

Bilateral same-session intravitreal injections of anti-vascular endothelial growth factors

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Abstract

• **AIM:** To document the indications, safety and possible complications of bilateral same-session intravitreal anti-vascular endothelial growth factor (VEGF) injections performed in the ophthalmic operating room.

• **METHODS:** A retrospective case series study. Consecutive records of seventy four patients receiving simultaneous bilateral intravitreal injections of either ranibizumab or bevacizumab, between September 2010 and September 2013, were reviewed and the outcomes were assessed. Data collected included number of injections, indications for injections, pre-injection and post-injection visual acuity (VA), pre-injection and post-injection intraocular pressure and ocular and systemic complications/complaints after each injection.

• **RESULTS:** A total of 342 injections were administered to 74 patients, with a mean of 4.62 injections per patient. Seventy-three patients received bevacizumab (Avastin; Genentech Inc., South San Francisco, California, USA) alone, and only one patient received both bevacizumab and ranibizumab (Lucentis; Genentech Inc.) distributed between the injections. Pre- and post-injection VA follow-up measurements were available for 65 patients. Mean follow up period was 22mo. The indications for initiating therapy were choroidal neovascular membrane from age-related macular degeneration (3 patients) and diabetic macular edema (71 patients). The mean Snellen VA before each injection was 6/22. The next post-injection follow-up mean Snellen VA was 6/20. One patient had a painful, culture-positive endophthalmitis in one eye 3d after bilateral bevacizumab. Another patient had a painless subconjunctival hemorrhage in one eye. No other ocular or systemic adverse side effects/complaints have been registered in this study group.

• **CONCLUSION:** Bilateral same-session intravitreal injections using a separate povidone-iodine preparation, speculum, needle, and syringe for each eye are well-tolerated. None of the subjects in this study requested to switch to alternating unilateral injections. Proper patient counseling as to the risk of complications with this procedure is necessary.

• **KEYWORDS:** anti-vascular endothelial growth factor; diabetic macular edema; age-related macular degeneration; endophthalmitis; visual acuity

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INTRODUCTION

Intravitreal eye injections of medications and vitreous substitutes have been widely used in the treatment of several ophthalmic diseases like wet age-related macular degeneration (AMD), macular edema attributable to a variety of causes, ocular inflammations, endophthalmitis, to tamponade retinal detachments and to address other ocular diseases^[1]. Among the most famous medications injected are the anti-vascular endothelial growth factor (VEGF) agents. Bevacizumab is a humanized full-length monoclonal antibody that binds to and inhibits VEGF. It is widely used in an off-label manner to inhibit VEGF in the eye^[2]. Ranibizumab is a recombinantly produced humanized antibody (Fab) fragment that binds all active forms of VEGF-A, and is FDA approved for ophthalmic use^[3].

Choroidal neovascularization (CNV) attributable to AMD is most commonly treated with intravitreal injections of ranibizumab or bevacizumab, either monthly or less frequently, according to a preset protocol^[4,5]. Intravitreal anti-VEGF injections are now considered by many experts to be the standard of care for diabetic macular edema involving the fovea, and has been proven effective in treating macular edema secondary to central and branch retinal vein occlusions^[6-8]. They are also used peri-operatively in diabetic vitrectomy^[9]. This, coupled with the post-injection follow-ups and increased risk of side effects, constitutes a real burden to

the patient, his family and the ophthalmologist as well, especially if each eye is given the injection separately. Many patients continue to inquire about and request bilateral injections on the same day.

The purpose of this study is to review indications, characteristics and adverse events after bilateral intravitreal injection of anti-VEGFs and to document patients' reactions to this regimen and whether any of them requested to change to unilateral injections instead.

SUBJECTS AND METHODS

Subjects This retrospective review has granted approval by the Institutional Ethics Committee and follows the principles outlined in the Declaration of Helsinki (2008). When creating a medical file for the first time, patients treated at our institution grant access to their medical records for retrospective review and analyses. Each patient signed an informed consent form before each injection. A search through patients' files was conducted for all those who underwent bilateral intravitreal injections performed between September 2010 and September 2013. None of those patients refused to grant access to their medical files for research purposes thus no cases were excluded for that reason. The following data were recorded from the clinical notes: age and gender of the patient, diagnosis, intravitreal drugs received by the patient, number of injections, site of injections, visual acuity (VA) and intraocular pressure (IOP) before each injection and at the next visit after the injection and ocular and systemic complications/ complaints after the injections. In case a patient took multiple injections, data was drawn from the first follow up visit following the last injection.

The patients were asked in the first follow-up specifically about pain, redness, reduced vision, floaters and or flashes of light to assess for any post-injection complications, such as endophthalmitis, vitreous hemorrhage, or retinal tears. Findings were recorded in the patients' files. In addition, new medical problems, such as a recent heart attack, stroke, or systemic infection were also looked for during the following visits. Further, a review of medical records, where available, was performed to assess for possible systemic complications. A review was also conducted to look for any patient who requested to switch to alternating unilateral injections because of intolerance to simultaneous bilateral injections.

