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Original research

Intravitreal bevacizumab versus ranibizumab: Effects on the vessels of the fellow non-treated eye

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Abstract

Purpose: To evaluate the effects of anti-vascular endothelial growth factors (anti-VEGF) on the vessels of the non-treated eyes following intravitreal injections.

Methods: In this prospective, non-randomized trial, a total of 38 patients were recruited. 21 patients received ranibizumab, and 17 patients received bevacizumab. Fundus photography was carried out at baseline immediately before injection and at 3 days, 7 days, and one month after the injections. Using image analysis software, measurements were summarized as the central retinal artery equivalent (CRAE) and central retinal vein equivalent.

Results: In non-treated eyes, CRAE decreased significantly from 153.23 ± 15.20 μm before injection to 148.77 ± 17.21 μm 3 days after intravitreal bevacizumab ($P = 0.004$). There was no significant difference in CRAE, between the pre-injection baseline, one week, and one month after intravitreal bevacizumab injection in non-treated eyes ($P > 0.05$). No significant difference was noted in CRAE in the non-treated eyes of the ranibizumab group at any post-injection visit ($P = 0.1$).

Conclusion: A significant transient narrowing effect of bevacizumab on retinal arterioles in the fellow non-treated eyes on the third day after intravitreal injection may show that plasma concentrations of these drugs are sufficient to spread the effect to the other eye.

Keywords: Intravitreal; Bevacizumab; Ranibizumab; Systemic effect; Vessel diameter; Anti-vascular endothelial growth factors

Introduction

Therapeutic intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents represent a novel therapy in ophthalmology that appears to have the potential to enable patients with age-related macular degeneration (AMD) to achieve significant and sustained vision improvements. Full-length humanized monoclonal antibody bevacizumab (Avastin, Genentech, South San Francisco, CA) and VEGF-fragment ranibizumab (rhuFabV2, Lucentis, Genentech, South San Francisco, CA) have repeatedly been shown to promote significant regression of intraocular neovascularization in AMD.[1,2]

Previous studies have shown an association between both bevacizumab and ranibizumab, and retinal vascular and choriocapillaris changes following their respective intraocular injection.[3–6] For example, significant constriction of the

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retinal arterioles was reported in the treated eyes, seven days after injection of ranibizumab, and in another report, constriction of retinal vessels was noted at the one-year follow-up after injection.[7] Similarly, Fontaine et al. reported a significant and persistent retinal arteriolar constriction following intravitreal bevacizumab injection.[8] More recently, Wickremasinghe and his colleagues studied 53 patients over a 12-month period and reported venular caliber dilatation after ranibizumab injection in treated eyes, as well as a tendency toward arteriolar constriction in non-injected eyes at the one-year follow-up.[9] These circulatory changes could be due to the interference of anti-VEGF agents with nitric oxide (NO) production and consequent changes in ocular microvascular autoregulation.[10]

There is also some evidence that support the systemic absorption of intravitreal anti-VEGF agents. Bevacizumab was detected in the fellow non-treated eyes in an animal study.[11]

Furthermore, serum VEGF concentrations were significantly lower after intravitreal bevacizumab in the IVAN study [A randomized controlled trial of alternative treatments to inhibit VEGF in age-related choroidal neovascularization (CNV)], but little is known about the potential systemic vasoactive effects of these drugs.[12]

Therefore, we conducted the present study to evaluate the effect of intravitreal ranibizumab and bevacizumab on the diameter of retinal vessels in the fellow non-treated eyes. This will help indicate an idea whether plasma concentrations of these drugs following intravitreal injections are sufficient to affect VEGF-dependent physiologic processes elsewhere in the body.

Methods

This study was a prospective, non-randomized trial. Patients with AMD, who were scheduled for intravitreal injection of ranibizumab or bevacizumab, met the inclusion/exclusion criteria, and agreed to participate in this project were recruited. The study was conducted with the approval of the Ethical Committee Board of University Malaya and it adhered to the tenets of the Declaration of Helsinki [clinicaltrials.gov: NCT01626339].

