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Research Article

The Effect of Intravitreal Ranibizumab Injection on Systemic Blood Pressure: A Prospective Study

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ABSTRACT

Introduction: Hypertension is a common disease, which may be induced or precipitated by antivascular endothelial growth factor therapy with many studies reporting this complication of this therapy.

Methods: This is a prospective study to evaluate blood pressure changes in normotensive, controlled and uncontrolled hypertensive patients on regular medical treatment after a 0.05 ml (0.5 mg) intravitreal Ranibizumab injection. It was held in Ibn-alhaitham eye teaching hospital in Baghdad between May 2019 and December 2019. It included patients with variable retinal diseases receiving either unilateral or bilateral intravitreal Ranibizumab injections, their blood pressure was measured before the treatment as a baseline, and then 2 hours, 1 month, and at 3 months from the first injection(s). These were allocated to three groups; Group A included normotensive patients without history of hypertension; Group B included controlled hypertensives and those with grade 1 hypertension with antihypertensive treatment. Group C included those with Grade 2 hypertension or more with antihypertensive treatment. Blood pressure was measured in all patients using the manual sphygmomanometer in sitting position. Paired t-test was used to analyze blood pressure measurements and compare mean arterial, systolic and diastolic pressure. A P-value of ≤ 0.05 was considered significant, and a P-value of ≤ 0.001 was considered highly significant.

Results: Seventy-five patients (n=75) were included in the study with a mean age of 59.1 ± 11.4 years 58.7% males and 41.3% females, 44% were controlled-hypertensives, 26.7% were uncontrolled-hypertensives, 29.3% were normotensives. Group C showed highly significant reduction in the mean arterial, and systolic pressures in all three measurements after baseline (P ≤ 0.001), and significant reduction of diastolic blood pressure at one and three months after baseline (P ≤ 0.05). Both groups A and B showed a reduction in most measurements, but most were statistically insignificant (P ≥ 0.05). Unilateral and bilateral injection groups showed similar reduction in the mean arterial pressure at 2 hours and 3 months (P ≤ 0.05), mean systolic blood pressure was reduced in unilateral group in all 3 measurements (P ≤ 0.05, P ≤ 0.05, P ≤ 0.001, respectively) and also in the bilateral group at 2 hours and 3 months (P ≤ 0.001, P ≤ 0.05 respectively), and mean diastolic blood pressure was reduced at 2 hours in the unilateral group (P ≤ 0.05), and at 3 months in the bilateral injection group (P ≤ 0.05).

Conclusion: There is an overall reduction of blood pressure with Ranibizumab Intravitreal injections especially in the moderate to severely uncontrolled hypertensive patients, while controlled-hypertensive, mildly uncontrolled hypertensive showed statistically insignificant changes which indicates that, it is acceptable to continue using Ranibizumab in both normotensive and hypertensive patients in the short term.

Keywords: Antivegf; Ranibizumab; Blood pressure

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INTRODUCTION

VEGFR-1 stimulates hematopoiesis, but exhibits weak tyrosine phosphorylation, which indicates that the effects of VEGF-A on vascular endothelium occur mainly through VEGFR-2 [1]. The interaction between VEGF and VEGFR-2 leads to activation of an internal signaling pathway that alters the transcription of genes involved in angiogenesis and vascular permeability. In this pathway, VEGF-A abundance acts as a rate-limiting step for angiogenesis and vasculogenesis [1,2]. There is also evidence that PIGF interacts with VEGF-A in these processes and blockage of PIGF is of benefit to some retinal diseases [3].

Studies with Bevacizumab showed that the inhibition of VEGF induces or exacerbates hypertension in some patients [4-7]. Systemic side effects were associated with the intravitreal injection of Bevacizumab such as a rise in blood pressure (BP), cerebrovascular accidents, myocardial infarction, transient ischemic attacks, Gastrointestinal bleeding and deep vein thrombosis [8,9].

