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THE EFFECT OF INTRAVITREAL AVASTIN ON SYSTEMIC BLOOD PRESSURE IN CONTROLLED HYPERTENSIVE PATIENTS

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SUMMARY: To study the effect of intravitreal avastin on systemic blood pressure in controlled hypertensive patients.

This is a retrospective study to evaluate blood pressure changes in hypertensive patients with ischemic ocular pathologies after a 0.05 ml (1.25 mg) intravitreal avastin injection. It included 40 patients with retinal vascular diseases; their blood pressure was measured before the treatment (IVA) as a baseline, and then it was measured after1 day, 1 week, 4 weeks, and then monthly for at least 3 months. All patients were given the same concentration of avastin intravitreally (0.05 ml), and their blood pressure was measured in supine position using the digital sphygmomanometer.

The elevation in blood pressure was noted in 90% of the patients from the baseline on the first day postinjection. No significant changes were observed on blood pressure in 1 week, 4 weeks, and other readings postinjection.

Treating ocular vascular diseases with intravitreal avastin is safe in controlled hypertensive patients.

Key words: avastin, systemic blood pressure, ocular pathology, digital sphygmomanometer.

INTRODUCTION

Avastin (bevacizumab) is an angiogenesis inhibitor drug that acts on protein called vascular endothelial growth factor (VEGF); this protein is important in the formation of new blood vessels. It is a recombinant human monoclonal antibody against VEGF, and has been used systemically for the treatment of certain tumors (1), including colorectal carcinoma, renal cell carcinoma, and breast carcinoma, and intravitreally for the treatment of certain ocular vascular diseases such as diabetic retinopathy (2), retinal vascular occlusion (3), choroidal neovascularizations (age-related macular degeneration) (4), neovascular glaucoma, and retinopathy of prematurity (5).

One of the common complications of systemic avastin treatment is hypertension (6). The mechanism by which the anti-VEGF drugs increase the systemic blood pressure is incompletely understood, but it is believed to be that VEGF increases nitric oxide (NO)-synthase expression by the activation of protein kinase-C pathway and leads to increase in arterial pressure. Other systemic complications include the followings: cerebrovascular accident, myocardial infarction, transient ischemic attack, deep vein thrombosis,

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Table 1: Definitions and Classification of Blood Pressure Levels.

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
Normal	<130	<85
High – Normal	130–139	85–89
Grade 1 Hypertension ("mild")	140–159	90–99
Grade 2 Hypertension ("moderate")	160–179	100–109
Grade 3 Hypertension ("severe")	180	110

delay in wounds healing, gastrointestinal perforation, and serious bleeding.

Side effects of intravitreal bevacizumab injection are rare (7), which include transient elevation in intraocular pressure (IOP), infections (endophthalmitis), uveitis, vitreous hemorrhage, and retinal detachment (tractional or rhegmatogenous).

The patients were graded according to the blood pressure values described in 1999 WHO–ISH guideline for the management of hypertension (Table 1) (8).

This study was carried out to evaluate the effect of intravitreal avastin treatment on systemic blood pressure in patients with controlled hypertension, keeping in mind the difference in avastin concentration between intravitreal and systemic administrations.

MATERIALS AND METHODS

Forty patients, presented in our clinic in King Hussein Medical Centre from March to August 2011, were included in this study. They had ocular vascular diseases such as proliferative diabetic retinopathy, central retinal vein occlusion, chronic macular edema, and age-related macular degeneration. All patients underwent complete ophthalmic examination, including Snellen visual acuity measurements, slit-lamp evaluation, and a biomicroscopic fundus examination. Fluorescein fundus angiography with or without optical coherence tomography were used to confirm the diagnosis. These patients had controlled hypertension. The exclusion criteria includes non-hypertensive patients, uncontrolled hypertensive patients, and patients with glaucoma.

