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CLINICAL STUDY

Blood pressure changes after intravitreal bevacizumab in patients grouped by ocular pathology

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Abstract

Purpose **We evaluated the effects of intravitreal injection of bevacizumab (Avastin; Novartis, Basel, Switzerland) on blood pressure (BP) in the context of ocular vascular pathology.**
Methods **This study retrospectively examined 135 consecutive patients treated with intravitreal injections of 1.25 mg bevacizumab for retinal vascular disease; there were 61 cases of diabetic retinopathy, 30 of retinal vein occlusion, 35 of choroidal neo-vascularization (CNV), and 9 of other retinal vascular diseases. BP was measured before injection and at 30 min, 1 day, 1 week, 3 weeks, and thereafter monthly over a 6-month period.**
Results **In the CNV group, 30-min post-injection systolic values were significantly higher than baseline, and systolic and diastolic values after 1 day, 1 week, and 3 weeks were significantly lower than before injection. No other pressure measurement differed significantly from baseline values in the other groups.**
Discussion **Intravitreal bevacizumab injection is safe in terms of its effect on BP, regardless of ocular pathology.**

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Keywords: Avastin; bevacizumab; blood pressure; ocular pathology

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Introduction

Bevacizumab (Avastin; Novartis, Basel, Switzerland) has shown efficacy in retinal vascular diseases, such as diabetic retinopathy (DR), retinal vascular occlusion (RVO), and choroidal neo-vascularization (CNV).[1–4] The pathologic mechanisms of these diseases differ in detail, but many studies have indicated that vascular endothelial growth factor (VEGF) has an important function in ocular neo-vascularization.[5,6] Data have been obtained implicating VEGF in the pathologic vascular growth seen in DR, retinal vein occlusion, iris neo-vascularization, and age-related macular degeneration (AMD).[7–11]

Although the specific mechanism is unknown, VEGF inhibition is known to induce hypertension- and hypertension-related systemic complications in patients. Intravitreal bevacizumab injection was introduced to avoid such systemic complications; however, ocular adverse reactions have been observed, including transiently elevated intraocular pressure (IOP) and endophthalmitis.[12,13] Systemic side effects were associated with the intravitreal injection of bevacizumab such as rise in blood pressure (BP), cerebrovascular accidents, myocardial infarction, transient ischemic attacks, and deep vein thrombosis.[12,13] A recent study found that bevacizumab treatment caused endothelial dysfunction and reduced the number of microvessels; these closely associated effects could be responsible for the increase in BP.[14] We postulated that intravitreal bevacizumab injection might differentially influence BP, depending on the type of ocular pathology present, which might reflect differences in systemic disease and/or in the age of the affected patient populations.

Thus, this study retrospectively examined BP changes after intravitreal bevacizumab injection in patients with DR, RVO, CNV, and other retinal vascular disorders.

Materials and methods

Patients treated with intravitreal bevacizumab injection from May 2007 to February 2008 were

included. We obtained informed consent for the administration of intravitreal bevacizumab injection from all participants, after giving them detailed information about the potential risks and benefits of the procedure, and the off-label nature of the treatment. Patients with known hypertension consulted with the staff in our department of cardiology, to verify their BP status before injection, and those with a history of cerebrovascular attack consulted with the staff in neurology. Exclusion criteria were as follows: patients using anti-glaucomatic agents, those earlier treated with vitrectomy, those with poorly controlled hypertension after consultation with a cardiologist, and those who did not complete their final follow-up. Patients with intravitreal injection of triamcinolone within earlier 4 months were excluded too. The study was approved by the local institutional review board. All procedures conformed to the Declaration of Helsinki for research involving human subjects.

The procedure was performed aseptically in an operating room. Lidocaine (4%) was administered topically for local anaesthesia, and 1.25 mg of bevacizumab was injected at the inferior temporal sclera (3.5 mm from the limbus) into the vitreous cavity, using a 30-gauge needle. The fundus was examined using an indirect ophthalmoscope to confirm the perfusion of the optic nerve head, and each patient was instructed to take an oral antibiotic (cefdinir), and to apply a topical antibiotic (levofloxacin) for 1 week post-operatively.