Although the mechanism of hypertension due to AntiVEGF therapy is not fully understood, it is believed to be through nitric oxide (NO). 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 [7]. Another study found that Bevacizumab treatment caused endothelial dysfunction and reduced the number of micro vessels; these closely associated effects could be responsible for the increase in BP [8].

Hypertension is a widespread disease with incompletely understood mechanisms. Hypertension-related complications, such as stroke, myocardial infarction, and heart failure put an enormous burden to health care systems. The prevalence of 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 [9].

In the light of the above-mentioned knowledge, this study was designed to determine the short-term effect of intravitreal Ranibizumab administration on systemic blood pressure levels of patients both with and without hypertension with variable indications of intravitreal Ranibizumab injections.

AIM

To evaluate the effects of Intravitreal Ranibizumab injections within the first three months of injections on systemic blood pressure in normotensive and hypertensive subjects.

PATIENTS AND METHODS

A prospective observational study, the population of which, included patients with variable diagnoses of retinal diseases, the patients were enrolled into AntiVEGF treatment after being diagnosed by retina specialists in Ibn-Alhaitham eye teaching hospital.

A written informed consent was approved by the patient to be enrolled into the treatment regimen. The study sample was taken between May 2019 and December 2019.

The patients enrolled in the study is divided into 3 groups according to the 1st blood pressure measurement before intravitreal injection as the following:

Inclusion criteria and groups

Group A: Patients who claimed to be normal in terms of Blood pressure (BP) and were found to be normal in the baseline measurement of both systolic (SBP) and diastolic (DBP) blood pressures (SBP ≤ 139 mmHg, DBP ≤ 89 mmHg).

Group B: Include:

- Patients who had systemic hypertension and were controlled by taking regular antihypertensive treatment prescribed by an Internist and who did regular (at least once weekly) BP checkup, and were found to be normal at baseline measurement (SBP ≤ 139 mmHg, DBP ≤ 89 mmHg).
- Patients who had systemic hypertension but were uncontrolled despite taking regular antihypertensive treatment, prescribed by an Internist and who did regular (at least once weekly) BP checkup and were found in the grade 1 category SBP or DBP or both; (SBP between 140-159 mmHg, DBP between 90-99mmHg).

Group C: Patients who had systemic hypertension but were uncontrolled despite taking regular antihypertensive treatment, prescribed by an Internist and who did regular (at least once weekly) BP checkup and were found in the grade 2 or more in either SBP or DBP or both; (SBP ≥160 mmHg, DBP ≥ 100mmHg).

N.B: The above-mentioned values for blood pressure are chosen according to what is described in the World Health Organization International Society of Hypertension (WHO-ISH) Guidelines for the Management of Hypertension 1999,10 (Table-1).

Exclusion criteria

- Patients who claimed to be normal but found to be hypertensive on baseline testing.
- Patients who didn't take their antihypertensive treatment or didn`t do Blood Pressure checkup on a regular basis.
- Patients who had stroke, Myocardial infarction, Angina pectoris, heart failure, renal failure, or on systemic steroids.
- Patients who were treated with Anti-VEGF treatments by any route within the previous six months.

Measurement of blood pressure levels

- All patients receiving intravitreal injection of Ranibizumab underwent systemic blood pressure measurement, as described in 1999 World Health Organization International Society of Hypertension (WHO-ISH) Guidelines for the Management of Hypertension [10]. A standardized setting was adapted for all patients for the measurement of blood pressure; the patient was allowed to sit for two hours 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, and the sphygmomanometer cuff was

placed at heart level, and whether the patients' left or right arm was used in the measurement was also recorded, so that the same arm is used for future readings. Blood pressure measurements were performed 1 hour before Ranibizumab injection (baseline) and repeated at 2 hours after injection and at 1 and 3 months after injection. The systolic (SBP) and diastolic (DBP) arterial blood pressure was measured. The mean arterial pressure (MAP) was calculated according to the equation: MAP=DBP+1/3 (SBP -DBP).

