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

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Abstract

Introduction:
Therapeutic intra vitreal 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, 4, 5, 6 For example, significant constriction of the 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 intra vitreal bevacizumab injection.8 More recently, Wickrema singhe 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 intra vitreal 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 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-intra vitreal 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 intra vitreal 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