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Ocular Hemodynamic Response to Intravitreal Pegaptanib in Eyes with Exudative Age-Related Macular Degeneration

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Abstract

Purpose: To assess ocular hemodynamic response to intravitreal pegaptanib in patients with age related macular degeneration (AMD).

Methods: Both eyes of twenty patients with choroidal neovascular membrane of at least four MPS (Macular Photocoagulation Study) disc area in one eye due to AMD were undergoing ocular hemodynamic evaluation. Blood flow velocities of both eyes were measured by Color Doppler Ultrasonography (CDU) before and at first, fourth weeks after intravitreal pegaptanib injection and calculated the arterial resistivity indices. The Wilcoxon-signed rank test was used for statistical analysis.

Results: In the treated eyes, the mean PSV (Peak Systolic Velocity) of OA (Ophthalmic Artery) increased significantly to a value of 45.37±17.92 at the first (p=0.007), then returned to an insignificant value of 42.19±14.35 at the fourth week (p>0.05). The mean PSV of CRA (Central Retinal Artery) increased significantly to a value of 21.59±6.21 at the first week (p=0.12) and, then remained in a significant value of 21.06±4.95 at the fourth week (p=0.006). The mean EDV (End-Diastolic Velocity) of CRA increased significantly to a value of 6.07±2.30 at the first week (p=0.001) and, then remained in a significant value of 6.20±2.24 at the fourth week (p= 0.001). The mean PSV of PCA (Posterior Ciliary Artery) increased significantly to a value of 30.66±10.73 at the first week in comparison to the value of at the fourth week (p=0.038). However, there was no significantly difference with value of 26.57±5.91 at the fourth week (p>0.05), when compared with pretreatment measurement (27.60±7.84). CDU measurements in untreated eyes did not show any significant change following and before the injection.

Conclusion: Resistivity indices of CRA, PCA and OA were not altered following intravitreal pegaptanib as an anti-VEGF agent in patients with AMD.

Keywords: Colour Doppler ultrasonography; Orbital blood flow; Pegaptanib

Introduction

Age-related macular degeneration is a major cause of irreversible visual loss in developed countries in 65 years and older. Although the etiology of AMD is not clearly understood, vascular irregularities and circulatory dysfunctions have been proposed in the pathogenesis of this disease. The two types of AMD are non-exudative type and neovascular type. Neovascular AMD is characterized by choroidal neovascular membrane (CNVM) that due to the formation of abnormal blood vessels, which grow from the choroid into or under the retina [1]. CNVM, is present in only 10% of patients with AMD. However, it is responsible for 90% of cases with severe vision loss from hemorrhage and fibrosis. The pathogenesis of CNVM is a complex process involving disturbance between proangiogenic and antiangiogenic factors. The reduction of the blood flow in choriocapillaries and degenerative change in Bruch's membrane resulting in hypoxia of retina pigment epithelium (RPE) cells initiate the procedure [2]. The Vascular endothelial growth factor (VEGF) that released by RPE cells in response to hypoxic stress is the most important of the angiogenic factors to stimulate the growth of new vessels [3]. The formation of CNVM in AMD has been shown to be related to increase levels of VEGF. Anti-VEGF agents have drammatically improved the prognosis of patients with neovascular AMD [4,5].

Pegaptanib is a pegylated ribonucleic acid aptamer and is the first intravitreal anti- VEGF agent approved by the FDA for the intravitreal treatment of neovascular AMD. Previous clinical and experimental trial data have demonstrated that pegaptanib is effective for the treatment of neovascular AMD. The VEGF Inhibition Study in Ocular Neovascularization (VISION) trial showed that intravitreal injection every six weeks resulted in a reduction in the number of patients who experienced severe vision loss [6-8].

Color Doppler ultrasonography (CDU) is noninvasive method that measures flow velocities of retrobulbar blood vessels, allows calculations of the resistivity index, and gains reproducible data in CRA and OA and in PCA. CDU was often shown to be useful in evaluating blood flow velocities in orbital and retinal vascular diseases in which vascular or occlusive etiology has been implicated [9-12]. This study was designed to investigate ocular hemodynamic responses in eyes with CNV administered intravitreal pegaptanib and in the fellow eyes of these patients with unilateral exudative AMD.