The patients were asked to rest in a comfortable sitting position for at least 5 min before measuring their systolic and diastolic BP before injection, and again at 30 min and 1 h after injection, using a BP-203RV III monitor (OMRON Healthcare Co. Ltd, Tokyo, Japan). Follow-up examinations were performed 1 day, 1 week, 3 weeks, 1 month, and then every month until 6 month-post-injection to measure BP in the same manner. Slit lamp and fundus examinations were performed at each visit.

To minimize the effect of diurnal variation on BP, baseline measurements were taken 1–2 h before the procedure, and the intravitreal bevacizumab injection and follow-up examinations were performed in the afternoon (1500 and 1700 hours).

Statistical analyses were performed using SPSS (Windows version 13.0, SPSS Inc., Chicago, IL, USA). One-way ANOVA was used to examine any differences in baseline characteristics among groups, and Wilcoxon's signed rank test was used to reveal any changes in systolic and diastolic BP after injection, relative to pre-injection baseline values. P-values <0.05 were deemed to indicate statistical significance. Where a patient received more than one injection, statistical analysis was limited to data from the eye receiving the first injection.

Results

Over a 6-month period, a total of 185 eyes in 135 patients seen in our department received intravitreal bevacizumab injection; of these, 50 patients (37%) received repeated injection in the same eye (14 patients) or in the other eye (36 patients) over a mean period of 2 months. Only the first eye injected per patient was used in the statistical analysis, so that 135 eyes in 135 patients were included in this study. These were divided into groups of DR, RVO, CNV, or other diseases (central serous chorioretinopathy, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, etc). More specifically, bevacizumab was given for macular oedema (78.7%) and neo-vascularization (21.3%) in the DR group, 83.3 and 16.7% in the RVO group, respectively.

The basic characteristics of the patients did not differ significantly among groups, except in the presence of underlying hypertension and diabetes mellitus (Table 1). The incidence of hypertension was significantly lower in

Table 1 Baseline characteristics of patients with different ocular pathologies receiving intravitreal bevacizumab injections

Basic characteristics (N = *eyes)*	*DR group* (N = *61)*	*RVO group* (N = *30)*	*CNV group* (N = *35)*	*Others* (N = *9)*	*Total* (N = *135)*
Age (years)					
Mean ± SD	56.92 ± 11.93	56.20 ± 12.98	57.86 ± 14.53	62.44 ± 11.82	57.37 ± 12.82
Range (minimum, maximum)	(26, 76)	(30, 81)	(31, 88)	(44, 73)	(26, 88)
Gender					
Male	28 (45.9%)	13 (43.3%)	22 (62.9%)	5 (55.6%)	68 (50.4%)
Female	33 (54.1%)	17 (56.7%)	13 (37.1%)	4 (44.4%)	67 (49.6%)
Underlying diseases					
Hypertension	30 (49.2%)	19 (63.3%)	7 (20.0%)*	5 (55.6%)	61 (45.2%)
Diabetes	61 (100.0%)*	6 (20.0%)	8 (22.9%)	2 (22.2%)	76 (56.3%)
Stroke	5 (8.2%)	2 (6.7%)	2 (5.7%)	0 (0.0%)	9 (6.7%)

CNV, choroidal neo-vascularization; DR, diabetic retinopathy; RVO, retinal vascular occlusion; SD, standard deviation.
*Significant difference among groups (one-way ANOVA, $P<0.05$).