The same technique was used with all patients for the blood pressure measurement. The patients were allowed to sit for almost half-an-hour in a quiet room before beginning blood pressure measurement, using the digital sphygmomanometer with the ideal cuff, while the patient in the supine position. Blood pressure was measured just before bevacizumab injection (baseline), and repeated on day 1, week 1, week 4, and monthly thereafter for 3 months.

Any patient with systolic blood pressure of >140 mmHg and/or diastolic blood pressure >90 mmHg as a baseline measurement was excluded and referred to an internist for further evaluation.

Each patient in this study had a single intravitreal bevacizumab injection (0.05 ml, 1.25 mg). The eye was topically anesthetized with topical eye drop (tetracaine), and povidone–iodine (5%) drops were applied over the ocular surface for at least 2 min. Then povidone–iodine (10%) scrub was performed on the eyelids and lashes, and a sterile speculum was placed between the lids. An amount of 0.05 ml (1.25mg) of Bevacizumab (Avastin) was injected through the pars plana (3.5 mm posterior to the limbus) into the vitreous cavity using a 30-gauge needle. Following the procedure, light perception was evaluated to rule out the central retinal artery occlusion. Then, all patients were instructed to apply topical antibiotics to the injected eye four times a day for 1 week. The possible side effects of this procedure were explained to all patients.

RESULTS

Forty patients (23 males and 17 females) presented in our clinic over a period of 6 months were involved in this study, and they received single dose of

Table 2: Gender Distribution of Ocular Pathology.

Ocular pathology	Males	Females	Total
Diabetic retinopathy	11	8	19
Choroidal neovascularization	5	6	11
Retinal vein occlusion	4	3	7
Macular edema*	3	0	3
Total	23	17	40

*Caused by uveitis, ocular surgeries, and medications side effects.

intravitreal avastin. Most of them, i.e., 19 patients, had diabetic retinopathy, 11 patients had choroidal neovascularization, 7 patients had retinal vein occlusion, and 3 patients had macular edema due to ocular diseases or surgeries other than that mentioned above (Table 2).

No ocular complications occurred during and/or after this procedure except that three patients had subconjuctival hemorrhage.

DISCUSSION

One of the recently used drugs by ophthalmologist is bevacizumab in treating neovascular eye diseases, which includes: diabetic retinopathy, retinal vascular occlusion, choroidal neovascularizations (age-related macular degeneration), neovascular glaucoma, and retinopathy of prematurity. Intravitreal bevacizumab is given without significant intraocular toxicity.

In our study, we noted that there is a mild increase in blood pressure on the first day postinjection (Table 3); this might be explained by emotional stress associated with this procedure rather than a side effect of bevacizumab, because the avastin peak serum level ranged from 5 to 8 days postinjection (9).

Many studies wereperformed on intravitreal bevacizumab side effects; systemic side effects of avastin was avoided in this route of administration (intravitreal). Local side effects of this procedure were studied in many centers. Some of these showed changes in IOP (10), endophthalmitis (11), tractional retinal detachment (12), uveitis (13), and visual hallucination (14) in contrast to our study, which showed that there were only subconjuctival hemorrhage.

Systemic blood pressure changes were also studied after this procedure. Most of these studies showed that intravitreal bevacizumab injection is safe in terms of its effect on BP, regardless of ocular pathology as in the study done by Chung *et al.* in Republic of Korea (15). Their study had the same conclusion as that in

Table 3: Blood Pressure Changes According to Ocular Pathology Groups.

