Original Research

Influence of Intravitreal Injection of Bevacizumab on Systemic Blood Pressure Changes in Patients with Exudative Form of Age-Related Macular Degeneration

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Bevacizumab, age-related macular degeneration, hypertension, gender.

Introduction: The aim of our study was to examine blood pressure (BP) changes in hypertensive and non-hypertensive patients after intravitreal bevacizumab injections and to assess whether intravitreal bevacizumab carries an associated vascular risk in patients with exudative ocular disease. We also aimed to estimate the influence of gender.

Methods: The study included 57 patients with age-related macular degeneration who received an intravitreal injection of 1.25 mg (0.1 mL) of bevacizumab. We analyzed systolic and diastolic BP values separately. Patients were divided into males and females, and into hypertensives and normotensives based on their BP values. BP was measured before bevacizumab administration, and 10 minutes, 1 hour, 2 days, 7 days and 6 weeks after the injection.

Results: Males had a statistically significant decline in systolic BP values 1 hour and 6 weeks after drug administration ($p<0.05$). The most notable significant decline in diastolic BP values was for males and for normotensive participants 1 hour after drug administration ($p<0.05$), while the most notable decline in diastolic BP values for females and for hypertensive participants was 7 days after drug administration, with statistical significance only for hypertensive patients ($p<0.01$). For males it was noticed that a statistically significant decline in diastolic BP persisted after 6 weeks ($p<0.05$).

Conclusions: An intravitreal bevacizumab injection is safe as regards BP changes over 6 weeks post administration. Regular follow up for 6 weeks should be mandatory in order to promptly recognize individuals who have changes in BP values and include them in BP treatment in order to prevent complications.

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In the treatment of neovascular and exudative ocular diseases, off-label intravitreal injections of bevacizumab have been administered since May 2005.[1,2] When using a product for an indication not included in the approved label, doctors have the responsibility to be well informed about the product and its potential risks, and to base its use on firm scientific rationale and sound medical evidence.[3,4] Previously, it was noticed that the most concerning drug-related adverse events after high dose systemic intravenous bevacizumab application are hypertension and an increase in thromboembolic risk, including myocardial infarction and cerebrovascular accidents.[5] The intravitreal administration of bevacizumab was introduced in an effort to minimize these potential systemic side effects.[6] Intravitreal bevacizumab injection has been reported to be a safe procedure in terms of

blood pressure (BP) for both hypertensive and non-hypertensive patients,[7-9] but other studies pointed out several cases of acute elevation of systemic BP, cerebrovascular accidents, myocardial infarction, and transient ischemic attack.[10,11] The observer bias must be assumed to be high, because there was no standard and systematic method of measuring parameters such as BP[12] and other adverse events following the intravitreal administration of bevacizumab.

Therefore, the aim of our study was to examine BP changes in hypertensive and non-hypertensive patients after intravitreal bevacizumab injections and to assess whether intravitreal bevacizumab carries an associated vascular risk in patients with exudative ocular disease. In addition, we aimed to estimate the effect of gender on the intravitreal administration of bevacizumab.

Methods

This prospective study included 57 eligible patients who received an intravitreal injection of 1.25 mg (0.1 mL) bevacizumab at the Medical Retina Department of the University Eye Clinic in Belgrade, Serbia, between May 2010 and December 2011. The study was approved by the Ethics Committee (Institutional Review Board of Clinical Centre of Serbia in Belgrade, Serbia) and the Ministry of Health of the Republic of Serbia. Informed and signed consents from all patients were obtained after they were given a sheet with information about the potential risks and complications of the procedure and were forewarned that the drug was off-label. They were also informed about the prognosis of their illness and the benefits of bevacizumab prior to inclusion.

The criteria for the inclusion of eligible participants were: acute choroidal neovascularization in the exudative form of age-related macular degeneration (AMD). Patients who had been previously diagnosed with cerebrovascular disease (i.e. stroke or transient ischemic attack within 12 months before the injection) or who had uncontrolled systemic arterial hypertension (BP≥160/100 mmHg) at the time of drug administration were excluded. Patients with hypertension who were included in the study were under controlled antihypertensive treatment and had obtained permission for bevacizumab treatment from a board-certified cardiologist. The treatment regimens included the following: angiotensin-converting enzyme (ACE) inhibitors or angiotensin (AT) inhibitors alone were administered in 10 (27.78%) patients, whereas ACE/AT inhibitors along with diuretics were given in 12 (33.33%). Ca antagonists alone were given in 4 (11.11%) patients, diuretics alone in 3 (8.33%), and beta-blockers alone in 2 (5.56%). A diuretic along with beta-blockers was given in 5 (13.89%).

