



REVIEW ON INTRAVITREAL INJECTION AND ITS TECHNIQUES

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Abstract:

In ophthalmology, injecting or implanting drugs directly into the vitreous cavity has become a regular practice. Intravitreal injections are used to treat neovascular age-related macular degeneration, clinically significant macular edema/proliferative diabetic retinopathy, cystoid macular edema following retinal vein occlusions, uveitis, endophthalmitis, and choroidal neovascular membrane secondary to multiple retinal diseases, among other conditions. The process for intravitreal injection according to VRSI guidelines has been detailed in full. Intravitreal injection complications include those related to the procedure as well as those related to the substance used. It is critical for retina experts to master the proper method for intravitreal injection in order to ensure patient safety and minimize problems.

KEYWORDS: Intravitreal injection, Retina, Antimicrobials, Antivirals and Steroids

I. INTRODUCTION

In ophthalmology, intravitreal injection is becoming a more essential tool. Ohm reported the first injection of air into the vitreous cavity for the treatment of retinal detachment in 1911, and interest in the technique grew in the 1940s with research employing antibiotic injections for endophthalmitis. [1]

In ophthalmology, delivering drugs directly into the vitreous cavity through injection or implant has become standard. When compared to other means of drug delivery, it provides for larger concentrations in the eye with a lower probability of systemic absorption. It also gets around the eye's blood-retinal barrier. In 1911, Ohm performed a retinal detachment (RD) repair by injecting air into the vitreous cavity. [3]

In 1944, Von Sallman used intravitreal penicillin injection to successfully cure endophthalmitis in rabbits. Intravitreal antibiotics and steroids remained the mainstays of endophthalmitis treatment for the next two decades. In 1998, the Food and Drug Administration (FDA) approved fomivirsen (Vitrvavene) as the first intravitreal drug for the treatment of cytomegalovirus (CMV) retinitis. Since then, the FDA has approved pegaptanib (Macugen), ranibizumab (Lucentis), and aflibercept (Eylea) for the treatment of exudative age-related macular degeneration (ARMD). Off-label use of bevacizumab (Avastin) for choroidal neovascularization and macular edema is prevalent. Intravitreal injections are used to treat neovascular AMD (AMD), clinically severe macular edema/proliferative diabetic retinopathy, cystoid macular edema (CME) caused by retinal vein occlusions, uveitis, endophthalmitis, and choroidal neovascular membrane caused by numerous retinal disorders. [2]

II. GUIDELINES

VRSI guidelines for Intravitreal injection guidelines are as follows: ^[4]

Preoperative preparation and precautions

The need for and type of intravitreal injection should be determined by the individual patient and the attending/injecting eye specialist's best clinical judgment. To ensure a patent nasolacrimal duct (NLD) and a negative regurgitation test, thorough screening is required.

There is a substantial risk of postinjection endophthalmitis if you have an active infection (blepharitis and meibomitis) or a blocked NLD/positive regurgitation test. Any active infection should be treated first, and then injections should be arranged.

Before injecting, double-check the patient's name, intravitreal agent, and laterality. Injections in both eyes are not recommended, and the other eye should be injected at least one week later. The treatment of uncontrolled systemic illnesses like diabetes should come first. Topical antibiotics must be used for a day before and three days after the injection. [4]

Patient preparation

The patient should sign a written consent form that explains the surgery and the hazards involved. Off-label bevacizumab use should be included in the permission and carefully discussed to the patient. Before entering the preoperative holding area/operating room, each patient should be given a clean operation theatre gown, protective headgear, and booties. [4]

III. PHARMACOLOGIC AGENTS USED FOR INTRAVITREAL ADMINISTRATION

Antimicrobials

Experimental models of endophthalmitis in rabbit eyes were treated with intraocular antibiotics such as penicillin and sulfonamides as early as the 1940s ^[5]

Table 1: Commonly used intravitreal antimicrobial doses and mode of preparation

Intravitreal antimicrobial agents	Dose	Preparation
Vancomycin hydrochloride	1 mg/0.1 ml	Powder form is available (500 mg). To get 50 mg/ml, add 10 ml of water to the injection. Fill a tuberculin syringe with 0.2 mL of the component and dilute to 1.0 mL. This yields 10 mg/ml, or 1 mg/0.1 ml.
Ceftazidime hydrochloride	2.25 mg/0.1 ml	It comes in a 500 mg powder form. To prepare for injection, dilute with 2 mL water to a concentration of 250 mg (active component 225 mg) per mL. Withdraw 0.1 mL into a tuberculin syringe and dilute with 0.9 mL diluent to 1 mL. This results in a concentration of 22.5 mg/ml (2.25 mg/0.1 ml).
Cefazolin	2.25 mg/0.1 ml	Ceftazidime hydrochloride is the same as ceftazidime.