Materials and Methods

Twenty patients (eight women and 12 men) were chosen from among the patients with neovascular AMD who attend to regular check-ups in the retinal outpatient clinic in our university hospital. CNVM was defined by the viewing the dye leakage from classic or occult lesion though fundus fluorescein angiography.

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All patients underwent a complete ophthalmologic and general examination. The subjects were instructed to avoid caffeine, tobacco, and exercise for at least three hours before the study visits. The study was designed as an interventional, prospective, institutional, single-blinded, controlled, clinical trial.

The protocol for the study was reviewed and approved by the institutional review board of our university. The tenets of the Helsinki declaration were followed throughout the study. Informed consent was obtained from each subject including detailed explanation of all procedures before participation in the study.

In this study, a control group including the patients with wet AMD remaining without treatment was not formed. We preferred the use of the second eyes of the patients as controls because of ethical reasons.

The pars plana injection technique

Before the injection was performed, 10% povidone-iodine wash was applied directly to the ocular surface, lid margins, and lashes using a sterile applicator or a flush injector. After a lid speculum was placed, an additional drop of povidone-iodine was applied to the intended injection site. The needle was inserted 6 mm toward the eye's centre, and drug was injected into the mid vitreous cavity. The intravitreal of 0.3 mg pegaptanib (Macugen; Eyetech Pharmaceuticals, New York, USA) injection was performed by one surgeon (BT) through the pars plana in the inferotemporal quadrant 3.0 mm (pseudophakic eyes) to 4 mm (phakic eyes) from the limbus. In order to avoid vitreous wick syndrome, the conjunctiva was shifted with a cotton-tipped applicator before injection and then roll a cotton-tipped applicator over the entry site to minimize reflux as the needle withdrawn.

Color doppler ultrasonography [11]

The patients that scheduled for intravitreal pegaptanib were underwent ocular hemodynamic evaluation by CDU before and one and four weeks after injection. Non-injected fellow eyes were also evaluated.

For the measure, the patient was laid in the supine position with eyes closed and gaze directed towards the ceiling. The examiner's hand was placed upon the orbital margin to minimize the effect of pressure on the globe when the 7.5 MHz linear phased transducer was applied with contact jelly on the upper eyelid. All ocular hemodynamic evaluations were performed by one experienced examiner. Samples of pulsed Doppler signal were analysed to calculate blood velocities. Although orbital vessels frequently go parallel with the ultrasound beam, angle correction was used when needed. Retrobulbar blood flow velocities of the OA, CRA, CRV (central retinal vein) and temporal and nasal short PCAs were measured by CDU (Toshiba Applio SSA 770 A/80 (Tokyo, Japan). PSV and EDV were defined as the highest velocity of blood flow during the systolic phase of the cardiac cycle, and as the velocity of blood flow at the end of the diastolic phase of the cardiac cycle, respectively. Pourcelot's resistive index (RI), a measure of peripheral vascular resistance, was calculated automatically using formulae "RI= (PSV-EDV)/PSV" by the CDU software. The OA was examined approximately 25 mm behind the globe at the straighter portion of the vessel in the nasal orbit to gain the most reliable results. The CRA was measured behind the optic nerve head within the retrolaminar portion of the optic nerve. The short PCAs were detected 10–20 mm behind the globe nasal and temporal to the optic nerve. All measurements of CDU were revealed from both eyes of each patient in order to evaluate whether the hemodynamic parameter changes were due to intravitreal pegaptanib injection and whether pegaptanib has an effect on the hemodynamics of the other eye though systemic absorption.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 13.0 (SPSS, Inc., Chicago, IL, USA). The Wilcoxon-signed rank test was used to compare CDU measurements before intravitreal injection and at the first and fourth weeks following administration of intravitreal pegaptanib. Results were given as means ± standard deviations. P value less than 0.05 was considered as statistically significant.

Results

The mean age of the patients enrolled in the study was 73.58±8.2 years (range: 65-81 years).

Mean±standard deviation values of CDU measurements in the treated eyes are shown in (Table 1). At the first week following treatment, the mean PSV of OA was significantly higher compared with that before treatment (p= 0.007). The mean EDV and RI of OA were not shown a significant difference among pre and post treatment measurements (p>0.05). At the first week following treatment, the mean PSV and EDV of CRA were significantly higher compared with that before treatment (p= 0.006 and p= 0.001, respectively). The mean RI of CRA were not shown a significant difference among pre and post treatment measurements (p>0.05).

