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CLINICAL STUDY

The effect of intravitreal bevacizumab (avastin) administration on systemic hypertension

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Abstract

Aims **To determine the short-term effect of intravitreal bevacizumab administration on systemic blood pressure levels of patients and to evaluate the safety of the drug in these patients.**

Methods **Study population was divided into two groups: group A comprised patients who had hypertension and were under medication with antihypertensive drugs; group B comprised patients with normal blood pressure and were not under medication with antihypertensive drugs. All patients were graded according to their blood pressure levels before single dose of bevacizumab (0.05 ml; 1.25 mg) injection, and at day 1 and weeks 1, 3, and 6 thereafter. The blood pressure levels were analysed using repeated measures of analysis of variance (ANOVA). A *P*-value of <0.05 was considered significant.**

Results **The study population included 82 patients with a mean age of 67.2 ± 5.2 years. In group A, the systolic blood pressure levels showed significant increases at weeks 1, 3, and 6 ($P=0.001$, $P<0.001$, and $P=0.003$, respectively) compared with baseline. Similarly, diastolic blood pressure levels were significantly higher at weeks 3 ($P<0.001$) and 6 ($P=0.016$). In group B, the mean systolic and diastolic blood pressure levels showed significant elevations only at week 3 ($P=0.004$ and $P<0.001$, respectively). The percentages of both group A and B patients with normal blood pressure decreased at week 3 compared with baseline ($P<0.001$ and $P=0.012$ for groups A and B, respectively).**

Conclusions **The findings of this study show that there is a risk of disregulation of blood pressure levels or persistence of hypertension in hypertensive patients after intravitreal bevacizumab injections.**

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Introduction

Vascular endothelial growth factor (VEGF) has been identified as a protein that increases capillary permeability and functions as an endothelial cell mitogen in 1989. It plays a critical role in both adult and developmental blood vessel growth.[1–3] Because VEGF is a crucial regulator of angiogenesis, it has become an attractive target for pharmacologic manipulation to treat cancers and ophthalmic diseases. Bevacizumab, a recombinant human monoclonal antibody against VEGF, has been used as an antiangiogenic agent for the treatment of tumours, including renal cell carcinoma, colorectal carcinoma, and breast carcinoma.[1–3] Recently, anti-VEGF drugs, including bevacizumab, have increasingly been used in the clinical practice as an 'off-label' intravitreal treatment option for the management of intraocular neovascular, oedematous, and proliferative disorders.[4,5]

Hypertension is a common but incompletely understood disease. Hypertension-related diseases, including stroke, myocardial infarction, and heart failure pose an enormous burden to health care expenditures.[6] The prevalence of hypertension, especially systolic hypertension, increases in the elderly subjects. Therefore, new strategies to lower blood pressure and identify patients at high risk for

complications could have a strong beneficial impact on public health.[7] Studies with bevacizumab showed that the inhibition of VEGF induces or exacerbates hypertension in some patients.[6,8–10] Although the mechanism of hypertension due to antiangiogenic therapy is not fully understood, it is believed to be nitric oxide (NO)-mediated. Preclinical *in vivo* studies showed that VEGF increases endothelial NO synthase (eNOS) expression by the activation of protein kinase-C pathway and leads to an increase in arterial pressure.[11]

In the light of the above-mentioned knowledge, this study was designed to determine the short-term effect of intravitreal bevacizumab administration on systemic blood pressure levels of hypertensive patients and to evaluate the safety of the drug in these patients.

Materials and methods

Study population and design

Study population included patients who had increased central retinal thickness due to wet age-related macular degeneration (AMD), as determined by optical coherence tomography. Increased central retinal thickness was characterized with subretinal fluid and/or cystic changes within the retina. All patients had choroidal neovascular membrane as determined by fluorescein fundus angiography. The study was carried out between January and June 2007. A written informed consent was signed by every patient who fulfilled the inclusion criteria and accepted to participate in the study before enrolment. The study was approved by an ethics comittee.

The study population was divided into two groups: group A comprised patients who had hypertension and were under medication with antihypertensive drugs, whereas group B comprised patients with normal blood pressure, and were not under medication with antihypertensive drugs.

