacizumab were included in this study. All patients gave informed consent to the study, and the tenets of the Declaration of Helsinki were followed. Bevacizumab was used with agreement of Ministry of Health.

Primary exclusion criteria included intraocular surgery within past 3 months, focal macular edema, ophthalmic artery or retinal vein occlusion, hypertensive retinopathy, known history of significant carotid stenosis, advanced glaucomatous optic nerve damage, other optic neuropathy, macular dystrophies, ocular inflammatory disease, retinal detachment, choroid neovascularization and any known vascular disease. The central macular thickness was measured before and one day and 4 weeks after bevacizumab injection with optic coherence tomography in all patients. Ultrasound Doppler imaging (UDI) a noninvasive technique, and obtained written informed consent from all participiants. Ethics committee approval was not needed for this test.

Methods All patients underwent a detailed ophthalmologic examination, including best-corrected visual acuity (BCVA) with ETDRS chart at 4 meters in logarithm of minimum angle resolution(logMAR),anterior and posterior segment examination, and fundus fluorescein angiography. The decision to treat with bevacizumab was made with the patient after a through discussion of the risks, benefits and alternatives to treatment. A commercially available bevacizumab was prepared for each patients 1.25mg/0.05mL. All injections was performed under sterile conditions in the operating room at the inferotemporal area via pars plana by using 27 G needle.

The Doppler examinations were performed by the same radiologist. The equipment used was an Aplio XV system (Toshiba, Tokyo, Japan) with a high frequency small part probe. All examinations were performed with the patient in supine position. The resistive indices (RI), peak systolic velocities (Vps) and end-diastolic velocities (Ved) were measured in the OA, CRA, TPCA and NPCA viewed within a protocol previously decribed[8-10].

Statistical Analysis Resistance index was calculated automatically by the software of ultrasound equipment. Mean PSV, VED, RI, VA and CMT are expressed as means ± SD. All measurements taken before and one day and 4 weeks after bevacizumab injection were compared using the Wilcoxon test A $P<0.05$ was considered statistically significant.

RESULTS

Measurements of twenty-one eyes of 21 patients for VA and CMT with diffuse diabetic macular edema were compared between before andafter 4 weeks bevacizumab injection. The velocities of blood flow before and one day after injection were compared.

Mean BCVA was 0.88±0.21 logarithm of the minimum angle of resolution (logMAR) and after injection at 4 weeks was 0.54±0.19logMAR units ($P<0.01$). Mean CMT decreased from 440.57±54.58μm before injection to 250.33±31.12 (-190.24±36.00; $P<0.01$)μm. Visual acuity was increased and macular thickness decreased in all patients (Table 1).

The mean PSV changed before and one day after injection from 34.28±15.44cm/second to 33.96±11.13cm/second ($P=0.751$); mean EDV changed from 8.42±3.32cm/second to 9.0±4.26cm/second ($P=0.602$), and mean RI changed from 0.75±0.06 to 0.74±0.07 ($P=0.628$) in the OA.

The mean PSV changed before and one day after injection from 9.5±3.0cm/second to 9.3±3.2cm/second ($P=0.889$); mean EDV changed from 2.35±0.84cm/second to 2.09±0.7cm/second ($P=0.339$), and mean RI changed from 0.75±0.07 to 0.88±0.51 ($P=0.238$) in the CRA.

The mean PSV changed before and one day after injection from 22.16±8.57cm/second to 23.07±8.168 ($P=0.602$); mean EDV changed from 6.46±3.64cm/second to 6.28±3.44cm/second ($P=0.566$), and mean RI changed from 0.7±0.09 to 0.7±0.1 ($P=0.311$) in the TPCA. The mean PSV changed before and one day after injection from18.2±6.29cm/second to 21.1±7.1cm/second ($P=0.122$); mean EDV changed from 4.96±1.88cm/second to 5.88±2.4cm/second ($P=0.251$), and mean RI changed from 0.72±0.06 to 0.71±0.07($P=0.343$) in the NPCA(Table 2). The mean PSV and EDV and RI before and one day after injection showed no

Table 1 Demographic characters, BCVA, CMT of patients

(n=21)

Parameters	Preinjection	After injection	P
Mean age (yrs)	65.47±12.06		
Gender(F/M)	12/9		
BCVA(logMAR)	0.88±0.21	0.54±0.19	0.001
CMT(μm)	440.57±54.58	250.33±31.12	0.001

Table 2 The velocities of blood flow

Arteries	Preinjection	After injection	P
OA velocities			NS
PSV	34.28±15.44	33.96±11.13	NS
VED	8.42±3.32	9.0±4.26	NS
RI	0.75±0.06	0.74±0.07	NS
CRA velocities			
PSV	9.5±3.0	9.3±3.2	NS
VED	2.35±0.84	2.09±0.7	NS
RI	0.75±0.07	0.88±0.51	NS
TPCA velocities			
PSV	22.16±8.57	23.07±8.168	NS
EDV	6.46±3.64	6.28±3.44	NS
RI	0.7±0.09	0.7±0.1	NS
NPCA velocities			
PSV	18.2±6.29	21.1±7.1	NS
EDV	4.96±1.88	5.88±2.4	NS
RI	0.72±0.06	0.71±0.07	NS