Table 2 Mean systolic blood pressure change (mm Hg) in patients grouped by ocular pathology

Group	*Baseline*	*30 min after injection*	*1 h*	*1 day*	*1 week*	*3 weeks*	*2 months*	*6 months*
DR	135.51 ± 19.00	136.30 ± 21.38	131.57 ± 21.15	136.89 ± 22.35	135.34 ± 20.56	136.63 ± 19.47	137.95 ± 20.74	136.46 ± 16.59
RVO	133.60 ± 15.79	137.07 ± 20.24	129.10 ± 17.13	132.60 ± 14.93	133.73 ± 14.22	137.17 ± 15.85	129.30 ± 17.55	135.12 ± 13.04
CNV	128.40 ± 15.37	132.06 ± 16.89*	129.29 ± 20.28	122.46 ± 15.28*	123.43 ± 17.08*	125.00 ± 19.05*	124.96 ± 14.67	129.75 ± 16.14
Others	125.44 ± 11.07	129.56 ± 11.10	131.22 ± 15.61	125.00 ± 14.47	124.56 ± 9.40	123.75 ± 17.03	125.34 ± 14.35	128.43 ± 10.93
Total	132.57 ± 17.17	134.92 ± 19.47	130.41 ± 19.60	131.40 ± 19.53	131.18 ± 18.45	132.64 ± 19.26	132.05 ± 18.73	134.24 ± 15.29

CNV, choroidal neo-vascularization; DR, diabetic retinopathy; RVO, retinal vascular occlusion.
*Significant change compared with baseline measurement (Wilcoxon's signed rank test, $P<0.05$).

Table 3 Mean diastolic blood pressure change (mm Hg) in patients grouped by ocular pathology

Group	*Baseline*	*30 min after injection*	*1 h*	*1 day*	*1 week*	*3 weeks*	*2 months*	*6 months*
DR	79.38 ± 11.20	80.08 ± 12.03	77.89 ± 12.81	80.13 ± 11.21	79.30 ± 12.24	80.10 ± 11.82	80.48 ± 12.20	83.46 ± 9.94
RVO	83.70 ± 10.98	85.87 ± 12.55	82.77 ± 12.17	81.53 ± 12.59	83.83 ± 8.78	84.00 ± 9.55	79.85 ± 12.70	81.25 ± 6.36
CNV	79.91 ± 12.10	80.17 ± 13.52	79.40 ± 13.96	75.46 ± 12.06*	74.74 ± 12.45*	77.33 ± 12.26*	75.43 ± 10.44	78.13 ± 13.93
Others	81.00 ± 11.79	83.22 ± 11.09	81.22 ± 12.11	77.44 ± 8.55	81.56 ± 9.08	78.50 ± 11.36	83.64 ± 10.82	80.24 ± 9.83
Total	80.59 ± 11.43	81.60 ± 12.59	79.59 ± 12.94	79.05 ± 11.71	79.27 ± 11.77	80.05 ± 11.56	79.26 ± 12.17	81.38 ± 10.30

CNV, choroidal neo-vascularization; DR, diabetic retinopathy; RVO, retinal vascular occlusion.
*Significant change compared with baseline measurement (Wilcoxon's signed rank test, $P<0.05$).

the CNV group, whereas that of diabetes was significantly higher in the DR group, relative to other groups ($P<0.05$).

The mean systolic and diastolic BP measured preoperatively was 132.57 ± 17.17 and 80.59 ± 11.43 mm Hg, respectively. There was no significant difference in mean baseline systolic or diastolic BP between the groups (systolic, $P=0.14$; diastolic, $P=0.39$; Tables 2 and 3).

Mean systolic BP was increased significantly from baseline values at 30 min after intravitreal bevacizumab injection in the CNV group ($P=0.023$; Figure 1c). This group then showed significant decreases in systolic and diastolic BP from baseline values at 1 day (systolic, $P=0.014$; diastolic, $P=0.005$), 1 week (systolic, $P=0.023$; diastolic, $P=0.001$), and 3 weeks after injection (systolic, $P=0.015$; diastolic, $P=0.001$), but no significant change was found after 2 months (Figure 1c). None of the other groups showed any significant post-treatment change in BP (Figures 1a–d). No hypertensive crisis was reported in any of the groups during the 6-month follow-up period (Tables 2 and 3).