Intravitreal bevacizumab was primarily offered to patients who were losing vision while under treatment with FDA-approved therapies for neovascular AMD or as a first-line therapy after evaluating all therapetic options for the patient. At each visit, the patients underwent Snellen visual acuity measurements as part of routine clinical care and an ophthalmic examination, including slit-lamp evaluation and a biomicroscopic fundus examination. Ocular imaging consisted of fluorescein angiography and/or optical coherence tomography at the time of bevacizumab injection and at each visit.

Measurement of blood pressure levels

All patients receiving intravitreal injection of bevacizumab underwent blood pressure measurement, as described in 1999 World Health Organization International Society of Hypertension (WHO-ISH) Guidelines for the Management of Hypertension.[12,13] A standardized technique for the measurement of blood pressure was used; the patient was allowed to sit for several minutes in a quiet room before beginning blood pressure measurement, a standard cuff with a bladder that is 12 ± 13 cm by 35 cm, with a larger bladder for fat arms and a smaller bladder for thin arms was used. Phase V Korotkoff sounds (disappearance) was used to measure diastolic blood pressure; the blood pressure was measured in standing position in elderly subjects, diabetic patients, and in other conditions in which orthostatic hypotension is common, and the sphygmomanometer cuff was placed at heart level. Blood pressure measurements were performed just before bevacizumab injection (baseline), and repeated at day 1 and weeks 1, 3, and 6 thereafter. The patients were graded according to the blood pressure values as described in 1999 WHO-ISH Guidelines for the Management of Hypertension (Table 1).[14] Patients with systolic blood pressure of >140 mmHg and diastolic blood pressures of >90 mmHg (grade 1 hypertension according to WHO-ISH) at baseline measurement were referred to the internists for further evaluation and excluded from the study.

Table 1 Classification of blood pressure levels according to 1999 WHO-ISH Guidelines for the Management of Hypertension

Category	*SBP (mmHg)*	*DBP (mmHg)*
Optimal	<120	<80
Normal	<130	<85
High-normal	130–139	85–89
Grade 1 (mild)	140–159	90–99
Grade 2 (moderate)	160–179	100–109
Grade 3 (severe)	>180	>110

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Intravitreal bevacizumab administration

Only one eye of each patient was injected with bevacizumab. Antibiotic eye drops were not used before bevacizumab administration. All eyes received a single dose of bevacizumab. First, the eye was topically anaesthetised with 0.5% propacaine, and povidone-iodine (10%) scrub was performed on the eyelids and lashes. Then, a sterile speculum was placed between the lids, and povidone-iodine (5%) drops were applied over the ocular surface three times. Additional topical anaesthesia was achieved by applying a sterile cotton swab soaked in sterile 4% lidocaine to the area designated for injection in the inferotemporal quadrant. Bevacizumab (Avastin, Genentech Inc., South San

Francisco, CA, USA; 0.05 ml; 1.25 mg) was injected through the pars plana into the vitreous cavity inserted into the sclera 3–4 mm posterior to the limbus using a 30-gauge needle attached to a tuberculin syringe. Following the procedure, light perception was evaluated and the intraocular pressure was monitored until it was below 21 mmHg. Then, the patients were instructed to apply topical antibiotics to the injected eye four times a day for 1 week. All patients received a phone call within 24 h to check their health status and were reminded to use their antibiotic drops as prescribed.

Statistical analysis

All statistical analyses were performed using SPSS version 12.0 software package. The blood pressure level was presented using descriptive statistics, using mean ± SD for numeric variables and percentage for categorical ones. The blood pressure levels at different time points were analysed using repeated measures of the analysis of variance (ANOVA). A *P*-value of <0.05 was considered significant.

Results

Study population included 82 patients (44 women and 38 men) with a mean age of 67.2 ± 5.7 years (range, 53–81 years). All patients had subfoveal choroidal neovascularization due to AMD. Group A comprised 42 patients who had hypertension and were under medication with antihypertensive drugs; group B comprised 40 patients with normal blood pressure and were not under medication with antihypertensive drugs. In group A, all patients continued to use their usual antihypertensive medication regularly before and after bevacizumab injection. No new antihypertensive medication was initiated before the injection. In group A, patients with systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg (grade 1) at baseline were referred to the internists for modification of their medications.