The study was carried out at the University of Malaya Medical Center, Kuala Lumpur, Malaysia between April 2014 and May 2015. The sample size was calculated using G*Power software. The calculated effect size was 0.5 with a power of 0.8. The Type I error probability of the null hypothesis was 0.05. The calculated sample size was 38.

The criteria for inclusion in the study were that subjects must be patients with a diagnosis of primary subfoveal CNV secondary to AMD, who wanted and needed bevacizumab or ranibizumab treatment for underlying disease. The exclusion criteria included a history of previous systemic or ocular anti-VEGF therapy or previous intravitreal injection with any drug. Patients with glaucoma, intraocular pressure (IOP) $\geq$ 22, history of any intraocular surgery, a history of thromboembolic events, smoking, hypertension, diabetes mellitus, or ocular media opacity were also excluded.

Of the 310 patients assessed for their eligibility in this study, 23 patients were recruited in the bevacizumab group and 26 patients in the ranibizumab group. Six patients were lost to follow-up in the bevacizumab group, as were five patients in the ranibizumab group. In the end, there were 21 patients treated with ranibizumab and 17 patients treated with bevacizumab. The allocation ratio was 1:1.2 [bevacizumab:ranibizumab].

At baseline, all patients underwent an assessment of the best corrected visual acuity (BCVA) and IOP measurement. Fundus examination was performed using a 90 diopter non-contact lens and IOP was measured using Goldmann applanation tonometry. Peripheral finger oxygen saturation was measured using a pulse oximeter (Pulse Oximeter CMS50D, USA).

Intravitreal injections of ranibizumab or bevacizumab were performed under sterile conditions in the operating room. Before injection, topical anesthesia was applied using a 0.5% proparacaine hydrochloride ophthalmic solution. The bulbar conjunctiva and the fornices were rinsed with povidone–iodine 5%, which was also applied to the eyelid margins and lashes. After application of a sterile drape, a lid speculum was inserted. A volume of 0.05 ml containing 0.5 mg of ranibizumab (Lucentis, Genentech, South San Francisco, CA) or 1.25 mg bevacizumab (Avastin; Genentech, South San Francisco, CA) was then injected 3.5–4.0 mm posterior to the limbus, through the pars plana, with a 30-gauge needle.

All patients had dilatation of the study eye with tropicamide 1% 15 min before the measurements were performed. Each patient was placed in front of the fundus camera and was asked to look at a fixation bar positioned inside its viewing system.

The first (baseline) photos were taken prior to the first intravitreal injection and subsequent measurements were performed at day 3, day 7, and one month following the injection. Both systolic and diastolic blood pressures were measured prior to the photo capture.

Two photographic fields were taken of each eye of each participant: the first centered on the optic disc, and the second centered on the fovea. Fifty-degree photos were taken using a Topcon TRC-NW8 mydriatic fundus camera (Topcon, Tokyo, Japan). The retinal vascular caliber was measured using a computer program (IVAN; University of Wisconsin, Madison), based on a detailed protocol. For this study, disc center photographs were selected for measurement. For each photograph, all arterioles and venules coursing through an area one half to one disc diameter from the optic disc margin were measured and summarized as the central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE), using formulas developed by Hubbard et al.[13] and later modified by Knudtson et al.[14] These equivalents are projected calibers for the central retinal vessels, measured away from the optic disc. Two expert graders masked to the baseline, carried out the analysis of the fundus photos in this study. The grader confirms the correct detection of the optic disc and the two concentric subzones by the program, and then the grader

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executes the program to generate a line tracking of the retinal vessels. The grader subsequently checks whether all arterioles and venules are correctly identified, and the software allows the grader to make any corrections if required.

Potential side effects related to the intravitreal injection were monitored in follow-ups including endophthalmitis, ocular vessel occlusion, inflammation, retinal tear, hemorrhage, detachment, vitreous hemorrhage, ocular hypertension and glaucoma, disturbed vision, and infection.