All participants had been previously screened by a retinologist. They were given the bevacizumab intravitreally if they had signs of an active neovascular membrane, according to fluorescein angiography and optical coherence tomography. Patients were evaluated ophthalmologically every month and were injected every 4 to 6 weeks, since the intravitreal concentration of the drug declines after a period of 4 weeks. The eligible participants included in our study were those patients who underwent 3 courses of bevacizumab administration during the 4-6 week cycles.

After sterile draping and rinsing with topical 5% povidone-iodine, topical anesthesia was provided with 1% tetracaine hydrochloride eye drops. The intravitreal bevacizumab injection was performed at the 8 o'clock position of the *pars plana* with a sharp, 26-27 prescribed gauge needle. After the injection, 0.3% ciprofloxacin eye drops were prescribed for the patients 4 times over 7 days. Blood pressure was measured before bevacizumab administration (T1), 10 minutes (T2), 1 hour (T3), 2 days (T4), 7 days (T5) and 6 weeks (T6) after the injection, during each course of treatment, and obtained values were divided by 3. All patients were fully assessed ophthalmologically on the second day after drug administration, and 1 week, 4-6 weeks, and every month after the procedure until the completion of the treatment course.

We analyzed systolic and diastolic BP values separately, and patients were divided into two groups based on gender (male and female) and BP values (hypertensive and normotensive). Hypertension in adults, according to the latest recommendations, is defined as systolic BP values ≥140 mmHg and/or diastolic BP ≥90 mmHg.[13] Patients also attended checkups by a cardiologist 4-6 weeks after intravitreal injection.

Statistical analysis

Results are presented as mean values with standard deviation (SD). The unifactorial ANOVA test was used to test the difference in BP during the course of treatment. Student's t-test was used to test the difference in BP at different time points. The chi-squared test was performed for statistical evaluation of the gender distribution in hypertensive and normotensive patients. Statistical significance was set at $p<0.05$.

Results

There were 30 (52.63%) males and 27 (47.37%) females. Normotensive participants comprised 21 (36.84%) patients while 36 (63.16%) of the evaluated population were hypertensive. Mean values of systolic BP are presented in Table 1 separately for males and females and for hypertensive and normotensive groups at the different follow-up points. There was a notable decline in systolic BP values in both males and females, as well as in the normotensive and hypertensive groups of participants, 1 hour after drug administration, although the decrease was not significant except in males (Tables 1 & 2). Systolic hypertension was more frequent in males (58.33%), although the difference was non-significant (chi-squared 2.000, $p>0.05$; Tables 1 & 2).

Males showed a statistically significant decline in systolic BP values 1 hour and 6 weeks after drug administration ($p<0.05$), while such a significant decline was not observed in females (Table 2). Concerning the presence of hypertension, we found non-significant changes in the mean values of systolic BP at follow up (Table 2).

There was no significant difference in systolic BP values between genders in either the normotensive or hypertensive group over the course of treatment (Table 3). The ANOVA test of variance confirmed that there were no significant changes in systolic BP values for males and females in the normotensive group at the different time points during treatment (Table 3). The same applied to males and females in the hypertensive group (Table 3).

The mean values of diastolic BP are presented in Table 1 separately for males and females, and for the hypertensive and normotensive groups, at the different follow-up points. There was a notable and statistically significant decline in diastolic BP values for males and for normotensive participants 1 hour after drug administration ($p<0.05$, Tables 1 & 2), while the most notable decline in diastolic BP values for females and for hypertensive participants was 7 days after drug administration, with statistical significance only for hypertensive patients ($p<0.01$, Tables 1 & 2). For males it was noticed that the statistically significant decline in diastolic BP persisted after 6 weeks ($p<0.05$, Table 2). As with systolic BP, diastolic hypertension was more frequent in males (55.56%), although the difference was non-significant (chi-squared 0.889, $p>0.05$; Tables 1 & 2).

There was no significant difference in diastolic BP values between genders, in either the normotensive or hypertensive group, over the course of treatment (Table 3). The ANOVA test of variance confirmed that there were no significant changes in diastolic BP values for males and females in the normotensive group at the different time points during treatment (Table 3). The same applied for males and females in the hypertensive group (Table 3).

