


Safety of Intravitreal Injection Guide

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Abstract

Purpose: To evaluate the safety of our developed intravitreal injection guide. **Methods:** Retrospective review of all case notes for consecutive patients treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections at the Department of Ophthalmology, Nagasaki University Hospital in Japan between January 2013 and December 2014. We included all patients who had at least 1 intravitreal anti-VEGF injection done within the study period. Data collected included demographics, indications of intravitreal anti-VEGF injections, type of injected drug, usage of intravitreal guide, experience of physicians, and any complication that occurred during or after the procedure. **Results:** The study included 256 patients (154 males and 102 females) who underwent 992 intravitreal anti-VEGF injections from January 2013 until December 2014. The mean age of the patients was 70.8 ± 11.3 years. Of total injections, 907 (91.44%) were done using the intravitreal guide, 60 (6.04%) were done without using the guide, and only 25 (2.52%) injections were not determined. Local complications include 1 (0.1%) case uveitis, 1 (0.1%) case retinal tear, and 1 (0.1%) case amaurosis fugax. There were no major complications as cataract, retinal detachment, and endophthalmitis. No systemic complication was encountered. All complications occurred in the guide group without statistically significant difference in comparison to without guide group ($P = 1.0$). All complications were related to experienced group without significant difference in comparison to limited experienced group ($P = .28$). **Conclusion:** We conclude that the process of intravitreal injection with our developed intravitreal injection guide is safe and easy even for limited experienced physicians.

Keywords

intravitreal injection guide, anti-vascular endothelial growth factor (anti-VEGF), complications of intravitreal injection

Introduction

Intravitreal injections of air were first used in 1911 for the purpose of repairing retinal detachments.¹ Since that time, intravitreal injections have been used to treat a variety of ophthalmic problems. Anti-vascular endothelial growth factor (anti-VEGF) agents are the most commonly administered intravitreal agents today and are used to manage a wide variety of ocular diseases that previously had limited treatment options.²⁻⁵ Commonly treated ocular diseases include age-related macular degeneration (AMD),² diabetic retinopathy,³ retinal vein occlusion (RVO),⁴ and intraocular tumors.⁵ It is important to master the technique of effective injection for the patient safety. For the injection, in-depth knowledge of the surgical anatomy of the eye is essential to avoid complications, such as lens touch and retinal injury. In order to achieve this safety, we developed an intravitreal injection guide.

The intravitreal injection guide is very light (weight = 6 g) and is made of titanium alloy. The intravitreal injection guide (length = 105 mm) consists of 3 parts; main body, fixation ring, and guide for the needle (Figures 1 and 2). The main body portion is made up of an elongate rod with the handle at one end for holding the device. The main body is connected to

incomplete circular ring (approximately 315°) for fixation of the globe. The handle makes an obtuse angle with the fixation ring of approximately 120°. This obtuse angle allows good visualization of the fixation ring during its insertion on the patient's eye. The fixating ring is provided with few ridges in its undersurface to facilitate good contact and fixation with the patient's eye. These ridges are sufficiently raised to hold the device steady in position on the patient's eye during an intravitreal injection without injuring the eye. By placing the fixation ring (12 mm diameter) on the limbus of the cornea, fixation of the patient's eye could be easily attained (Figure 2). Incomplete fixating ring with a break of nearly 5.5 mm width enables the physician to access the limbus of the patient's eye.

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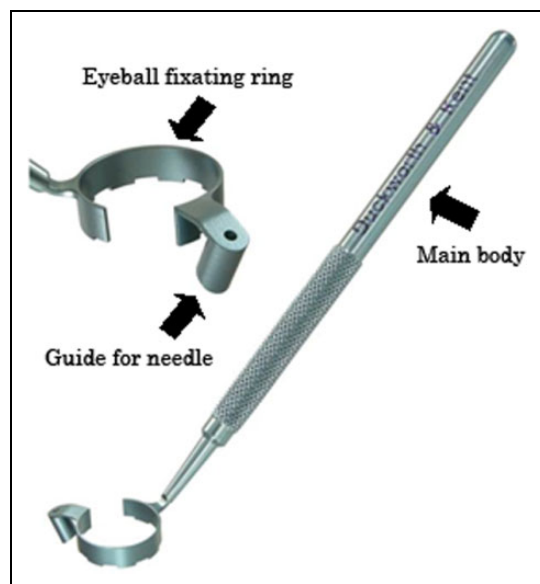


Figure 1. Injection guide consist of main body, eyeball fixation ring, and a guide for needle.