Amikacin sulfate	400 mcg/0.1 ml	Available as 100 milligrams in 2 ml vial. Draw 0.08 ml (4 mg) into a tuberculin syringe and dilute to 1 ml for a concentration of 4 mg/1 ml (400 mcg/0.1 ml).
Gentamicin sulfate	200 mcg/0.1 ml	Available as a service 2 ml/80 mg To make a concentration of 4 mg/2 ml or 2 mg/ml (=200 mcg/0.1 ml), draw 0.1 ml (4 mg) into a tuberculin syringe and dilute with 1.9 ml sterile water.
Amphotericin-B	5 mcg/0.1 ml	Refill a 50 mg vial with 10 mL of 5% dextrose and shake well. To reach a concentration of 500 mcg/10 ml or 5 mcg/0.1 ml, remove 0.1 ml (0.5 mg) of solution and dilute to 10 ml with 9.9 ml of 5% dextrose.

Antivirals

Ganciclovir, foscarnet, and cidofovir are the most common drugs used to treat CMV retinitis. Ganciclovir is given weekly to treat CMV retinitis at doses of up to 2000 mcg in 0.05-0.1 ml concentrations. [6] In addition, ganciclovir can be given as an intravitreal implant. Foscarnet has a shorter intravitreal half-life and is given twice weekly at a dose of 2.4 mg/0.1 ml.

Foscarnet has been demonstrated to be effective in the treatment of CMV infections that are resistant to ganciclovir. [7] In individuals who are refractory to or do not tolerate standard medication, a combination of intravitreal ganciclovir and foscarnet has been shown to be successful. [7]

Fomivirsen induction doses of 330 mcg are given intravitreally once every two weeks for two doses, followed by maintenance therapy at the same dose every four weeks. The disadvantage for AIDS patients getting antiviral intravitreal injections or implants is that there is no protection against infection, either systemically or in the contralateral eye. [8]

Steroid

Machemer was the first to utilize dexamethasone intravitreally to stop cellular proliferation after RD surgery in 1979. In the treatment of bacterial endophthalmitis, dexamethasone (400 g in 0.1 ml) is given combined with medicines to reduce inflammation. Triamcinolone (4 mg in 0.1 ml) suppresses VEGF molecule synthesis. Through their inhibitory impact on plasmin, it stabilizes endothelium and basement membranes and reduces vascular permeability and leakage.

In diabetic macular edema, edema secondary to retinal vein occlusions, pseudophakic CME, uveitic CME, macular edema in retinitis pigmentosa, radiation-induced macular edema, and CME following penetrating corneal graft, intravitreal triamcinolone acetonide (IVTA) is used for its anti-edematous effect. [9]

IV. INTRAVITREAL INJECTION TECHNIQUE

Setting of Injection

Intravitreal injections should be administered in a sterile environment. A clean room is a designated area for intraocular injections and other sterile procedures.

Before using the space, it should be cleaned to the same standard as an operating theatre. Injections can be given in an operating room, however operating room standards dictate that preparing the patient and doing the appropriate checks can take up to 15 minutes, which may be an inefficient use of staff time.

There is a need of full source of light to see the patient eyes. The patients should be lying flat on a comfortable couch or bed that is high enough for you to administer the injections without having to bend over. [10]

V. EQUIPMENT USED

- Anti-VEGF drug
- Syringe – usually 1 ml as only a very small volume (0.05–0.1 ml) is injected
- Large bore needle – for drawing up the drug
- 30g needle – for giving injection
- 5% (aqueous) povidone iodine solution for disinfection of skin and conjunctiva
- Local anaesthetic drops
- Topical antibiotic drops
- Sterile cotton buds
- Sterile gloves
- Drapes
- Eyelid speculum
- Calliper or other measuring device [10]

VI. PROCEDURE:

Most patients will be naturally apprehensive about having a needle inserted into their eye. You must reassure your patient and explain each phase of the procedure so that he or she understands exactly what will happen next.