OP	baseline	1 day	1 week	1 month	2 months	3 months
DR	S 125 ± 11	129 ± 19	130 ± 13	127 ± 9	131 ± 12	124 ± 15
	D 77 ± 9	80 ± 12	79 ± 11	81 ± 10	78 ± 13	82 ± 6
CNV	S 131 ± 12	135 ± 16	129 ± 13	132 ± 16	130 ± 9	128 ± 11
	D 79 ± 11	84 ± 13	80 ± 6	81 ± 9	78 ± 8	79 ± 7
RVO	S 128 ± 15	131 ± 19	130 ± 10	133 ± 12	129 ± 15	130 ± 14
	D 81 ± 10	83 ± 12	80 ± 10	82 ± 11	79 ± 12	78 ± 9
MO	S 133 ± 17	132 ± 16	129 ± 17	130 ± 13	132 ± 16	131 ± 14
	D 83 ± 8	82 ± 9	80 ± 12	79 ± 9	81 ± 7	82 ± 8

S: systolic, D: diastolic, OP: ocular pathology, DR: diabetic retinopathy, CNV: choroidal neovascularization, RVO: retinal vein occlusion, and MO: macular edema.

our study. Another study in Turkey by Rasier *et al.* showed that there is a risk of disregulation of blood pressure levels or persistence of hypertension in hypertensive patients after intravitreal bevacizumab injections (16).

CONCLUSION

From our study and other studies performed on this subject, we noted that it is safe to give intravitreal bevacizumab to patients with controlled hypertension, regardless of ocular pathology.

REFERENCES

1. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov 2004; 3: 391–400.

2. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, et al. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema.Ophthalmology 2007; 114: 743–750.

3. Gündüz K, Bakri SJ. Intravitreal bevacizumab for macular edema secondary to branch retinal vein occlusion. Eye 2008; 22: 1168–1171.

4. Rich RM, Resenfeld PJ, Puliafito CA et al. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Retina 2006; 26: 495–511.

5. Azad, Rajvardhan; Chandra, Parijat "Intravitreal bevacizumab in aggressive posterior retinopathy of prematurity". Indian Journal of Ophthalmology (2007) 55 (4): 319.

6. Kernt M, Neubauer AS, Kampik A. Intravitreal bevacizumab (Avastin) treatment is safe in terms of intraocular and blood pressure. Acta Ophthalmol Scand 2007; 85: 119–120.

7. Fung AE, Rosenfeld PJ, Reichel E. The international intravitreal bevacizumab safety survey: using the internet to assess drug safety worldwide. Br J Ophthalmol 2006; 90: 1344–1349.

8. Guidelines Subcommittee. 1999 World Health Organization International Society of Hypertension Guidelines for the Management of Hypertension. J Hypertens 1999; 17: 151–183.

9. Ziemssen F, Zhu Q , Peters S, Grisanti S, El Wardani M, Szurman P et al. Intensified monitoring of circadian blood pressure and heart rate before and after intravitreous injection of bevacizumab: preliminary findings of a pilot study. Int Ophthalmol 2009; 29: 213–224.

10. FALKENSTEIN, IRYNA A. CHENG et al. Changes of Intraocular Pressure After Intravitreal Injection of Bevacizumab (Avastin) October 2007 - Volume 27 - Issue 8 - pp 1044-1047.

11. MASON, JOHN O, MILTON et al. Incidence of Acute Onset Endophthalmitis Following Intravitreal Bevacizumab (Avastin) Injection April 2008 - Volume 28 - Issue 4 - pp 564-567.

12. Arevalo JF, Maia M, Flynn HW et al. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. Br J Ophthalmol 2008; 92:213-216.

13. PIERAMICI, DANTE J, AVERY et al. Case of Anterior Uveitis After Intravitreal Injection of Bevacizumab. September 2006 - Volume 26 - Issue 7 - pp 841-842.

14. Mitrut I, Chua P, Aslam T et al. Short-term changes of visual hallucinations after intravitreal injection of ranibizumab in neovascular age-related macular degeneration. Eye (2010) 24, 1825.

15. Chung YR, Lee K, Cho EH et al. Blood pressure changes after intravitreal bevacizumab in patients grouped by ocular pathology. Eye (2010) 24, 1320–1324.

16. Rasier R, Artunay O, Yuzbasioglu E et al. The effect of intravitreal bevacizumab (avastin) administration on systemic hypertension. Eye (2009) 23, 1714–1718.

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