The fixation ring is attached to a guide for the needle used for intravitreal injection. The guide for the needle has a narrow hollow pass (lumen = 0.5 mm in diameter) for needle introduction with 2 holes. The superior hole for introduction of the needle and the inferior hole touch the sclera at predetermined distance of 3.5 mm from the limbus. The axis of the lumen makes an angle of 65° with the horizontal plane. Through this lumen, half inch of needle could be inserted to the vitreous cavity through the pars plana without fear in touching the lens or the retina (Figure 3). In addition, the distance between the 2 holes (length of the lumen) equals 5 mm that is sufficient to keep the needle in its place without holding the syringe.

Injection procedure became much easier compared to the conventional method because physicians, after piercing the needle inside the vitreous cavity, can do intravitreal injection by pressing the plunger without the need for holding the syringe. By using this intravitreal injection guide, the procedure is easy and safe even for physicians with no or limited knowledge of ocular surface anatomy.

In order to prove our claim about the safety of our intravitreal guide, we organize this study. In this study, we evaluated the safety of using our developed intravitreal guide by determining ocular and systemic complications during and following its use for anti-VEGF injection.

Materials and Methods

Retrospective review of all case notes for consecutive patients treated with intravitreal anti-VEGF injections at the Department of Ophthalmology, Nagasaki University Hospital in Japan between January 2013 and December 2014 was conducted.

This retrospective study adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with the

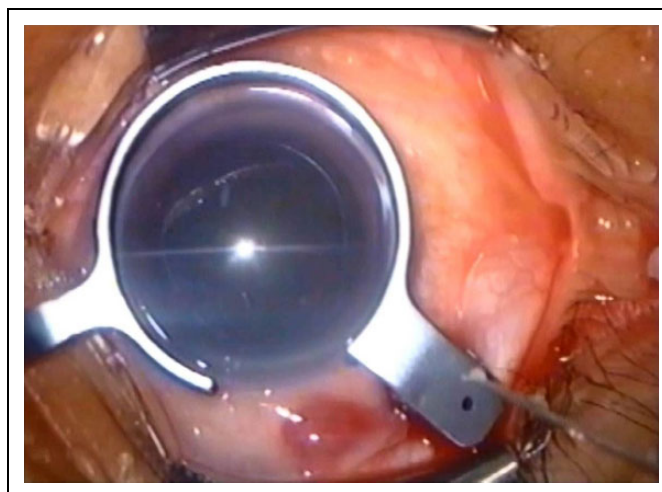


Figure 2. Fixation of eyeball with the injection guide.

Health Insurance Portability and Accountability Act regulations. We included all patients who had at least 1 intravitreal anti-VEGF injection done within the study period. Anti-VEGF drugs used in this study included ranibizumab (Lucentis; Novartis, Basel, Switzerland), aflibercept (Eylea; Bayer, Leverkusen, Germany), pegaptanib (Macugen; Eyetech Pharmaceuticals/Pfizer, New York, New York), and bevacizumab (Avastin; Genentech, San Francisco, California). Data collected included demographics, indications of intravitreal anti-VEGF injections, type of injected drug, usage of intravitreal guide, and any complication that occurred during or after the procedure. Complications include both systemic and ocular adverse events that occurred related to the procedure. Comparison between using guide group and not using guide group was done to confirm the safety of procedure. Also, comparison between experienced group and limited experienced group was done to reveal any difference on using our intravitreal device. Limited experienced one is the physician with less than 3 years of practicing ophthalmology. Patients with insufficient or incomplete data were excluded from this study.