Check the notes and prescription before doing anything to your patient. Because you can't see which eye needs to be treated, make sure you're injecting the right medicine into the right eye. To avoid any confusion, it's a good idea to mark the eye.

Scrub your hands and put on sterile gloves after the patient is comfortably lying down. Some people choose to wear a sterile gown, although it is not required.

Inject a few drops of local anaesthetic. Because the iodine solution is irritating and can migrate into the other eye, I normally apply drops in both eyes. The drops take a few minutes to function, so while you're waiting, prepare the anti-VEGF. Using a large bore needle, pull up 0.1 ml into the 1 ml syringe in a sterile manner. Remove the air from the syringe and replace the 30G needle. Using the syringe, eject the excess medicine until there is just 0.05ml remaining in the syringe.

Clean and disinfect the eye to be injected with a 5 percent aqueous povidone iodine solution. Wipe the skin around the eye and make sure the solution gets into the conjunctival sac, disinfecting the eye's surface as well. Allow a minute or so for the solution to take effect. Apply some antibiotic drops to the skin (the patient must complete the course). Remove any extra povidone iodine from the skin around the eye and drape a sterile drape over your patient's face so that only the eye to be treated is visible. Make sure the drape doesn't get in the way of your patient's breathing.

Place the speculum in the eye to keep it open (Figure 1). Normally apply a swab soaked in local anaesthetic to the injection site and leave it there for one minute (Figure 2). Measure a safe distance behind the limbus in the inferotemporal quadrant with the measuring calliper or another measuring equipment (Figure 3). This is 3.5 mm in patients who have had cataract surgery. It is 4 mm in phakic patients who still have their own lenses. Inform the patient that you are about to inject, then rapidly insert the needle and inject the medicine (Figure 4). Give the patient more topical antibiotic drops and make sure his or her vision is unaffected. Even a modest amount of fluid injected into the eye can cause a significant increase in intraocular pressure. Patients will experience eyesight loss if this occurs. To discharge aqueous from the anterior chamber, an urgent paracentesis is the optimum treatment. If this isn't possible, ocular massage can typically help to reduce IOP. It is prudent to perform ocular massage before administering the injection to patients who are at high risk of an increase in IOP (e.g., those with severe glaucoma). Topical antibiotic drops should be prescribed for 4 days after the injection [10].

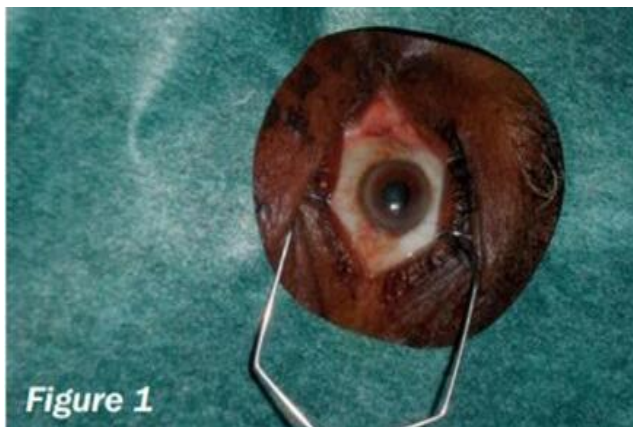


Table 2. Recommendations for Intravitreal Injection Technique.

Step of Procedure	Recommendations
Pre-injection	Glaucoma and active blepharitis treatment There will be no changes to anticoagulant drugs. Antibiotics are not used as a preventative measure. Topical anaesthetic with drops and clean cotton swabs
Sterile preparation	Surgical gloves are worn (need not be sterile) On the lids and lashes, use 10% povidone-iodine. sterile bladed lid speculum placement 5% povidone-iodine solution or drops on the ocular surface
Injection	Needles with a gauge of 30, 31, or 32 are sterile. Inferotemporal quadrant, 3.5 to 4mm behind limbus, straight or transmitted insertion Injection speed should be slow to moderate. Tamponade and displace conjunctiva with sterile cotton swab
Post-injection	To dilute remaining povidone-iodine, use antibiotic drops. Light perception vision, intraocular pressure of less than 35mm Hg, or direct visibility of central retinal artery perfusion are all things to look for. Written instructions to the patient in a font size of 18+, as well as directions to contact the physician's office promptly if any symptoms develop.