Statistical analyses were performed with SPSS software (Statistical Program for Social Sciences version 19 for Windows, 2010, SPSS Inc., Chicago, IL, USA). Demographic data and retinal vascular calibers were summarized as mean ± standard deviation (SD) for continuous variables, and number (%) for categorical variables. Intraclass coefficient correlations (ICCs) were employed to calculate interobserver reliability regarding the quantitative variables in image analysis. Intraobserver variation was evaluated using photo subset of five randomly chosen subjects. These images were re-assessed twice by each analyzer one month after the first assessment. In the comparison between pre- and post-intravitreal injections, an ANOVA test was performed for the continuous data because they followed a normal distribution. Pearson's Chi-square test was performed for the categorical variables. Furthermore, a Fisher's exact test was performed for the limitation of numbers <5. All statistical assessments were considered significant when $P < 0.05$.

Results

Recruited patients included 24 men and 14 women. The mean age of patients at the time of recruitment was 63.5 years (range, 55–72 years) in the ranibizumab group and 64.3 years (range, 54–75 years) in the bevacizumab group with no significant difference between the two groups ($P > 0.05$). 80% of lesions were non-predominantly classic. None of the studied patients developed adverse effects related to the intravitreal injections.

There was no significant difference between mean arterial systolic blood pressure and the mean value of peripheral finger blood SpO2 before and after the injections at all time points in both groups (Table 1).

Furthermore, no significant change in IOP was noted during the study period at all follow-ups ($P = 0.19$) (Table 1).

Both intra and interobserver measurements elicited acceptable ICCs (in all cases >0.91 and $P < 0.001$). Interobserver ICC, measured using the sample of 38 photographs, was 0.992 (95% CI: 0.990–0.997) for CRAE, and 0.978 (95% CI: 0.950–0.989) for CRVE. Intraobserver ICC, measured using the sample of 5 photographs, was 0.994 (95% CI: 0.989–0.996) for CRAE.

At baseline, there were no differences in CRAE and CRVE between the injected and non-injected eyes ($P = 0.71$ and $P = 0.49$, respectively).

Bevacizumab group

In the non-treated eyes of subjects in the bevacizumab group, retinal arteriolar diameter decreased significantly from 153.23 ± 15.20 μm before injection to 148.77 ± 17.21 μm 3 days after injection (Fig. 1). However, there was no significant difference between the pre-injection baseline and one week (151.65 ± 16.15) and one month after injection (152.56 ± 18.26) in the non-treated eye ($P = 0.01$ using repeated measure ANOVA and paired t-test $P = 0.04$ [day 0 − day 3], $P = 0.16$ [day 0 − day 7] and $P = 0.62$ [day 0 − 1 month]) (Fig. 1).

There was no significant difference in CRVE in non-treated eyes in the bevacizumab group (before injection: 217.44 ± 18.16, 3 days after injection: 218.58 ± 17.00, 7 days after injection: 218.48 ± 17.55, and one month after injection: 220.98 ± 15.64 repeated measure ANOVA, $P = 0.094$) (Fig. 2).

Ranibizumab group

In this group, no statistically significant change in diameter of CRAE of the non-treated eye was detected after the injection of ranibizumab. Before injection, the mean CRAE was 151.42 ± 17.61 μm. The mean CRAE was 150.458 ± 17.965 μm 3 days after injection, 151.21 ± 18.20 μm one week after injection,

Table 1
Recruited patient characteristics.