Discussion

The present study shows that after intravitreal bevacizumab administration there were no significant changes in systolic BP in either the hypertensive or normotensive group of participants over the entire follow-up period. However, in the hypertensive group of participants a significant decline in diastolic BP values was observed 7 days after the intravitreal bevacizumab injection, whereas such a significant difference was not present 6 weeks after drug administration. For the normotensive group of participants, a significant decline in diastolic BP was noticed one hour after bevacizumab injection, but significance was not observed in later checkups. Such findings could suggest that diastolic BP in both hypertensive and normotensive groups of participants who were diagnosed with AMD might be more sensitive to intravitreal bevacizumab administration. Such sensitivity seems to be present early in the normotensive group and could be explained by the fact that blood vessels in the normotensive population have preserved their physiological function in terms of vasodilatation and vasoconstriction and thus respond more promptly to an intravitreal bevacizumab injection.

In the study of Sane et al, it was stressed that hypertension could be a disease of inappropriate response to angiogenic growth factors (AGF).[14] There is a positive correlation between more severe hypertension and higher vascular endothelial growth factor (VEGF) in hypertensive patients.[15] Therefore, therapy that includes inhibition of VEGF could be effective, particularly in patients with AMD, in preserving adequate visual function. Since it has been suggested that VEGF could have a significant influence on pathological conditions of the posterior pole, particularly with reference to macular edema and/or intraocular neovascularization, it is important to stress that control of VEGF could be one of the possible treatment modes in the therapy of patients with AMD.[10] One of the drugs that is used in the treatment of these patients is off-label bevacizumab.[1-3] It

Table 1. Gender distribution and mean values of systolic and diastolic blood pressure at different times of follow up.

Systolic (mmHg)	Male gender n=30	Female gender n=27	Normotensive group n=21	Hypertensive group n=36
T1	127.17 ± 15.57	121.85 ± 15.45	115.71 ± 15.02	130.14 ± 13.50
T2	127.33 ± 18.37	120.19 ± 15.35	109.50 ± 13.95	131.81 ± 13.64
T3	117.17 ± 15.41	118.89 ± 16.43	107.62 ± 13.38	124.03 ± 13.93
T4	121.83 ± 18.22	123.89 ± 17.12	110.71 ± 10.99	129.86 ± 16.92
T5	125.33 ± 15.92	121.30 ± 17.63	113.81 ± 13.96	129.03 ± 15.76
T6	119.67 ± 10.58	125.74 ± 13.35	116.67 ± 8.99	125.97 ± 12.70
Males (%)			9 (42.86%)	21 (58.33%)
Females (%)			12 (57.14%)	15 (41.67%)
Diastolic (mmHg)	Male gender n=30	Female gender n=27	Normotensive group n=21	Hypertensive group n=36
T1	80.00 ± 8.71	76.48 ± 8.75	75.24 ± 8.58	80.14 ± 8.58
T2	79.83 ± 10.04	77.04 ± 9.73	73.33 ± 7.13	81.53 ± 10.13
T3	74.50 ± 10.53	73.70 ± 12.14	68.57 ± 7.93	77.36 ± 11.68
T4	76.17 ± 11.50	76.67 ± 7.72	71.43 ± 6.55	79.31 ± 10.29
T5	77.00 ± 9.61	73.33 ± 10.65	73.33 ± 10.17	76.39 ± 10.18
T6	75.50 ± 6.07	77.96 ± 6.54	73.81 ± 4.72	78.33 ± 6.65
Males			10 (47.62%)	20 (55.56%)
Females			11 (52.38%)	16 (44.44%)

Table 2. Statistical interpretation (t-test values) of systolic and diastolic blood pressure changes and gender distribution regarding the time of evaluation.

Systolic (mmHg)	Male gender n=30	Female gender n=27	Normotensive group n=21	Hypertensive group n=36
T1 / T2	0.04	0.40	1.39	0.52
T1 / T3	2.50*	0.68	1.84	1.89
T1 / T4	1.22	0.46	1.23	0.08
T1 / T5	0.45	0.12	0.42	0.32
T1 / T6	2.18*	0.99	0.25	1.35
ANOVA (F value)	2.092	0.658	1.652	1.447
Males/females (chi-squared)			0.857	2.000
Diastolic (mmHg)	Male gender n=30	Female gender n=27	Normotensive group n=21	Hypertensive group n=36
T1 / T2	0.07	0.22	0.78	0.63
T1 / T3	2.20*	0.97	2.62*	1.15
T1 / T4	1.45	0.08	1.62	0.37
T1 / T5	1.27	1.19	0.66	2.99†
T1 / T6	2.32*	0.70	0.67	1.21
ANOVA (F value)	1.707	1.086	1.919	1.342
Males/females (chi-squared test)			0.095	0.889

*$p<0.05$; †$p<0.01$

was stated previously that a major side effect of bevacizumab is hypertension.[14] The mechanism of action of bevacizumab as a VEGF inhibitor is via its influence on NO metabolism (diminishing NO synthesis). Since NO is a vasodilator, such a mechanism will increase peripheral resistance and, ultimately, increase BP.[16] However, our initial findings indicated that intravitreal administration of bevacizumab was not associated with any significant increase in BP values over the follow-up period of the study.