Procedure of Intravitreal Injection Using Intravitreal Guide

All patients were checked for their intraocular pressure and blood pressure before the injection procedure. All injections were performed in the minor surgical room in outpatient clinic in the hospital. The entire procedure was performed under strict aseptic conditions. Ophthalmologists wear sterile gloves and facemask for administration of injections. We explained to the patient about the procedure of an intravitreal injection using the guide. Topical anesthesia was accomplished by 0.4% Benoxil (oxybuprocaine hydrochloride) eye drop. Disinfection of the lids and the conjunctival sac was done using PA iodine wash after a sterile lid speculum was applied. Also, 5% povidone-iodine was used to disinfect the periocular skin for at least 30 seconds. Then we apply 1 drop of 4% Xylocaine (lidocaine)

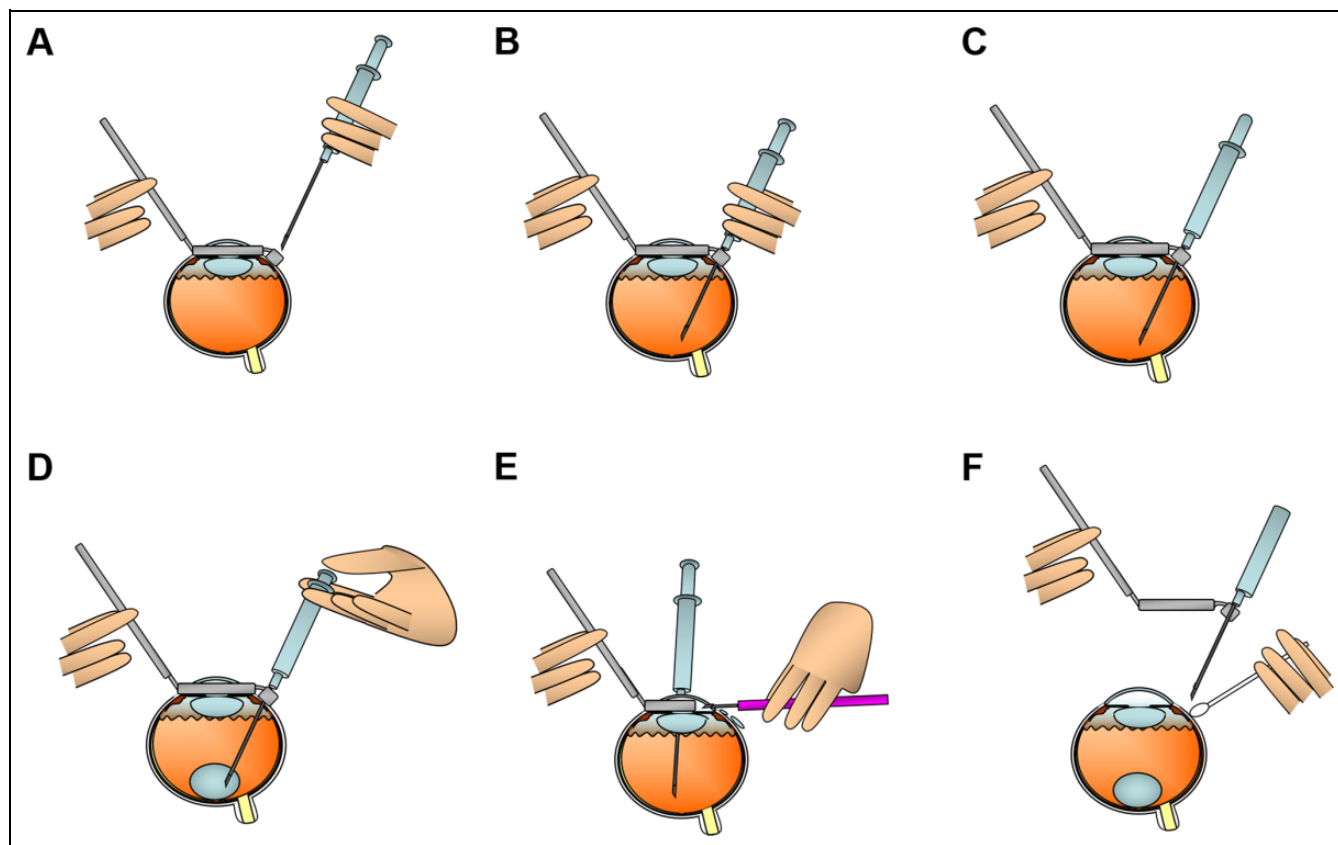


Figure 3. Steps of intravitreal injection using intravitreal guide. (A) Fixation of the eye. (B) Introduction of the needle. (C) Needle in the eye without hand holding. (D) Injection. (E) Paracentesis for aqueous tapping. (F) Removal of the needle and guide.

eye drop and 1.5% Cravit (levofloxacin) eye drop for each. Holding the intravitreal guide with nondominant hand and applying the fixating ring to the limbus of the patient's eye are shown in Figure 3. The physician must confirm that the whole ring is stuck to the patient's eye to accomplish good fixation of the globe. The physician holds the syringe with his dominant hand and passes the needle (30 gauge) through the lumen of the guide for the needle until touching the eyeball. After piercing the eyeball with the needle, injection of intravitreal drug is completed. The physician can remove the needle after checking the intraocular pressure. If the intraocular pressure is high, the needle is kept inside the globe, and paracentesis of the cornea is done to decrease the pressure through the incomplete part of the fixating ring. Then, the removal of the intravitreal needle is completed. By this way, vitreous is protected from protrusion from the wound during the removal of the needle while high intraocular pressure. After the injection, the patient is checked for ability to count finger.