VII. RISKS AND BENEFITS OF INTRAVITREAL INJECTION

Intravitreal injections allow a physician to administer medication to the targeted target tissue with a higher likelihood of therapeutic effect and a lower risk of systemic side effects. These benefits are appealing in the treatment of many ocular illnesses, but they must be weighed against the procedure's hazards. The introduction of germs and subsequent endophthalmitis is the most serious risk of any intraocular injection. All other therapeutic drugs had a risk of 0.1 percent per injection, but triamcinolone injections had a risk of 0.6 percent each injection. Although this has not been confirmed, the greater risk linked with intravitreal injection of triamcinolone could be due to localized immunosuppression caused by the medicine. Retinal detachment, intraocular inflammation, sustained ocular hypertension, subconjunctival or intraocular hemorrhage, lens damage, cataract formation or progression, hypotony, and one instance of allergy have all been recorded [11]. Evidence of toxicity from high-dose intravenous bevacizumab in cancer patients implies that after local administration, there could be a risk of myocardial infarction or stroke [12].

VIII. COMPLICATIONS OF INTRAVITREAL INJECTIONS

Intravitreal injections are a safe therapeutic intervention when performed following to recognized guidelines and protocols. These can include issues with the operation or the intravitreal agent employed. Peri-injection discomfort, bleeding (intraocular and subconjunctival), high IOP, wound leak, and ocular surface toxicity due to the use of pre-injection washing agents are all risks connected with the operation (such as povidone-iodine). After intravitreal injection, infectious endophthalmitis is the most dangerous consequence. The rate of occurrence varies between 0.019 percent and 1.6 percent. [13]

The use of 5% povidone-iodine in the conjunctival fornices to avoid endophthalmitis is widely acknowledged and strongly recommended. When using a gel-based topical anaesthetic, the bactericidal capabilities of povidone-iodine are not compromised, as long as adequate contact time is permitted. A sterile lid speculum is used to avoid needle contact with the lids and lashes. It is extremely advised that gloves be used. Antibiotics taken before and after the injection had no effect on the occurrence of endophthalmitis in these patients. [14] After intravitreal injection, the risk of rhegmatogenous retinal detachment is extremely low, ranging from 0% to 0.67 percent. [15] This complication could be caused by the induction of a posterior vitreous detachment or an improper injection method. It is recommended to use a smaller gauge needle and to indicate the injection location (4 mm behind limbus in phakic and 3 mm behind in pseudophakic). [13] Antimicrobials applied intraocularly have the potential to be harmful to the retina. Macular infarction is a known side effect of intravitreal gentamycin, especially when the antibiotic is administered at a higher dose. [19] Steroids have been linked to an increased risk of cataracts. [16]

Acute rise in IOP, endophthalmitis, rhegmatogenous RD, ocular hemorrhage, lens damage, and other complications are all linked to the method. Complications associated to the substance being injected, such as an increased risk of IOP elevation and cataract formation, as in the case of steroids. There is an increased risk of IOP elevation, intraocular inflammation, and systemic adverse effects (gastroenterology bleeding, subdural hemorrhage, transient ischemic attack, and cerebral vascular accident), among other things, with anti-VEGF injections. [17]

IX. CAUTIONS

These guidelines do not cover injections for ROP (Retinopathy of prematurity). Injections of Antivascular endothelial growth factor (VEGF) are not given to pregnant women or those with uncontrolled diabetes (no evidence-based guideline for a cutoff of blood sugar or glycated hemoglobin level). [18]

X. CONCLUSION

Ophthalmic intravitreal injection technique is useful to treat ophthalmic bacterial infections, viral infections, glaucoma and other ophthalmic disorders. Lower dosage of injection produces more safety to retina and ophthalmic tissues. The recovery from the ophthalmic diseases is faster and efficient

CONFLICTS OF INTEREST

There are no conflicts of interest and disclosures regarding the manuscript.

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