It is important to underline that the majority of patients with AMD are seniors with other comorbidities, increased BP values in particular (different degrees of hypertension). Therefore, special attention should be paid to such a population when off-label bevacizumab is administered, in order to prevent pos-

Table 3. Gender distribution and mean values of systolic and diastolic blood pressure at different times of follow up.

Systolic (mmHg)	Normotensive group			Hypertensive group		
	Male gender n=9	Female gender n=12	t-test values	Male gender n=21	Female gender n=15	t-test values
T1	119.23 ± 14.39	113.21 ± 15.11	0.92	134.79 ± 12.68	127.62 ± 13.61	1.62
T2	111.41 ± 14.84	109.03 ± 13.76	0.38	134.15 ± 14.52	128.92 ± 13.27	1.10
T3	106.93 ± 12.52	108.03 ± 13.34	0.19	127.93 ± 13.72	122.83 ± 14.03	1.09
T4	109.76 ± 11.28	111.02 ± 10.87	0.26	131.76 ± 17.03	128.86 ± 16.72	0.51
T5	114.72 ± 14.07	112.96 ± 12.73	0.30	130.11 ± 15.04	128.94 ± 15.68	0.23
T6	117.39 ± 9.62	116.06 ± 8.12	0.34	126.83 ± 13.16	125.04 ± 12.56	0.41
ANOVA test	1.192	0.672	-	1.058	0.472	-
Diastolic (mmHg)	Normotensive group			Hypertensive group		
	Male gender n=10	Female gender n=11	t-test values	Male gender n=20	Female gender n=16	t-test values
T1	77.28 ± 8.85	74.03 ± 7.92	0.89	82.73 ± 8.94	79.42 ± 7.95	1.16
T2	74.62 ± 7.51	73.08 ± 7.06	0.48	83.02 ± 10.06	79.83 ± 11.02	0.91
T3	68.63 ± 7.29	68.44 ± 8.17	0.06	77.05 ± 10.97	77.95 ± 11.86	0.24
T4	71.95 ± 6.93	70.98 ± 6.11	0.34	78.69 ± 9.32	80.17 ± 11.07	0.44
T5	74.08 ± 10.21	73.14 ± 9.97	0.21	75.97 ± 9.64	77.52 ± 10.93	0.45
T6	74.12 ± 4.98	73.25 ± 4.32	0.43	79.84 ± 7.13	77.87 ± 5.98	0.88
ANOVA test	1.393	0.857	-	1.896	0.208	-

sible side effects involving an eventual additional increase in BP.

Previous studies have shown that possible side effects could be present if bevacizumab is administered by infusion, particularly within the first 6 weeks, in terms of a mild elevation of BP.[6] Nevertheless, while intravitreal administration of bevacizumab showed acute elevation of systemic BP in study participants in some cases, Wu et al concluded that the drug was safe and well tolerated within the first year of follow up after intravitreal administration.[10]

In order to evaluate possible gender differences concerning BP changes in patients who were treated with intravitreal bevacizumab, we analyzed males and females separately, for both systolic and diastolic BP values. We found that males were more sensitive to intravitreal bevacizumab administration, in terms of both systolic and diastolic BP values, and especially one hour and 6 weeks after drug injection. Such significant changes were not noticed in females who underwent intravitreal bevacizumab treatment. Further, we have shown that there were no significant differences in BP values (systolic and diastolic BP) between genders in either the normotensive or the hypertensive group of participants. These findings suggest that males are more sensitive in terms of both systolic and diastolic BP changes, but further studies with a larger number of participants are needed to evaluate the exact role of gender and its influence on potential sensitivity to intravitreal bevacizumab injection.

However, based on the ANOVA test that was performed in our study, it is important to stress that for both males and females non-significant changes in both systolic and diastolic BP values were noticed over the entire period of follow up.

Given the facts above, even though the study group encompassed a small number of participants, our initial findings demonstrated to a certain degree that intravitreal bevacizumab injection is safe concerning BP changes over 6 weeks post administration. Further, it should be underlined that regular follow up over 6 weeks should be mandatory in order to promptly recognize individuals who have changes in BP values and include them in BP treatment in order to prevent eventual complications.

The main study limitation was the small number of eligible patients; therefore, further investigations are needed with a larger population of both normotensive and hypertensive patients.

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