Evaluation of systemic blood pressure

Table 2 shows the mean systolic and diastolic blood pressure levels of group A and B patients at baseline (before bevacizumab injection) and at day 1 and weeks 1, 3, and 6 following the bevacizumab administration. In group A patients, the mean baseline systolic and diastolic blood pressure levels were 110.2 ± 4.7 and 76.8 ± 3.5 mmHg, respectively. Systolic blood pressure level showed significant increases at weeks 1, 3, and 6 (123.0 ± 6.3 mmHg; $P=0.001$, 131.0 ± 13.8 mmHg; $P<0.001$, and 123.2 ± 8.1 mmHg; $P=0.003$, respectively) compared with baseline. Similarly, diastolic blood pressure levels were significantly higher at weeks 3 (83.0 ± 8.0 mmHg; $P<0.001$) and 6 (79.0 ± 4.7 mmHg; $P=0.016$) compared with baseline levels.

Table 2 The SBP DBP values of group A and B patients before bevacizumab injection (baseline) and at day 1and weeks 1, 3, and 6 after bevacizumab injection

	SBP (mmHg)	P-*value*	*DBP (mmHg)*	P-*value*
Group A (n = *42)*				
Baseline	119.2 ± 4.7		76.8 ± 3.5	
Day 1	120.2 ± 4.7	0.293	7.1 ± 3.5	0.674
Week 1	123.0 ± 6.3	**0.001**	78.1 ± 4.8	0.200
Week 3	131.0 ± 13.8	**<0.001**	83.0 ± 8.0	**<0.001**
Week 6	123.2 ± 8.1	**0.003**	79.0 ± 4.7	**0.016**
Group B (n = *40)*				
Baseline	119.6 ± 4.4		76.3 ± 4.0	
Day 1	120.3 ± 3.6	0.571	76.8 ± 3.7	0.460
Week 1	122.0 ± 5.2	0.066	77.9 ± 4.1	0.059
Week 3	124.9 ± 8.2	**0.004**	80.4 ± 5.2	**<0.001**
Week 6	120.0 ± 4.1	0.732	77.8 ± 3.4	0.089

DBP, diastolic blood pressure; SBP, systolic blood pressure.
The values are given as mean, SD.
P-values (as marked bold) show the statistical difference compared with the corresponding baseline (preinjection) values.
A *P*-value of <0.05 was considered significant.

Group B patients had mean systolic (119.6 ± 4.4 mmHg) and diastolic (76.3 ± 4.0 mmHg) blood pressure levels comparable to group A patients at baseline. In this group, mean systolic and diastolic blood pressure levels showed significant elevations only at week 3 (124.9 ± 8.2 mmHg; $P=0.004$ and 80.4 ± 5.2 mmHg; $P<0.001$, respectively).

Evaluation of the percentage of patients at different blood pressure categories

Table 3 shows the distribution of the patients into blood pressure categories at baseline and after bevacizumab injection. As the number of patients at each hypertension grade was not sufficient for statistical analysis, we grouped the patients into two blood pressure categories according to their blood pressure levels. One group included the patients with normal blood pressure and the other group included those with high-normal blood pressure + hypertensives. The analysis of the percentage of patients in these two categories at different time points after bevacizumab administration revealed that the percentages of both group A and B patients in the normal blood pressure category decreased at week 1, and this decrease reached a statistically significant level at week 3 compared with baseline ($P<0.001$ for group A and $P=0.012$ for group B, respectively). In Group A, the percentage of patients with normal blood pressure level showed a tendency to increase at week 6; however, it was

Table 3 Distribution of the group A and B patients into blood pressure categories before bevacizumab injection (baseline) and at day 1 and weeks 1, 3 and 6 after bevacizumab injection

	Baseline	*Day 1*	*Week 1*	*Week 3*	*Week 6*
Group A (n = *42)*					
Normal	42 (100)	42 (100)	39 (92.9)	27 (64.3)[a]	35 (83.3)[b]
High-normal + hypertension	0 (0)	0 (0)	2 (4.8)	8 (19.0)	6 (14.3)
Group B (n = *40)*					
Normal	40 (100)	40 (100)	38 (95.0)	33 (82.5)[b]	40 (100)
High-normal + hypertension	0 (0)	0 (0)	2 (5.0)	5 (12.5)	0 (0)

The values are given as *n* (%).
[a]$P < 0.001$.
[b]$P = 0.012$, compared with baseline.

still significantly lower in comparison to that of baseline ($P < 0.001$). On the other hand, the percentage of patients in the normal blood pressure category returned back to the baseline value in group B.

