ORIGINAL ARTICLE

# Bilateral concomitant intravitreal anti-vascular endothelial growth factor injection: Experience in a Nigerian tertiary private eye care facility

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## Abstract

**Objectives:** To evaluate the indication and safety profile of same-session bilateral intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF).

**Methods:** This is a retrospective case series of all the patients that received same-session bilateral intravitreal anti-VEGF in Eye Foundation Hospital, Ikeja, Lagos, from March 2013 to March 2015. Data retrieved from the patients' medical records includes demographics, indications for injections, complications, and systemic comorbidities.

**Results:** During the study period, a total of 442 injections were performed on 126 eyes of 63 patients (M:F ratio; 1.4:1) whose mean age was 55.7 ± 15.6 standard deviation years. The modal age group was 51–70 years. All the patients received injection Bevacizumab (Avastin; Genentech Inc., South San Francisco, California, USA-1.25 mg). The most common primary indication for initiating bilateral intravitreal therapy was diabetic macular edema 23 (36.5%). Mean follow-up period was 40.6 days (range: 1–364 days). A combined diabetes mellitus and hypertension accounted for most of the systemic comorbidities 28 (44.4%). Subconjunctival hemorrhage was the only complication seen in these patients with 6 (9.5%) occurring intraoperatively and 9 (14.3%) postoperatively. There was no association between intraoperative complication and age ($P$ = 0.66) or gender ($P$ = 0.96). Furthermore, there exist no association between postoperative complication and age ($P$ = 0.49) or gender ($P$ = 0.99).

**Conclusions:** No major systemic or ocular adverse events were noted. Given that there are potentially serious complications following anti-VEGF injection, further study with a larger number of patients will be necessary to definitively prove the safety of this treatment modality.

**Key words:** Bilateral concomitant, humans, intravitreal bevacizumab

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## Introduction

Vascular endothelial growth factor (VEGF) is a known mediator of ocular angiogenesis and thus is important in the pathogenesis of various ophthalmic diseases. Originally used for the treatment of neoplasia, intravitreal anti-VEGF (anti-VEGF) has been found to be effective and is increasingly being used for the treatment of various ophthalmic diseases which include but not limited to retinal vascular diseases, wet age-related macular degeneration (ARMD), and diabetic

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macular edema.[1-3] A major challenge is the required need for repeated injections. Factors that determine the frequency of injections include disease severity and clinical opinion of the physician. The patients are, however, burdened with frequent hospital visits.[4,5] A number of ophthalmic diseases are requiring treatment with intravitreal anti-VEGF agents typically occur in both eyes with a variable degree of severity. An Indian survey reported diabetic macular edema as second only to cataract as the cause of bilateral visual impairment.[6] In Nigeria, exudative ARMD accounted for 38.3% of bilateral blindness in a hospital population.[7] Thus, patients undergoing anti-VEGF treatment in both eyes will likely visit the hospital once every 1–2 weeks. This frequency of treatment would further present a significant burden on patients' time and productivity and increases the administrative load on the health care system.[8] Many hospitals now perform simultaneous bilateral intravitreal injections (IVIs) because it is more convenient and cost-effective, and many patients are reported to prefer bilateral injections.[9] However, underscoring the potential risk for this procedure is a reported incidence of two patients who developed potentially blinding bilateral acute endophthalmitis following bilateral IVI.[10] This practice is fast evolving, but there is no published data evaluating bilateral same-session intravitreal anti-VEGF injection in Nigeria. The purpose of this research is to review the indications and safety profile of bilateral intravitreal anti-VEGF injection in a hospital population of a tertiary private eye care facility Southwest of Nigeria.

## Methods

This study was a retrospective review of all the patients that received same-session bilateral intravitreal anti-VEGF injections in Eye Foundation Hospital and Laser Center, Ikeja, Lagos, from March 2013 to March 2015. Data retrieved from the patient's medical record include demographics, indications for injections, intraoperative and postoperative complications, type of anti-VEGF injected, systemic comorbidities, and further treatment received.

Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 18 (SPSS Inc., Chicago, Illinois, USA), and reported as frequency distributions, percentages, and means ± standard deviation (SD). Statistical tests for significance of observed inter-group differences were performed using the Chi-square test for categorical variables. In all comparisons, statistical significance was indicated by a $P < 0.05$.

### Protocol of procedure

All patients underwent a preprocedure counseling session where details of the procedure were well-explained with information on potential risks, benefits, and available options of the planned bilateral simultaneous injections. Each patient signed an informed consent form before each injection. All the bilateral same-session IVI were routinely performed by a consultant, ophthalmologists, and trained residents according to a defined protocol of Eye Foundation Hospital and Laser Center.