Then, application of 1.5% Cravit eyedrop and 0.3% Tarivid (ofloxacin) ophthalmic ointment to the conjunctival sac of the patient is done. The patient is instructed to use 1.5% Cravit eyedrop 4 times daily for 3 days.

All patients will have their blood pressures checked again before being discharged by the nurse, with advice to contact the hospital if they experienced increasing pain or worsening of vision in the days following the procedure. After finishing

the procedure, the guide is washed and sterilized to be ready for reuse.

Statistical Methods

Continuous variables were assessed for normality and summarized using the mean (standard deviation) as appropriate. Statistical analyses were conducted using StatMate (version 4.01; ATMS Co. Ltd., Tokyo, Japan). Values of $P < .05$ were considered statistically significant.

Results

The study included 256 patients (154 males and 102 females) who underwent 992 intravitreal anti-VEGF injections from January 2013 until December 2014. The mean age of the patients was 70.8 ± 11.3 years (range, 39-93 years). The intravitreal anti-VEGF injections were 554 (55.9%) injections for the treatment of AMD, 237 (23.9%) injections for central RVO, 128 (12.9%) injections for branch RVO, 70 (7%) injections for diabetic macular edema, and 3 (0.3%) injections for choroidal hemangioma (Figure 4). Intravitreal anti-VEGF injections given were ranibizumab 543 (54.7%), aflibercept 290 (29.3%), bevacizumab 152 (15.3%), and pegaptanib 7 (0.7%; Figure 5). Each patient had an average of 3.91 injections (range, 1-18). Of total injections, 907 (91.44%) were

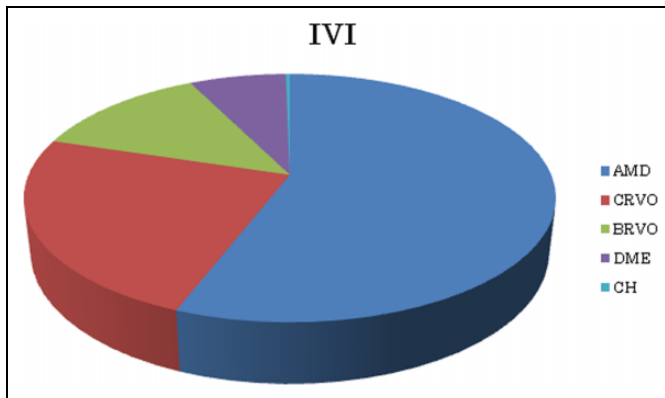


Figure 4. Diseases treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections. AMD indicates age-related macular degeneration; BRVO, branch retinal vein occlusion; CH, choroidal hemangioma; CRVO, central retinal vein occlusion; DME, diabetic macular edema; IVI, intravitreal injection.