Haemodynamic Value	Pre-treatment (n=20)	P value-1	Posttreatment (first week) (n=20)	P value-2	Posttreatment (fourth week) (n=20)
Ophthalmic artery					
PSV (cm/s)	39,24±11,09	0,007*	45,37±17,92	0,376	42,19±14,35
EDV (cm/s)	10,97±4,57	0,911	10,96±4,14	0,983	10,74±4,35
RI	0,74±0,08	0,386	0,74±0,09	0,324	0,74±0,08
Central retinal artery					
PSV (cm/s)	17,74±4,57	0,006*	21,59±6,21	0,472	21,06±4,95
EDV (cm/s)	4,10±1,32	0,001*	6,07±2,30	0,809	6,20±2,24
RI	0,76±0,06	0,183	0,73±0,09	0,545	0,69 ±0,16
Posterior ciliary artery					
PSV (cm/s)	27,61±0,84	0,198	30,66±10,73	0,038*	26,57±0,91
EDV (cm/s)	7,60±2,96	0,083	9,15±4,08	0,316	8,03±2,55
RI	0,72±0,07	0,627	0,71±0,05	0,888	0,71±0,05
Central retinal vein					
Flow velocities	8,19±2,25	0,236	7,54±1,20	0,349	7,74±1,76

CDU: Colour Doppler ultrasonography; CNVM: Choroidal Neovascular Membrane; EDV: End Diastolic Velocity; PSV: Peak Systolic Velocity; RI: Resistivity İndex; SD: Standard Deviation; *indicates significant difference. P value-1, P for the comparison of the values of Pre-treatment and Post-treatment first week. P value-2, P for the comparison of the values of Post-treatment first week and Post-treatment fourth week

Table 1: CDU measurements (mean± SD) at pre-treatment, first and fourth week following treatment of the treated eyes with CNVM.

Haemodynamic value	Pre-treatment (n=20)	P value-1	Posttreatment (first week) (n=20)	P value-2	Posttreatment (fourth week) (n=20)
Ophthalmic artery					
PSV (cm/s)	41.94±9.34	0.053	38.99±11.53	0.064	42.21±9.47
EDV (cm/s)	12.52±3.82	0.388	12.64±3.79	0.866	12.57±3.77
RI	0.67±0.09	0.419	0.67±0.10	0.239	0.68±0.10
Central retinal artery					
PSV (cm/s)	20.71±2.47	0.087	20.82±2.52	0.432	20.77±2.49
EDV (cm/s)	5.83±1.98	0.368	5.85±1.97	0.948	5.84±1.99
RI	0.69±0.10	0.306	0.69±0.10	0.625	0.69±0.10
Posterior ciliary artery					
PSV (cm/s)	26.69±5.57	0.614	26.75±5.35	0.840	26.74±5.51
EDV (cm/s)	9.17±2.69	0.053	9.29±2.62	0.295	9.26±2.58
RI	0.64±0.07	0.124	0.64±0.07	0.657	0.65±0.07
Central retinal vein					
Flow velocities	6.25±1.60	0.765	6.29±1.54	0.080	6.30±1.48

CDU: Colour Doppler ultrasonography; CNVM: Choroidal Neovascular Membrane; EDV: End Diastolic Velocity; PSV: Peak Systolic Velocity; RI: Resistivity İndex; SD: Standard Deviation. P value-1, P for the comparison of the values of Pre-treatment and Post-treatment first week. P value-2, P for the comparison of the values of Post-treatment first week and Post-treatment fourth week

Table 2: CDU measurements (mean± SD) at pre-treatment, first and fourth week following treatment of untreated opposite eyes with nonexudative AMD.

At the first week following treatment, the mean PSV of PCA was significantly higher compared with that in fourth week (p= 0,038). The mean EDV and RI of PCA were not shown a significantly difference among pre treatment and post treatment measurements (p>0.05).

Intravitreal pegaptanib treatment was not associated with statistically significant changes in the mean flow velocity of the CRV in treated eyes.

In the untreated opposite eyes with nonexudative AMD, the mean CDU measurements did not show any statistically significant change at the first and fourth week following pegaptanib treatment, when compared with the values before treatment (Table 2).