This was strictly an aseptic procedure. Each eye was prepared separately with cleaning of the periorbital skin and eyelashes using 10% dilute povidone-iodine scrub. A sterile drape was put in place. The eyelid was held open by a speculum. Then, 5% dilute povidone-iodine and topical tetracaine drops were instilled on the ocular surface and fornix and left for approximately 3 min. A caliper was used to mark out the site of injection approximately 3.5 mm from the limbus. The intravitreal anti-VEGF was then injected either in the superotemporal or the inferotemporal quadrants depending on the physician's preference using a 30 or 32-guage needles. All patients in this study received 1.25 mg/0.05 ml of bevacizumab (Avastin®, Genentech, South San Francisco, CA, USA). A paracentesis was done. A sterile cotton bud was used to tamponade the site of injection after removal of the injecting needle. The eyelid speculum was then removed and syringe/needles discarded. Same procedure was now repeated for the second eye. However, no drops, materials, or instrument were reused in the preparation and injection of the second eye. Postinjection, patient was counseled and placed on a topical second-generation fluoroquinolone (ciprofloxacine) 3 times daily for 5 days.

The patients were instructed to report to the hospital immediately in the event of pain or reduction in the vision of either or both eyes.

## Results

During the study period, a total of 442 injections were performed on 126 eyes of 63 patients (M:F ratio; 1.4:1) with a mean age of 55.7 ± 15.6 SD years. The modal age group was 51–70 years [Table 1]. All the patients received injection Bevacizumab (Avastin; Genentech Inc., South San Francisco, California, USA- 1.25 mg). The most common primary indication for initiating bilateral intravitreal therapy was diabetic macular edema 23 (36.5%) followed by proliferative diabetic retinopathy 18 (28.6%), Table 2. The mean follow-up period was 40.6 ± 13.1 SD days (range: 1–364 days). A total number of 26 (41.3%) patients' required additional treatment such as laser and vitrectomy. A combined diabetes mellitus and hypertension accounted for most of the systemic comorbidities 28 (44.4%), followed by diabetes 21 (33.3%), hypertension 7 (11.1%), and sickle cell disease 2 (3.2%). Subconjunctival hemorrhage was the only complication seen in this study group with 6 (9.5%) occurring intraoperatively and 9 (14.3%) postoperatively. There was no association between intraoperative complication and age ($P = 0.66$, confidence interval [CI]

**Table 1: Demographic characteristics of patients**

| Age range | Sex, *n* (%) | |
|---|---|---|
| | Male | Female |
| 10-20 | 2 (5.4) | 0 (0) |
| 21-30 | 1 (2.7) | 2 (7.7) |
| 31-40 | 3 (8.1) | 1 (3.8) |
| 41-50 | 4 (10.8) | 6 (23.1) |
| 51-60 | 10 (27) | 9 (34.6) |
| 61-70 | 10 (27) | 4 (15.4) |
| 71-80 | 7 (18.9) | 4 (15.4) |
| Total | 37 (100) | 26 (100) |

**Table 2: Primary indications for injection**

| Indication | Number (%) |
|---|---|
| Branch retinal vein occlusion | 1 (1.6) |
| Choroidal neovascularization | 1 (1.6) |
| Central retinal vein occlusion | 1 (1.6) |
| Hypertensive retinopathy | 2 (3.2) |
| Myopic choroidal neovascularization | 1 (1.6) |
| Nonproliferative diabetic retinopathy | 23 (36.5) |
| Nonproliferative sickle cell retinopathy | 1 (1.6) |
| Polypoidal choroidal vasculopathy | 7 (11.1) |
| Proliferative diabetic retinopathy | 18 (28.6) |
| Proliferative sickle cell retinopathy | 2 (3.2) |
| Pseudophakic macular edema | 1 (1.6) |
| Rubeotic glaucoma | 1 (1.6) |
| Wet age-related macular degeneration | 4 (6.3) |
| Total | 63 (100) |

0.81–0.97) or gender ($P = 0.96$, CI; 0.81–0.96). There was also no association between postoperative complication and age ($P = 0.49$, CI; 0.54–0.77) or gender ($P = 0.99$, CI; 0.95–1.00). No eyes developed endophthalmitis, anterior chamber cell or flare, vitritis, vitreous hemorrhage, retinal detachment, or retinal pigment epithelial tear. There was no recorded death of any patient during the follow-up period.

## Discussion

Treatment of ophthalmic disease by IVI has revolutionized the field of ophthalmology. It is estimated that over four million IVIs were performed in the United States in 2013, a number that is expected to continue to increase.[11] Prior to the advent of the anti-VEGF agents, bilateral, same day IVIs were usually performed only in patients with sight-threatening disease. There is a long history of bilateral injection of intravitreal antibiotics and antivirals for conditions such as viral retinitis and endogenous endophthalmitis.[8] Efficient study of the safety and tolerability of such injections, however, is precluded by a high instance of disease-related complications. However, common ocular adverse events following intravitreal anti-VEGF injections unrelated to the underlying ocular disease include endophthalmitis, rhegmatogenous retinal detachment, and ocular hemorrhages.[12-14] A recent study has found that intravitreally injected bevacizumab can flow into the serum via systemic circulation.[15] Consequently, there are several potential systemic adverse events of intravitreal anti-VEGF which includes thromboembolic events, myocardial infarction, stroke, hypertension, gastrointestinal perforations, and kidney disease.[16,17] Bilaterally same-session intravitreal anti-VEGF injection, therefore, potentially presents an increased risk for both ocular and systemic adverse events to the patients.