	Ranibizumab group	Bevacizumab group	P value
Age (Years)	63.52 (55–72)	64.29 (54–75)	0.2[a]
Baseline systolic blood pressure	123.40 ± 10	118.38 ± 9.56	0.12[a]
Systolic blood pressure at day 3	120.39 ± 8.95	121.25 ± 9.08	0.77[a]
Systolic blood pressure at day 7	124.26 ± 9.80	119.00 ± 10.14	0.11[a]
Systolic blood pressure at one month	116.59 ± 10.19	118.69 ± 12.51	0.57[a]
Baseline intraocular pressure (IOP)	16.20 ± 2.40 mmHg	17.07 ± 2.10 mmHg	0.24[a]
Intraocular pressure (IOP) at day 3	16.07 ± 3.38 mmHg	17.08 ± 2.12 mmHg	0.27[a]
Intraocular pressure (IOP) at day 7	15.86 ± 2.66 mmHg	16.46 ± 1.56 mmHg	0.40[a]
Intraocular pressure (IOP) in one month	16.67 ± 3.01 mmHg	17.01 ± 2.92 mmHg	0.72[a]
Gender (Male/Female)	12/9	9/8	0.60[b]
Baseline Vision (logMAR)	0.71 ± 0.34	0.65 ± 0.40	0.62
Vision at one month (logMAR)	0.58 ± 0.41	0.60 ± 0.47	0.88
Mean value of peripheral blood SpO2 before injection	98.7% ± 0.82	98.2% ± 0.96	0.09[a]

[a] Two independent samples t-Test.
[b] Chi square test.

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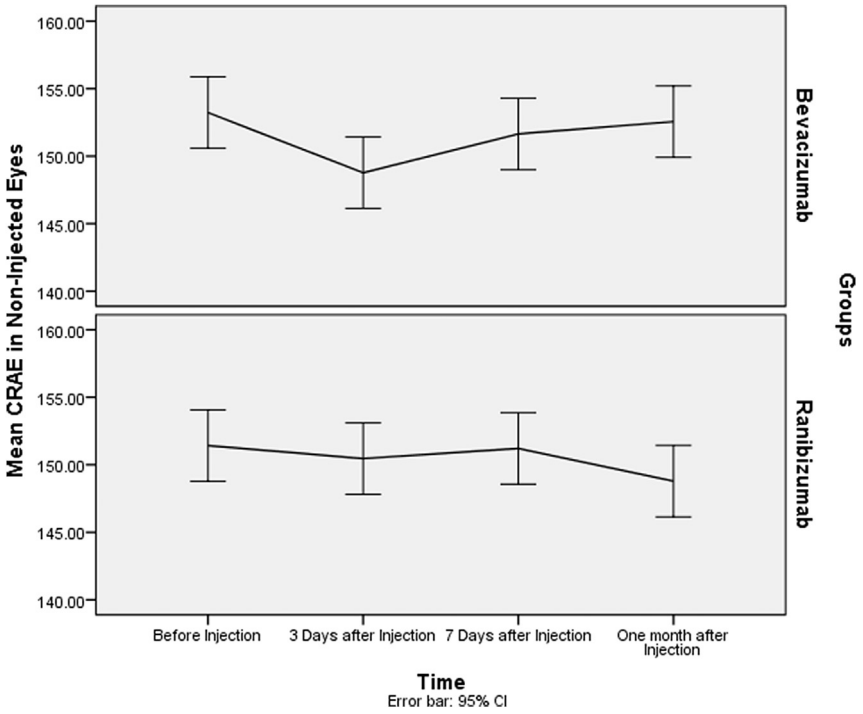

Fig. 1. Central retinal arteriolar equivalent (CRAE) of the non-treated eye with bevacizumab (upper) and ranibizumab (lower) before injection, and 3 days, 7 days, and 1 month after injection.