done using the intravitreal guide, 60 (6.04%) were done without using the guide, and 25 (2.52%) injections were not determined. The mean follow-up period was 83 ± 88.0 days after last injection.

No systemic complications have been encountered. Ocular adverse events potentially related to intravitreal injection were 3 (0.3%) cases. All complications occurred in the guide group without statistically significant difference in comparison to without guide group ($P = 1.0$). All complications were related to experienced group without significant difference in comparison to limited experienced group ($P = .28$). There were no major complications as cataract, retinal detachment, and endophthalmitis.

Local complications include 1 (0.1%) case uveitis, 1 (0.1%) case retinal tear, and 1 (0.1%) case amaurosis fugax. Amaurosis fugax was transient and occurred just after intravitreal injection. Disappearance of amaurosis fugax occurred after taking rest for a while in the hospital. Retinal tear discovered after 2 month of the injection and treated by laser therapy. Uveitis occurred after 3- and 6-month postinjection and improved totally with local use of corticosteroid eye drop. Uveitis case occurred after intravitreal injection of ranibizumab.

Discussion

Intravitreal injections have become a widely accepted treatment modality for several ophthalmic diseases.⁶ In recent years, new indications for the recurring use of anti-VEGF intravitreal injections have risen.^{2-5,7} Despite the potential risks of intravitreal injections,¹ there is little agreement among clinicians and researchers regarding acceptable injection techniques.^{8,9}

In this study, there was no statistical difference between the incidence of complications in both intravitreal injection groups with a guide and without a guide ($P = 1.0$). Local complications were not serious and almost not related to the method of injection. There were no complications in the limited experienced physicians group. Therefore, the guide might benefit

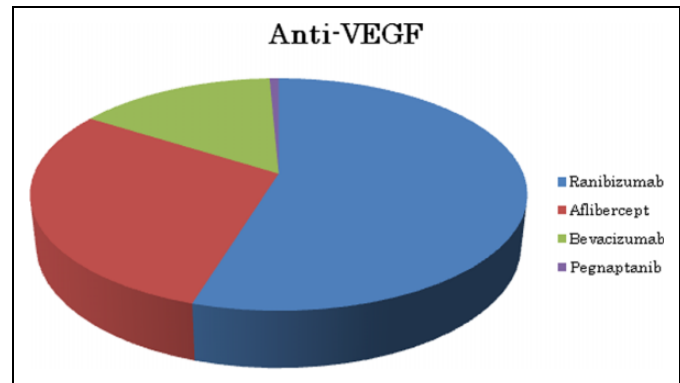


Figure 5. Anti-vascular endothelial growth factor (VEGF) drugs used in the study.

general ophthalmologists learning to do injections, residents in training, or support personnel such as nurses who are now performing injections in some countries.

We discovered 1 case of retinal tear after 2 month of intravitreal injection, and the case was treated successfully by laser therapy. Although retinal tears can occur during the natural history of neovascular AMD, most retinal tears seen in clinical practice appear to be temporally associated with anti-VEGF therapy in eyes with vascularized pigment epithelial detachments.¹⁰⁻¹² Various authors have attempted to explain the incidence of retinal tears in eyes shortly after treatment with intravitreal anti-VEGF therapy.^{13,14} Anti-VEGF therapy may cause contraction and fibrosis of the choroidal neovascularization, which rips the overlying retinal pigment epithelium.^{15,16} Other authors have suggested that the intravitreal injection procedure could cause vitreomacular traction¹⁷ or rapid shifts in intraocular pressure resulting in an retinal tear.¹⁸