Table 1: Definitions and classification of blood pressure levels (mmHg) according to (WHO-ISH) Guidelines for the Management of Hypertension 1999.

Category	Systolic	Diastolic
Optimal	120	80
Normal	130	85
High-normal	130 ± 139	85 ± 89
Grade 1 hypertension (mild)	140 ± 159	90 ± 99
Subgroup: borderline	140 ± 149	90 ± 94
Grade 2 hypertension (moderate)	160 ± 179	100 ± 109
Grade 3 hypertension (severe)	≥ 180	≥ 110
When a patient's systolic and diastolic blood pressures fall into different categories, the higher category should apply		

Statistical analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Paired t-test was used to compare the MAP, SBP, and DBP before and after intravitreal Ranibizumab injection. A level of p-value less than 0.05 was considered significant.

RESULTS

The total number of included study patients was 75 out of 115 patients, the rest was excluded as they didn`t meet the inclusion criteria set or they did not adhere to follow up or changed treatment during the study period. All of them were diagnosed with retinal diseases and managed with intravitreal Ranibizumab injections.

The study patients' age was ranging from 17-85 years with a mean of 59.1 years and a standard deviation (SD) of ± 11.4 years. The highest proportion of study patients was aged ≥ 60 years (58.7%). Regarding gender, proportion of males were higher than females (58.7% versus 41.3%) with a male to female ratio of 1.4:1.

Table 2 shows the difference in the mean of MAP at two hours, one month and three months after intravitreal Ranibizumab injection. It is noticed that the mean of MAP was highly significantly decreased (p value ≤ 0.001) in all three readings in group C, also significant in patients received unilateral and bilateral injection after 3 hours and 3 months.

No statistically significant change (p ≥ 0.05) detected in MAP all three readings in Group A nor in Group B.

Table 3 shows the difference in mean of SBP two hours, one month and three months after intravitreal Ranibizumab injection. The mean of SBP was highly significantly decreased in group C and in the unilateral injection and bilateral except after 1 month.

No statistically significant change (P ≥ 0.05) detected in SBP in group A, and B except the statistically significant reduction in mean SBP at three months for group A.

Table 4 shows the difference in mean of DBP two hours, one month and three months after intravitreal Ranibizumab injection. Mean of DBP was significantly decreased in patients received unilateral injections at two hours post injection. Group C showed significant reduction at one and three months after baseline. Bilateral injection group only had significant reduction at three months after baseline.

DISCUSSION

Anti-VEGF therapy has revolutionized ophthalmic treatment over the past two decades, and since it's used on a broad scale for various indications its necessary to assess its safety. This study was held to assess one aspect of the safety of AntiVEGF therapy in regard of the systemic blood pressure in patients with ocular diseases receiving antiVEGF via the intravitreal route due to systemic exposure to the drug. Most previous studies assessed the safety of bevacizumab and less so for Ranibizumab.

Table 2: Differences in mean arterial pressure MAP.

Variable	Before injection	After 2 hours from injection	After 1 month from injections	After 3 months after injection
Group A	92.3 ± 12.3	88.55 ± 10.0	93.8 ± 9.8	89.2 ± 10.3
Group B	98.5 ± 9.1	95.6 ± 13.2	99.0 ± 9.4	97.2 ± 9.3
Group C	117.2 ± 9.4	110.2 ± 13.6**	106.8 ± 9.8**	106.3 ± 13.7**
Unilateral	101.8 ± 14.4	98.1 ± 15.4 *	99.7 ± 11.5	98.3 ± 12.7*
Bilateral	101.3 ± 12.9	94.8 ± 12.5 *	99.3 ± 7.6	93.8 ± 11.4 *
Significant result with P value ≤ 0.5 * Highly Significant result with P value ≤ 0.01 **				

Table 3: Differences in systolic blood pressure SBP.