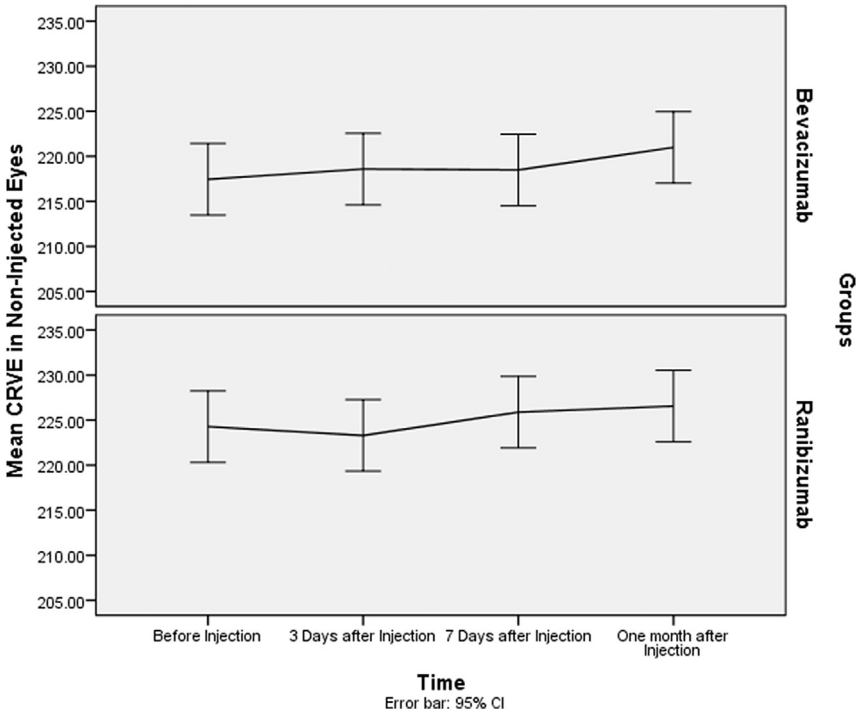

Fig. 2. Central retinal venular equivalent (CRVE) of the non-treated eye with bevacizumab (upper) and ranibizumab (lower) before injection, and 3 days, 7 days, and 1 month after injection.

and 148.79 ± 15.98 μm one month after injection ($P = 0.103$) (Fig. 1).

Similarly, no significant changes were seen in the fellow non-treated eye in term of CRVE. (before injection: 224.28 ± 19.08, 3 days after injection: 223.30 ± 17.48, 7 days after injection: 225.89 ± 17.51, and one month after injection: 226.56 ± 17.34 repeated measure ANOVA, $P = 0.219$) (Fig. 2).

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Discussion

In this prospective, non-comparative study, a single intravitreal injection of bevacizumab had a significant transient narrowing effect on retinal arteriolar diameter in the fellow non-treated eyes.

Although a clear association has been established between hypertension and peripheral arterial narrowing,[15] in our study, no significant difference was found in systolic blood pressure in follow-up visits at all time points. Thus, we may ignore the effect of systemic blood pressure fluctuations on the measured retinal vessel diameters. Effects of IOP and SpO2 on retinal vessel diameter as confounding factors were also eliminated. Furthermore, we excluded patients with a history of diabetes or high blood pressure.

The mechanism of arteriolar vasoconstriction after intravitreal injections of anti-VEGF agents in our study, as in previous studies,[3,7] can be explained by the property of VEGF in inducing the release of NO from vascular endothelial cells.[16] It is possible that with the systemic distribution of bevacizumab and after reaching the fellow non-treated eye, NO may release and consequent events cause change in microcirculation. Hence, it might be possible to visualize the effect of anti-VEGF agents by monitoring the diameter of retinal vessels. Using this mechanism, Domniki et al. have shown retinal arteriolar vasoconstriction after intravitreal ranibizumab injection in patients with neovascular AMD.[7] Mendrinos et al. reported sustained retinal arteriolar vasoconstriction in similar settings.[3] Furthermore, Fontaine et al. suggested a long-term effect of bevacizumab on vascular tone and persistent arteriolar constriction.[8]

In the current study, we found a statistically significant decrease in CRAE in the non-treated fellow eye, three days after intravitreal injection of 1.25 mg/0.05 mL bevacizumab in the treated eye. Surprisingly, this finding was seen as a transient effect, and no significant changes in retinal vessels diameter were noted seven days or one month after the injection. In contrast, after the injection of intravitreal ranibizumab vasoconstriction in the fellow non-treated eye was not significant at any of the follow-up observations. In this study, we have followed the routine protocol for follow-up after intravitreal injection, but a study of the vessels' diameter at an earlier time after injection, such as one day after injection, as well as investigations of longer-term effects would be helpful.