Evaluation of the safety of intravitreal bevacizumab administration

In group A, six patients experienced subconjunctival haemorrhage at week 3, which was resolved in 3 weeks without medication.

Conclusions

The findings of this study show that intravitreal bevacizumab injection to patients with subfoveal choroidal neovascularization due to AMD caused elevations in the systemic blood pressure levels 3–6 weeks after the injection. This effect was observed in both hypertensive patients who were under medication with antihypertensive drugs and in those with normal blood pressure. An international intravitreal bevacizumab safety survey reported that 0.21% of the patients ($n = 15$) experienced a mild increase in blood pressure following bevacizumab administration.[15] Intravitreal bevacizumab injections did not show an increased rate of potential drug-related ocular or systemic events. Thus, the results suggest that intravitreal bevacizumab seems to be safe. Michels *et al*[16] reported a mild elevation of systolic blood pressure after systemic bevacizumab administration for neovascular AMD. They reported that the elevated blood pressure was normalised 12 weeks after the injection. This study was then criticised by Rich *et al*[17] who claimed that blood pressure monitoring was performed by different examiners using different techniques. Thus, they postulated that the increase in systolic blood pressure was probably not clinically relevant with the systemic bevacizumab administration. In our study, the blood pressure measurements were performed by the same investigator using the same technique as mentioned in Table 1.

Rich *et al*[17] monitored the blood pressure for 3 months after intravitreal bevacizumab administration for the treatment of neovascular AMD and reported that there was no apparent change in systolic and diastolic blood pressure levels at months 1 and 2. The mean systolic blood pressure was increased from 131 mmHg at baseline to 148 mmHg at month 1, whereas the mean diastolic blood pressure (80 mmHg) remained unchanged. Gragoudas *et al*[18] reported the incidence of hypertensive disorders as 10% after the use of pegaptanib sodium for 1 year. On the other hand, the analysis of 248 patients with hypertension and other cardiovascular risk factors in ASCOT trial showed a positive correlation between more severe hypertension and higher serum VEGF levels.[19–22] This is a paradoxical finding as lower serum VEGF levels might predispose to a hypertensive state. However, total VEGF levels were measured instead of free VEGF levels in the study. The authors suggested that the increased VEGF levels were secondary to endothelial cell injury. Another interesting finding of this study was that serum VEGF levels were significantly reduced after 6 months of intensive cardiovascular risk factor management. These findings are consistent with the hypothesis that higher levels of VEGF are produced in response to endothelial trauma and that improved blood pressure control would lead to reduced VEGF levels.

Bakri *et al*[23] showed the presence of small amounts of bevacizumab in the fellow uninjected eye in rabbits after intravitreal bevacizumab injection. The drug concentration in the aqeous humour was higher than in the vitreous humour in the fellow eye at different time points. This finding implies that bevacizumab enters the eye from the systemic circulation through the anterior route, where it diffuses into the vitreous, rather than entering the choroidal blood flow.

The major systemic adverse events associated with bevacizumab therapy in cancer patients include

drug-induced hypertension and a doubling of the thromboembolic risk. In our study, blood pressure was increased in both groups at week 3 following the injection, and normalised at week 6 in patients without medication while persisting in some of the patients using antihypertensive medication. This may depend on the clearence of the drug from systemic circulation. In conclusion, this study shows that there is a risk of disregulation of blood pressure levels or persistence of hypertension in hypertensive patients after intravitreal bevacizumab injections. Thus, cardiological consultation is recommended before intravitreal bevacizumab injections, especially for hypertensive patients under medication with the antihypertensive drugs.

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