Variable	Before injection	After 2 hours from injection	After 1 month from injections	After 3 months after injection
Group A	130.2 ± 18.0	126.4 ± 15.2	130.0 ± 17.4	123.6 ± 13.9*
Group B	142.4 ± 14.9	138.8 ± 19.8	134.8 ± 16.6	138.3 ± 15.2
Group C	176.5 ± 10.9	162.5 ± 18.4**	159.0 ± 13.3**	156.0 ± 20.1**
Unilateral	147.7 ± 24.1	142.2 ± 23.3 *	142.4 ± 19.6*	139.1 ± 20.4**
Bilateral	148.8 ± 20.9	138.8 ± 20.7 **	149.1 ± 17.5	137.5 ± 19.8 *
Significant result with P value ≤ 0.5 * Highly Significant result with P value ≤ 0.01 **				

Table 4: Differences of diastolic blood pressure DBP.

Variable	Before injection	After 2 hours from injection	After 1 month from injections	After 3 months after injection
Group A	73.4 ± 11.1	69.5 ± 8.9	75.7 ± 12.4	72.0 ± 12.2
Group B	76.5 ± 9.1	73.9 ± 12.1	76.7 ± 8.2	76.7 ± 8.8
Group C	87.5 ± 13.7	84.0 ± 15.0	80.8 ± 12.0*	81.5 ± 13.5*
Unilateral	78.8 ± 12.6	76.0 ± 13.8 *	78.3 ± 11.4	77.9 ± 11.3
Bilateral	77.5 ± 11.3	71.9 ± 9.8	74.4 ± 6.3	71.9 ± 9.8 *
Significant result with P value ≤ 0.5 * Highly Significant result with P value ≤ 0.01 **				

No statistically significant change (P ≥ 0.05) detected in mean DBP in groups A and B in all three readings.

In this study, it was found that the reduction of mean arterial pressure (MAP) was more affected in the moderate to severely uncontrolled hypertensive patients (Group C) in all the 3 measurements after baseline with consistently highly significant reduction. There also was a significant reduction of (MAP) in the unilateral and bilateral injection groups at 2 hours and at 3 months of baseline (Table 2). The overall results of (MAP) reduction are mainly derived from the parallel reduction of the systolic blood pressure (SBP) in the same groups (Group C, unilateral and bilateral injection groups), see (Table 3), while for the mean diastolic blood pressure (DBP) readings we notice that there is an overall reduction in readings, but only a few reached statistically significant reductions, see (Table 4), which in return; is of less impact on the (MAP) than that seen with (SBP).

The overall reduction in blood pressure in all patients may explained by the elevated baseline reading of blood pressure compared to subsequent measurements due to heightened mental stress of the patients caused by the idea of getting an injection into their eye(s), which is supported by the elevated systolic blood pressure on baseline that declines on later measurements, especially after two hours of injection(s) rather than diastolic blood pressure which shows less fluctuation ; as

the systolic blood pressure is more liable for elevation under acute mental stress [11,12].

From the pharmacokinetics aspect; comparison the free-VEGF levels after intravitreal injection of Bevacizumab, Aflibercept and Ranibizumab, and it showed that systemic exposure of each anti-VEGF drug did not seem to differ by indication (age related macular degeneration, retinal vein occlusion, diabetic maculopathy) for which anti-VEGF treatment was administered and was consistently highest with Bevacizumab and lowest with Ranibizumab, and overall, there were no notable changes in mean and median free-VEGF levels from baseline for ranibizumab [13]. It may be attributed to longer half-life of Bevacizumab molecule which has an Fc fragment and undergoes systemic recycling that causes an increased systemic exposure and that bevacizumab undergoes systemic accumulation between doses 1 and 3 of intravitreal injection while Ranibizumab does not, thus reducing the chances of systemic adverse effect to take place with the use of intravitreal Ranibizumab usage. Also, the maximum serum concentration [Cmax] for Ranibizumab is reached at 24 hours after the injection, with systemic clearance of the drug from the circulation of about 2 hours, so the reduction of measurements at two hours post injection may rather be attributed to the stress factor rather than the systemic pharmacological effect of Ranibizumab.