The systemic half-lives of bevacizumab (20 days) and ranibizumab (6 h) may play role in interpretation of difference although our study looked at 3 days after injection of these agents; however, this is likely not the only factor that plays a role. The difference in responses after intravitreal injection of ranibizumab and bevacizumab may also stem from the distinct pharmacologic characteristics of these VEGF inhibitors. The properties of these drugs may vary with regard to their penetration, potency, systemic absorption, half-life, localization to the retina, and stimulation of the immune system. Hence, the safety and efficacy data from one agent cannot be extrapolated to another.

The systemic safety of intravitreal anti-VEGF treatment is a challenging subject. The potential for an increased risk of systemic adverse events such as cerebrovascular accidents with bevacizumab remains controversial.[11]

Bevacizumab was detected in the untreated fellow eye of a rabbit model of neovascular AMD.[11] Therapeutic effects after treatment with intravitreal bevacizumab were also noted in the fellow eyes of patients with proliferative diabetic retinopathy,[17] AMD,[18] type 2 idiopathic macular telangiectasia,[19] and uveitic cystoid macular edema,[20] supporting the concern that intravitreal anti-VEGF agents may lead to systemic exposure. This may be more significant when there is a breakdown in the blood retinal barrier which accompanies some ocular diseases.[21,22] A recent study has also shown that the effect of the monoclonal antibody dosage even in small amounts is often not linear, and thus, a small dose might have significant effects, which could be cumulative with repeated dosing.[23]

Although many studies have evaluated the systemic exposure of ranibizumab and bevacizumab following intravitreal injection, what remains unknown is whether plasma concentrations of these drugs are sufficient to affect VEGF-dependent physiological processes. The many roles that VEGF plays in physiologic processes give reason for concern that its inactivation could have potentially serious systemic consequences.[24]

The retinal vasculature is often regarded as a window into the general circulation, providing exemplary information about changes in vascular morphology and function.[25] Given that retinal, cerebral, and coronary blood vessels feature similar anatomy and physiology, we may correlate funduscopic evaluation of retinal blood vessels to systemic microcirculation.[26–28] Slight systemic vasoconstriction in arteriolar diameter may not be clinically significant in an otherwise healthy subject stimulation. It may have serious consequences in patients who are susceptible to developing vascular events such as a cerebrovascular accident or myocardial infarction.

The extrapolation of this new and emerging treatment modality to the retinopathy of prematurity (ROP) raises concerns with regard to the intravitreal injection of bevacizumab. Infants are still in the process of organogenesis, and VEGF plays a key role in the development of most organs,[24,29] including the processes of lung maturation and alveolar development.[30,31] Intravitreal bevacizumab is now extensively used in the treatment of severe ROP, and the inevitable systemic absorption of anti-VEGF agents may have serious consequences. This is especially the case in infants with ROP who have a low body mass, so that the current dosage of intravitreal anti-VEGF agents is excessively high.[25]

Variable factors, such as neurogenic, myogenic, and metabolic factors are involved in autoregulation to regulate blood flow. Anti-VEGF is the favored first-line treatment to interfere with autoregulation of the retinal and choroidal microcirculation, playing a significant role in reducing the progression of neovascularization.[32] This therapy might affect any of these factors over the short and long-term.

The lack of an effect on CRVE in our study contrasts with the findings of Wickremasinghe and colleagues,[9] who showed

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that CRVE increased after ranibizumab injection. This may mainly be due to the timing of the follow-up. Our study focused on the short-term effect of ranibizumab and bevacizumab, while the observed retinal venular caliber dilatation in that research occurred at one-year follow-up.

The main weakness of our study was the limited number of subjects largely due to the impact of the inclusion and exclusion criteria. This led to patient groups which were relatively small in size, but nearly homogeneous, with a minimal effect of known confounding factors. Furthermore, more frequent examination intervals could have revealed more information.

As a conclusion, systemic spread as well as the physiological effects of intravitreal bevacizumab raises concerns about the use of this agent in high risk groups such as those susceptible to cerebrovascular events or newborn babies who are still undergoing systemic angiogenesis. Future studies with larger sample size are needed to confirm the results of this study.

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