Discussion

Recent studies have revealed the efficacy of intravitreal bevacizumab injection, which is widely used for many chorioretinal vascular disorders.[1,3,4] Although many studies have investigated the elevation of IOP and BP after intravitreal bevacizumab,[12,13,15,16] none has evaluated its effects on BP in relation to the specific ocular pathology present. The mechanism by which inhibition of VEGF induces hypertension is unclear, but a recent study reported that endothelial dysfunction and capillary rarefaction are closely associated with the observed increase in BP.[14] This led us to ask how bevacizumab injection influenced BP in patient groups with differing ocular pathologies, among whom both the presence of systemic disease and the mean age of patients might be expected to differ.

In this study, CNV group showed a significant increase in systolic BP at 30 min after intravitreal bevacizumab injection, followed by significant decreases in systolic and diastolic BP at follow-up visits from 1 day to 3 weeks after injection. There was no other significant change in BP after injection in the other groups. The change seen in the CNV group may have been due to diurnal physiological changes, or may have been a response to the easing of surgery-related stress, as reported by Kernt *et al*.[15] The strict regulation of vascular tone by anti-hypertensive drugs in patients would be expected to reduce the chances of pre- or post-operative BP changes resulting from emotional stress, white coat syndrome, or diurnal variation. It might be suggested that the measured BP in the CNV group was more influenced by the factors mentioned above, relative to that seen in the other groups, because it included fewer hypertensive patients. This hypothesis can be supported by an earlier study reported by Lee *et al*,[16] for which similar results were obtained from evaluating the changes in BP in