In our study, we diagnosed 1 case of uveitis following intravitreal injection of ranibizumab. Studies monitoring the safety of intravitreal ranibizumab injections have identified noninfectious acute uveitis as a sequelae of the drug.¹⁹⁻²² The etiology of this drug-induced uveitis is speculative at best since it occurs rarely, and there is no histopathologic data with which to correlate the phenomenon. The following mechanisms have been proposed: (1) toxic response to the drug or excipients, (2) direct blood-aqueous or blood-retinal barrier compromise by drug or excipients, (3) immune response to the drug or excipients, and (4) rebound inflammation secondary to VEGF suppression.²³ So, we can determine that all previous complications are not related directly to the method of intravitreal injection guide.

In order to manage an intravitreal injection procedure, several instruments are needed all of which require sterilization prior to reuse. A speculum is needed to hold the eye open, a forcep is also used to hold and steady the eye as well as a set of callipers to measure the required distance from the limbus to the injection site. In addition to this level of instrumentation, the person undertaking the intravitreal procedure must also have a significant degree of skill and experience with such medical procedures. Accordingly, it is better to provide a

device for use during an intravitreal injection procedure, which reduces the number of instruments required during the procedure and reduces the complexity of the procedure.

More particularly, we need a device that relates to improved means for performing an intravitreal injection with the benefits of improved safety for the patient and increased efficiency for the practitioner. Nowadays, because of tremendous increase in the number of intravitreal injections, it cannot always be scheduled in advance, and each injection requires several steps to prepare the eye and safely perform the injection. The time required to perform injections can thus disrupt office schedules, resulting in unexpected prolongation of patient waiting times and increasing stress on experienced physicians. Therefore, it would be desirable to provide a method and system to standardize and simplify the intravitreal injection process, improve patient comfort and safety, and can be done by limited experienced physicians.

We developed an intravitreal injection guide to make these procedures less burdensome and safer. Our developed intravitreal injection guide can lead to reduction in the time and resources needed for the injection. Also, safer injections would be a boon to the profession and patients alike.

We can enumerate some advantages of our intravitreal injection guide in the following points:

1. We do not have to measure the location of the needle leading to quit the necessity for calipers.
2. Both eyeball and needle used for intravitreal injection are fixed with the use of our developed device. The location of the needle in the eyeball is unstable by conventional intravitreal injection method with possibility of touching the lens and/or the retina. When using intravitreal injection guide appropriately, the danger of touching the lens and/or the retina becomes very limited.
3. Protection against high ocular pressure occurring just after intravitreal injection.

The increase in ocular pressure is not often after intravitreal injection of a little amount of medicine as anti-VEGF medicine, but it is more frequently after intravitreal injection of large volume as gas which can lead to blockage of choroidal and optic nerve circulation. In addition, vitreous could be prolapsed from injection hole by the high ocular pressure. Using intravitreal injection guide, surgeon can remove aqueous humor to guard against the increase in intraocular pressure after introduction of the needle and before injection of big volume of gas or medicine.

4. The intravitreal injection guide is very light and at the same time is firm because it is made of titanium alloy.
5. The design of the device is excellent in which the handle makes an obtuse angle with the fixation ring of approximately 120°. This obtuse angle allows good visualization of the fixation ring during its insertion on the patient's eye.
6. Injection procedure with guide is easy and safe. Physicians or even nurses with limited or no knowledge of

ocular surface anatomy can do it. Reduction in the number of instruments required during the procedure.

7. In cases of intravitreal injection of large amounts of anticancer drugs using little by little technique every 5 minutes, using intravitreal injection guide adds more safety and becomes easier process.

We conclude that the process of intravitreal injection with our developed intravitreal injection guide is safe and easy. This guide might benefit general ophthalmologists learning to do injections, residents in training, or support personnel such as nurses who are now performing injections in some countries.

Ethical Approval

Ethical approval for this study was obtained from the Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences (Approval number: 08073132).

Statement of Informed Consent

Written informed consent was obtained from all subjects before the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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