Methods

Technique for intravitreal injection All patients got through a discussion of the risks, benefits, and alternatives of the planned injections. Each patient signed an informed consent form before each injection. The intravitreal injections were performed in the ophthalmic operating room by either a consultant or a qualified ophthalmology resident.

The surface of the eye was anesthetized by applying topical

preservative free oxybuprocaine hydrochloride 0.4% (Bausch & Lomb, France) drops initially to both eyes. Periocular area, eyelids, eyelashes, ocular surface and fornices were prepared by 5% diluted povidone-iodine, and oxybuprocaine hydrochloride 0.4% drops were instilled and were left on the surface of the eyes for approximately 3min. Next, eyelids of the right eye were held open by a speculum. Attention was paid not to touch the tip of any of the instruments. Next, the intravitreal drug was injected 3.5 mm posterior to the temporal limbus either in the superotemporal or the inferotemporal quadrants using 30 or 32-gauge needles. The drug was injected and then the needle was removed. The eyelid speculum was then removed from the eye and the syringe with its needle was thrown in a special container. A separate sterile eyelid speculum was placed in the other eye, and the same injection procedure was performed with a separate syringe and needle. An antibiotic ointment was applied on both ocular surfaces and the patient was given a prescription of ofloxacin eye drops to be taken four times daily for three days. Each patient received a phone call on day 3 or 4 after the injection to inquire about possible complications such as drop of vision and/or eye pain. The patients were encouraged to come to the emergency department if they complained of either eye pain or drop of vision.

Precautionary measures to limit the chances of bilateral infection included thorough preparation of each eye with povidone -iodine and using a separate sterile injection kit for each eye. For bevacizumab, each vial of the medication was used to prepare 15 injections. Those were drawn and prepared a few minutes before injection under sterile conditions. For ranibizumab, the medication in each vial was split into two injections under sterile conditions.

RESULTS

A total of 342 bilateral intravitreal injections were given to 74 patients, with a mean of 4.62 injections per patient (range 2 to 20 injections; standard deviation, 1.40). Of the 342 injections, 334 (97.7%) were of bevacizumab (Avastin; Genentech Inc, South San Francisco, California, USA - 1.25 mg), while 8 (2.3%) were of ranibizumab (Lucentis; Genentech Inc -0.5 mg). Mean follow up period was 22mo (range 6 to 36mo).

The primary indications for initiating therapy by bevacizumab or ranibizumab were CNV from AMD (3 patients) and diabetic macular edema (71 patients). All patients were followed 3-5d post-injection. Pre-injection IOP measurements were available for 65 (87.8%) patients while post-injection IOP follow-up measurements were available for 60 (81.0%) patients. Mean IOP was 13.66 mm Hg before injections and 14.41 mm Hg at the closest follow-up after the

injections. The mean VA by Snellen chart before each injection was 6/22. The next post-injection mean follow-up Snellen VA was 6/20. There was no significant difference in the mean Snellen VA before and after the injections in our study ($P=0.50$). The difference in IOP before and after the injections was also not significant ($P=0.30$).

One patient presented to the emergency room three days after his second bilateral intravitreal bevacizumab injection session complaining of right ocular pain, decreased vision, mild redness and photophobia. Vision was 6/120 before the injection, and deteriorated to hand motions on presentation 3d after the injection. Slit lamp examination revealed ciliary injection and a leveled hypopyon of 1 mm. The patient had previously received bilateral bevacizumab injections without complications. A parsplana vitreous tap with injection of intravitreal vancomycin and ceftazidime was performed on the same day. The vitreous specimen was culture-positive for coagulase-negative staphylococcus. The patient was managed with intravitreal antibiotic injections and fortified antibiotic eye drops and cycloplegics. The inflammation subsided but the patient continued to have persistent vitreous opacities that precluded a good fundus exam. B-scan ultrasonography showed a flat retina. This was addressed by performing a parsplana vitrectomy with gas tamponade and extraction of a concomitant cataract with intraocular lens implantation in that eye five months later. After an uneventful surgery her VA improved to 6/30 and the patient underwent further bilateral intravitreal injections several months later for worsening diabetic maculopathy with no further problems.

Another patient had persistent redness in one of his treated eyes which, after careful examination, was revealed to be a simple subconjunctival hemorrhage. This was treated conservatively by observing the patient. No patients had a stroke, cerebrovascular accident, cardiovascular or thromboembolic event during the follow-up period. None of the patients requested alternating unilateral injections at any stage of their treatment.

During the same three-year period, 3634 unilateral injections were performed in our institution, 89 percent of which were to treat diabetic macular edema, whereas the rest were administered for wet AMD and other ocular pathologies. According to unpublished morbidity reports, there were two cases of post-injection endophthalmitis (one being culture-positive and the other culture-negative). Both cases were treated successfully with vitreous tapping and injection of intravitreal antibiotics. Four cases who were unilaterally injected on the same day suffered from mild to moderate chemical corneal injury due to the use of concentrated povidone-iodine from a mislabeled container. They were

treated by irrigation followed by antibiotic ointment administration for 5d and recovered uneventfully. No major systemic complications were reported.