Sengul et al. studied the Short-term effects of intravitreal Ranibizumab and Bevacizumab administration on 24-h ambulatory blood pressure monitoring (ABPM) recordings in normotensive patients with age-related macular degeneration (AMD) [14]. They found that Ranibizumab injection had no impact on ABPM recordings and dipping status. While in the bevacizumab group, increased daytime (P=0.002) and nighttime systolic (P=0.001) BP and decreased daytime diastolic (P=0.001) BP were noted in the post-injection period, and that agrees with our study in that Ranibizumab did not cause any statically significant elevation of SBP in normotensives and patients but rather it was reduced compared to baseline.

Another study held by Nair et al. evaluated the effect of intravitreal Ranibizumab on blood pressure in patients with neovascular AMD, was conducted for controlled hypertensive patients who had blood pressure measured prior to intravitreal injection and at monthly follow up visits it showed that Ranibizumab does not appear to affect systemic blood pressure in the short term, which also agrees with our study in that controlled hypertensives were not significantly affected [15].

A study done by Wells et al. held in cooperation with DRCR.net (The Diabetic Retinopathy Clinical Research Network) which included normal and hypertensive patients ranging from borderline to moderate hypertension, and they followed patients over two years and revealed no significant changes in SBP, DBP or MAP in those patients who had DME and received either Aflibercept, Bevacizumab or Ranibizumab and this agrees with our study for both controlled hypertensive and normotensive patients who were not significantly affected [16].

Topical anesthesia may also play a role, in this study sample Tetracaine hydrochloride 0.5% (Tetracaine hydrochloride/ Cooper ®) was used, in a study by Nishiyama et al., hemodynamic changes and anesthetic effects of bupivacaine and tetracaine in 200 patients aged 40 to 75 years were studied and the results showed that blood pressure and heart rate decreased significantly in both groups. While in a study done by Haddadi et al., comparing the effect of topical anesthesia and retrobulbar block with intravenous sedation on hemodynamic changes and satisfaction in patients undergoing cataract surgery, it showed no significant hemodynamic effect on blood pressure [17,18].

For unilateral and bilateral intravitreal Ranibizumab injection groups both have shown similar results with significant reduction in the SBP measurements mainly with slightly more reduced results in the unilateral injection group, this indicates that despite that the Bilateral injection group are getting double the dose than those with unilateral injection it seems that doubling the dose per session didn`t have a major effect on BP readings and it doesn't have a clinical impact on the patients' systemic BP.

Till this study was held there were few published studies assessing the effect of Ranibizumab Intravitreal Injections on the blood pressure, furthermore most of these studies assessed its effect on BP in normal and controlled hypertensive patients, but in this study we enrolled uncontrolled hypertensive patients as they form a major proportion of our patients and for the fact that most of the patient receiving antiVEGF intravitreal injections are seniors with other comorbidities, it becomes a necessity to assess the safety of these drugs and it may give a broader insight to physicians while prescribing such drugs to such patients. This study shows that there is an overall reduction of blood pressure with Ranibizumab Intravitreal injections especially in the uncontrolled hypertensive patients, which indicated that it may be acceptable to continue using Ranibizumab in non-hypertensives and hypertensive patients in the short term.

CONCLUSION

study shows that there is an overall reduction of blood pressure with Ranibizumab Intravitreal injections especially in the moderate to severely uncontrolled hypertensive patients, while controlled-hypertensive, mildly uncontrolled hypertensive and normotensive patients showed statistically insignificant changes which indicates that, it is acceptable to continue using Ranibizumab in both normotensive and hypertensive patients in the short term.

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