Several investigators reported no significant difference in the occurrence rate of complications between bilateral simultaneous IVIs and unilateral injections.[8,18] Wang *et al.*[19] reported no significant difference in serum concentration of VEGF after bilateral injection of bevacizumab as compared to unilateral injections. The most dreaded result of bilateral, same day IVI was described in a case report of two patients who developed acute, bilateral endophthalmitis following bilateral IVI.[10]

This study recorded no major intra- or post-operative ocular or systemic complications. Other surveys have reported similar finding with no case of endophthalmitis.[8,18] However, in a larger sample population, Lima *et al.*[20] recorded 2 cases of culture-proven unilateral endophthalmitis representing 0.065% of the total number of injections given. There were too few injections in this study to truly estimate the rate of infectious endophthalmitis, as the incident rate is very low, being approximately 1 in 1291 to 1 in 4500 after intravitreal anti-VEGF agents.[21,22] A study involving a larger sample size population is, therefore, advocated to assess the true incidence rate of infection.

Simultaneous bilateral ocular hemorrhages are potential adverse effects following IVI of anti-VEGF agent in both eyes. This study recorded a few and variable events of intraoperative and postoperative subconjunctival hemorrhages. This is usually not sight-threatening. However, vitreous and subretinal hemorrhage, though rare, are potentially bilaterally blinding complications that could follow same-session injection of the two eyes. Although intravitreal bevacizumab has been used for the effective treatment of subretinal hemorrhage following neovascular ARMD,[23] Chieh and Fekrat[24] have reported a case of submacular hemorrhage that occurred 4 weeks after bevacizumab therapy for occult choroidal neovascularization in ARMD.[24]

In this study, bevacizumab was used for all the patients, and no ischemic strokes were reported. The MARINA (minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular AMD) study focused only on the relative risk for the different dosage regimen of intravitreal ranibizumab in causing stroke in the treated patients.[1] Due to the uncertainty of stroke risk with these

agents, it may be wise to be cautious in patients with strong risk factors for ischemic stroke (history of stroke/ischemia, uncontrolled hypertension, etc.).[25] Findings from this study showed that a combined medical history of diabetics and hypertension accounted for most of the systemic comorbidities seen in these patients.

The mean age of our cohort is relatively high. However, this is lower in a similar study by Davis *et al*.[8] This difference could be accounted for by the difference in the study population. The later study focused only on bilateral anti-VEGR injections in patients with ARMD - a disease with predilection for relatively older people. By the whole, this underscores the need for eye-care planners, implementers, and eye health policy makers to deploy the necessary resources and logistics for retinal disease care in the elderly.

Diabetes-related ophthalmic diseases accounted for majority of the primary indication for bilateral anti-VEGF IVI, in this study. In a similar study by Abu-Yaghi *et al*.,[25] diabetic macular edema was the primary indication for injection in 71 of 74 patients. There are approximately 93 million people with diabetic retinopathy, 17 million with proliferative diabetic retinopathy, 21 million with diabetic macular edema, and 28 million with vision-threatening diabetic retinopathy worldwide.[26] In Nigeria, several investigators have reported a prevalence of diabetic retinopathy ranging from 15% to 36%.[27,28] Longer duration of diabetes and poorer glycemic and blood pressure control are strongly associated with diabetic retinopathy. These data highlight the substantial and growing worldwide public health burden of diabetic retinopathy and the importance of modifiable risk factors in its occurrence.[26]

This study did not formally address the question of satisfaction after bilateral injections. However, follow-up experience shows that none of the patients who were switched from staggered injection regimen to same-session bilateral IVI or those who were primarily started on same-session bilateral injections switched back to a staggered injection design. However, a broad-based formal prospective research design of patient's satisfaction survey would be helpful in objectively evaluating patient's preference.

While this study provides a much needed early data on the safety profile and informal evidence of patient's acceptance of concomitant bilateral IVI of anti-VEGF agents, extrapolation of the findings is, however, limited by its retrospective nature, short study period, relatively small sample size, and drug monotherapy. A large sample size of longer duration comparing different anti-VEGF agents and multi-center design preferably involving diverse hospital/care setting is suggested.

## Conclusion

Despite the limitations, this study further supports the relative safety of bilateral same-session intravitreal anti-VEGF therapy. However, patients must be counseled regarding the possible complications and educated about the symptoms of endophthalmitis, vitreous hemorrhage, or retinal detachment. Furthermore, extra caution should be exercised on those with systemic comorbidities that present a higher risk of systemic adverse events in the patients.

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**Conflicts of interest**
There are no conflicts of interest.

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