DISCUSSION

In an attempt to reduce the burden on patients and practices, many clinicians have started to administer bilateral same-day intravitreal injections. In one survey done by Green-Simms *et al*^[10], forty-six percent of retina specialists in the United States performed bilateral same-day intravitreal injections.

Local complications of intravitreal injections have been reported and include IOP elevations, uveitis, retinal detachment and subretinal hemorrhage^[11]. The most dreaded ocular complication following intravitreal injections is endophthalmitis, which can be infective or sterile. Elevations in IOP after intravitreal injections of anti-VEGFs can be short lived or sustained, with most cases having a delayed onset (after 10 injections), perhaps reflecting a cumulative effect^[12,13]. Acute closed angle glaucoma was reported following injecting anti-VEGF intravitreally^[14].

Medications injected into the vitreous cavity reach the systemic circulation and can even exert an effect on the contralateral eye^[15]. Adverse systemic side effects of intravitreally administered anti-VEGF medications have been reported and include acute myocardial infarction, strokes and thromboembolic events^[16]. Although rare, it remains unknown whether an increase in systemic dose due to bilateral injections causes an increased risk.

A series of studies looked into the pharmacodynamics of intravitreal anti-VEGF medications and reported no significant difference in the occurrence rate of complications between bilateral simultaneous intravitreal injections and unilateral injections^[17-19]. Wang *et al*^[20] reported that there was no significant difference in serum concentration of VEGF after bilateral injection of bevacizumab compared to unilateral injections.

In this study, performing bilateral intravitreal injections on the same day was very well-tolerated by patients in an operating room setting. None of the patients requested alternating unilateral injections after receiving bilateral injections.

There were too few injections in this study to truly estimate the rate of infectious endophthalmitis, as the rate is very low, being approximately 1 in 1291 to 1 in 4500 after intravitreal anti-VEGF agents^[21,22]. Therefore, it would take many more patients in order to assess the true incidence of infection. Another adverse event is the occurrence of noninfectious endophthalmitis, which has been reported following intravitreal triamcinolone and intravitreal bevacizumab^[23]. These eyes are usually pain-free and typically present with blurred vision and a vitritis, with or without a hypopyon^[24].

The inflammation resolves without treatment, but it may take several months for the vitritis to clear.

The patient in our study who was treated with bilateral intravitreal bevacizumab had a culture-positive endophthalmitis in only one eye. Since the patient had ocular pain, typical signs and positive cultures, this was clearly a case of infectious endophthalmitis. We believe that this complication is not related to the bilateral procedure. Interestingly, bevacizumab from the same source vial was used for both eyes. This suggests the possibility that the inflammation may have been caused by something in the syringe, needle, or surface of the eye tracking into the eye with the injection, but not the drug itself. Furthermore, bevacizumab from the same vial was also used to treat 9 other patients on the same day without complications. Another patient complained of persistent redness in one of his eyes on his first follow up visit, but reported no pain or visual symptoms. This was found to be a simple subconjunctival hemorrhage and the patient was reassured and treated conservatively with observation. After 3wk, the subconjunctival hemorrhage had completely resolved. Again, this complication happened in only one eye and was not related to the bilateral administration of the injection. In the involved eye, the reason was most likely due to minor trauma, as the needle used to give the injection touched a small conjunctival vessel resulting in the observed hemorrhage, as was evident on slit lamp biomicroscopy.

Since this was a retrospective study, the time between the assessments before and after the injection was variable. The closest follow-up to the injection was used when recording VA or IOP, as we wished to determine whether the patient lost vision or had a change in IOP as a complication of the injection procedure, rather than ongoing disease process. The total follow-up was recorded as this allows time for any adverse systemic events to manifest.

To document systemic complications, patients' medical records were reviewed. Patients were also asked to report any new medical adverse events at any subsequent visit. In our study, no patients suffered from a stroke, cerebrovascular accident, or cardiovascular or thromboembolic event during the follow-up period.

None of the patients who received bilateral intravitreal injections requested alternating unilateral injections. Many patients preferred same day injections because this saved time and cost as they required less visits for their treatments. Similar preferences were reported by other researchers: for instance, Mahajan *et al*^[25] found that more than 90% of the patients in their study preferred bilateral injections to unilateral ones.

In conclusion, despite the limitations of this retrospective

study, it further supports the relative safety of bilateral same-session intravitreal anti-VEGF therapy. Bilateral anti-VEGF injections performed on the same day were preferred over alternating injections and were well-tolerated. Patients must be counseled regarding the possible complications and educated about the symptoms of endophthalmitis, vitreous hemorrhage or retinal detachment. A review of possible systemic complications is necessary. For naïve patients requiring bilateral intravitreal injections, we offer the option of same-session bilateral injections using the aforementioned aseptic technique as a practical and safe choice for patients and for care-providers with busy clinics alike. Further prospective studies with large patient numbers and extended follow up periods are necessary to better judge the characteristics, safety and possible local and systemic effects of bilateral intravitreal injections of anti-VEGF medications.

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