OA: Ophthalmic artery; CRA: Central retinal artery; TPCA: Temporal posterior ciliary artery; NPCA: Nasal posterior ciliary artery; NS: non significant.

statistically significant difference in the OA, CRA, TPCA and NPCA. No systemic or ophthalmologic side events after intravitreal bevacizumab injection was observed in patients.

DISCUSSION

Despite the availability of anti-VEGF drugs specifically designed for intraocular use, significant off-label use of intravitreal bevacizumab persists for various conditions, including wet-AMD, macular edema secondary to diabetic retinopathy or retinal vein occlusion, rubeozis iridis, neovascular glaucoma, intractable proliferative diabetic retinopathy[11-17]. After bevacizumab injection in diabetic macular edema as in AMD the short-term effects of anti-VEGF consisted of decrease in retinal thickening and improvment in VA[18, 19]. Bevacizumab therapy have been also used nevertheless intravitreal injection of anti-VEGF may cause systemic or ocular complications[20]. Although improvment in VA have been shown after 24 months in clinical trials the long-term safety of antiangiogenic of intravitreal therapy must be determined in eyes in which choroidal perfusion is often already impaired by ageing processes[21-25]. Ultrsaound imaging allows measurment of blood flow velocities in retrobulbar arteries and has been shown to be highly reproducible and independent of the investigator when standart procedures are used[26,27]. Color Doppler imaging (CDI) is one of the most important diagnostic methods for detecting hemodynamic alterations in orbital vessels[28-30]. The other methods include fluorescein angiography, vitreous fluorometry, blue-light entoptic phenomen, and laser Doppler velocimetry[31,32]. Bevacizumab exerts two successive effects: vasoconstriction occurs very soon after injection and relates to link between VEGF and nitric oxide (NO), and is followed by decrease in capillary dencity, which occurs from hours to a few days after injection. To our knowledge, the kinetics of capillary disappearance have not been described in humans, but have been described in experimantal murine models in mice[33]. Bevacizumab is one of the important anti-VEGF agents, but also it has serious systemic and ophthalmologic side events. For example in a study of 1173 patients that were followed up for 1 year, systemic and adverse events were reported in 18 (1.5%) patients. These included 7 (0.59%) cases of an acute elevation of systemic blood pressure, 6 (0.5%) cerebrovascular accidents, 5 (0.4%) myocardial infarctions, 2 (0.17%) iliac artery aneurysms, 2 (0.17%) toe amputation and 2 (0.17%) deaths. Ocular complications endopthalmitis (0.16%), tractional retinal detachment vitreous hemorrhage (0.02%), uveitis (0.09%), and rhegmatogenous retinal detachment (0.02%)[34]. An acute visual loss following the use of intravitreal bevacizumab for DME[35]. Color-coded Doppler imaging allows for measurement of perfusion in particular vessels such as the OA, PCA and CRA, and thus in different arterial territories, as well as the evaluation of whole eye perfusion[36]. A study showed decreased blood flow velocities after intravitreal bevacizumab injection at 4 weeks in the patients with wet-AMD in the OA, CRA and TPCA[37]. Another study showed a decrease in velocity only in the nasal and temporal posterior ciliary arteries in patients with wet-AMD[38]. The above two studies were performed in a study group with wet-AMD, however, our study group consisted of patients with diabetes mellitus. We didn't observe a change of mean velocities in the OA, CRA, TPCA and NPCA in patients with diabetic macular edema at one day after single intravitreal injection of bevacizumab.

The present study is, to our knowledge, the first clinical trial to determine the effects of intravitreal bevacizumab therapy on ocular hemodynamic parameters (in the OA, CRA, TPCA and NPCA) in patients with diabetic macular edema.

In the two recent studies recorded some significant decreases in blood flow velocities in some ocular arteries in patients with wet-AMD after intravitreal bevacizumab injection.

The limaitations of study are had no control group, small sampla size, and VEGF were not measured after injection at one day. We are planinig the same investigation with the control group.

We did not find effect of intravitreal bevacizumab on ocular blood flow parameters in the literature that evaluated in patients with diabeticmacular edema. We want to share results of this study.

In conclusion the visual acuity was increased, the central macular thickness was decreased significantly at 4 weeks, ocular blood flow parameters (PSV, EDV, RI) were not show

a significant difference in the OA, CRA, NPCA and TPCA after intravitreal intravitreal bevacizumab (1.25mg/0.05mL) injection at one day.

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