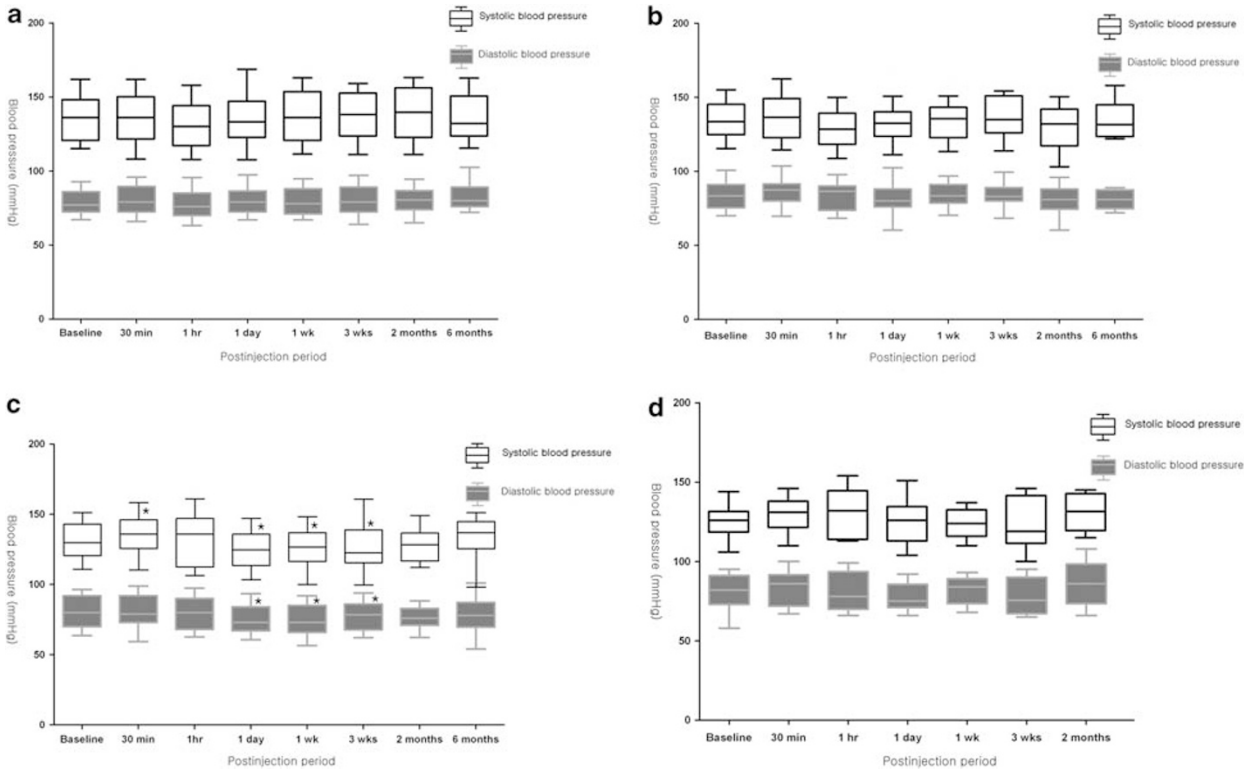

Figure 1 BP change in the DR group (a), the RVO group (b), the CNV group (c), and the group with other diseases (d), after a single 1.25 mg intravitreal injection of bevacizumab. The boxplot depicts the 50% interquartile range for BP among the patients. Error bars indicate SD. *Significant change, relative to baseline measurement ($P<0.05$).

patients with and without hypertension after intravitreal bevacizumab injection with the same population group.

Regardless, the initial increase of BP at 30 min after injection reported in the CNV group might reflect the emotional stress associated with the procedure rather than adverse effects of anti-VEGF therapy, because the maximal serum concentration of bevacizumab after intravitreal injection is reached at post-operative day 8, according to an animal study.[17] Although it is difficult to directly compare the pharmacokinetics of bevacizumab seen in rabbit model with that in human beings, it is suspected that systemic exposure may be less in human beings because of their larger serum compartment.[17] The pharmacokinetic data of serum concentration of bevacizumab after intravitreal injection from two hypertensive patients were reported, and peak serum levels of bevacizumab were 86.5 and 59.8 ng/ml at post-injection hours 120 and 168, respectively.[18] Taken these together, the increase in the 30-min systolic BP values was probably not because of the adverse effects of anti-VEGF therapy.

Limitations of this study include the relatively small sample size and the use of single BP measurement. Ambulatory BP monitoring has been proved to be clinically superior, compared with single sphygmomanometric measurements. However, the use of ambulatory BP monitoring to detect a rise after intravitreal bevacizumab injection is not practical and convenient for patients, considering that Mourad *et al*[14] recently reported that a significant increase in BP after systemic bevacizumab treatment (mean cumulative dose: 3.16 g) is known to occur after 6 months because of microvascular rarefaction and inhibition of NO pathway. Importantly, our results are similar to those of an earlier study using devices for automatic 24-h recording of circadian BP after intravitreal bevacizumab injection.[18] BP shows high intra- and interindividual variability, as well as diurnal changes.[19] In this study, baseline measurements were taken 1–2 h before the procedure, and follow-up examinations were performed in the afternoon, to minimize the effect of diurnal variation on BP.

It would have been very useful to analyse any differences in BP patterns of change according to CNV pathology and a diagnosis of hypertension. As risk factors of AMD include age and cardiovascular risk factor, the basic characteristics of patients with CNV caused by AMD would be different from that of patients with CNV secondary to other diseases. Taken these facts into account in the analysis, the results would have been

different. However, the number of patients in this study may still be too small to obtain any statistically meaningful results by such an analysis. Further studies with a larger sample size are needed to clarify this matter.

In conclusion, we have shown that intravitreal bevacizumab injection seems to be safe in terms of its effect on BP, regardless of ocular pathology.

Summary

What was known before
- VEGF inhibition is known to induce hypertension- and hypertension-related systemic complications in patients.
- Bevacizumab treatment was reported to cause endothelial dysfunction and reduce the number of microvessels.

What this study adds
- Intravitreal bevacizumab injection induced transient, but not significant changes in BP, regardless of ocular pathology.
- Intravitreal bevacizumab injection is expected to be safe for patients with well-controlled hypertension.

Conflict of interest

The authors declare no conflict of interest.

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The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/zhAJMj.

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