Discussion

Vascular endothelial growth factor is a soluble 46 kDa, endothelium-specific secreted, angiogenic glycoprotein that increases the vascular permeability and induces endothelium-dependent vasodilatation [13-19]. Nitric oxide (NO) is suggested to mediate VEGF signaling. In additionally, the VEGF-induced vasodilation and its effect on vascular permeability are inhibited by NO synthase inhibitors [19].

Laboratory studies have shown that the parenteral administration of VEGF could significantly improve perfusion in rabbit ischemic limb models. In addition, it has been demonstrated that VEGF administration in a pig coronary occlusion model resulted in improvement of coronary flow and preservation of regional hemodynamics in the compromised myocardium [19-21]. The data suggest that the VEGF-induced decrease in cardiac output is due to reduced stroke volume, which might be caused by a decrease in venous return. Pegaptanib inhibits to the VEGF165 isomer binding to its receptor which is considered to be primarily responsible for pathologic neovascularization in the eye, and it decreases vascular permeability and inhibits neovascularisation [6].

At light of the literature, it might be consider that the inhibition of VEGF165, eye-specific VEGF form by Pegaptanib, may be causing regional hemodynamic changes in the eye. Due to the potential vasoconstriction via anti-VEGF effect of Pegaptanib may have expected that an increase in retro bulbar blood flow velocity and the changes in vascular resistance.

If it is considered that VEGF causes vascular tortuosity and vasodilatation, then, theorically, anti-VEGF therapy can reverse these, which would improve the efficiency of blood flow within the eye. The indicator of this reverse effect in the eye may be a decreasing in the resistivity index.

Using CDU, Friedman demonstrated the reduced flow velocities and increased resistance indices in the CRA and the PCAs in the patients with both exudative and non exudative AMD, as compared with healthy control subjects [22]. In a later study, Ciulla reported decreased flow velocities in the PCAs and the CRAs in patients with non exudative AMD [22]. Although it has been reported that patients with unilateral CNVM have reduced PCA flow velocities in both eyes, other investigators have found that PCA blood velocities are more affected in the exudative eye than in the contralateral eye [22-24]. In addition, Dimitrova demonstrated an increased pulsality index in the CRA, PCA and OA in patients with exudative and non-exudative AMD, and decreased EDV in the PCA in patients with non-exudative AMD [25].

Our results show a temporary elevation in the PSV of the OA and the PCA appear to increase in the first week and return to their baseline values at the fourth week following treatment. The PSV and EDV of the CRA appear to increase at the first week and to remain in a similar value at the fourth week following treatment. In the present study, the PSV of the PCA and OA increased after treatment, and it returned to its baseline levels after 4 four weeks. These findings may be consistent with the requirement of treatment with intravitreal injection of pegaptanib every 6 weeks in AMD.

To data in literature, following the intervention of Anti-VEGF, it may be expect, initially, the formation of the vasoconstriction or the inhibition of vasodilatation, the decreasing in vascular permeability, and then decreasing of RI. In our study, the mean EDV and RI of PCA and OA, the mean RI of CRA and the mean flow velocity of CRV were not shown a significant difference among pre and post treatment measurements.

These results suggest that the resistivity indices in CRA, PCA and OA do not alter following intravitreal pegaptanib as an anti-VEGF agent in patients with AMD.

In the fellow eyes, that intervention was not carried out, the CDU parameters before and after intervention on other eyes did not show any difference. This finding may be possibly arising from intravitreal injection of the drug.

In our study, even if it is not statistically significant, the decreasing in RI of the PCA was determined at the first week after the intervention in comparison to that before treatment and, at the fourth week, this decreasing was remained at about the levels of first week. The decreasing in resistance the vessel wall and the prevention of the vasodilatation on account of decreasing of tissue edema around the

vessel might be responsible from the insignificantly reduction at the ratios of RI though a relief in retinal circulation in the present study.

To the best of our knowledge, this is the first study investigating the ocular hemodynamic response in AMD patients who underwent pegaptanib injection.

Although, this study suggests that pegaptanib is seemed as it doesn't affect ocular hemodynamics, further clinical trials is needed to elucidate the effects of the drug on ocular blood flow velocities.

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